Original Article

DOI: 10.7860/IJNMR/2024/69436.2418

Paediatrics Section

Antimicrobial use and Adverse Drug Reaction in Newborns with Neonatal Sepsis: A Prospective Observational Study from a Tertiary Care Teaching Hospital

RIDDHI C PARMAR[1], ANIL P SINGH[2]

ABSTRACT

Introduction: Neonatal Sepsis (NS) is a major cause of morbidity and mortality worldwide, especially in developing countries like India. The role of antimicrobials is life-saving in NS. To achieve a good prognosis, early diagnosis and appropriate treatment are required. Data related to the irrational use of antimicrobials in neonates are limited.

Aim: To evaluate the drug usage pattern and Adverse Drug Reactions (ADRs) of antimicrobials in NS.

Materials and Methods: A prospective observational study was conducted among 350 neonates who were admitted and diagnosed with NS from January to December 2021 in the Neonatal Intensive Care Unit (NICU) of PDU Medical College and Civil Hospital, Rajkot, Gujarat, India. Demographic data such as age, sex, birth weight, and clinical data such as type of delivery, type of sepsis, culture-sensitivity status, and antimicrobials used were recorded. Suspected ADRs were reported in the pharmacovigilance database. Categorical data were analysed in percentage, whereas some clinical data were analysed with mean and median using Microsoft Office Excel-2019.

Results: In the present study, 172 (49.15%) male and 178 (50.85%) female neonates were almost equally affected. The mean gestational age and birth weight were 35±3.6 weeks and 2±0.7 kg, respectively. Early-Onset Neonatal Sepsis (EONS) cases were more at 273 (78%) compared to Late-Onset Neonatal Sepsis (LONS). Seventeen different antimicrobials were used. The average number of antimicrobials used per case was 2.9. The Piperacillin Tazobactam was the most commonly used antimicrobial in 173 cases (49.43%) in early-onset sepsis, while Meropenem was used in 40 cases (11.43%) in late-onset sepsis. *Coagulase-negative Staphylococcus* was the most commonly isolated organism in 15 cases (4.2%), followed by *Klebsiella Pneumoniae* in 13 cases (3.7%). Twelve out of 17 antimicrobials (70.59%) were not included in the first list of essential medicines for children of India in 2011. Six ADRs were reported in the present study.

Conclusion: In all admitted cases of sepsis, empirical therapy was given, but variations from standard recommendations were observed in dose and frequency. A periodic survey of antimicrobial use patterns in NS will be useful in the rational selection of empirical therapy.

Keywords: Antimicrobial stewardship, Bacterial sensitivity test, Blood culture, Newborn, *Staphylococcal* infection

INTRODUCTION

The term NS refers to an infection involving the bloodstream in newborn infants less than 28 days old, which is a major cause of morbidity and mortality worldwide in neonates [1]. According to the World Health Organisation (WHO), Neonatal infections result in over 550,000 neonatal deaths every year [2]. The course and severity of NS depend on a variety of factors, including the virulence, resistance of the organism, gestational age, birth weight, place and type of delivery, breastfeeding, pre-lacteal feeding, etc., [3].

In developing countries, Neonatal infection is a critical health issue, justifying early diagnosis and appropriate treatment with antimicrobials. Delay in the initiation of effective antimicrobial therapy can result in serious consequences such as respiratory distress, shock, neonatal seizures, meningitis, neurodevelopmental deficits, and death [4]. Therefore, it is recommended to start empirical antimicrobials without waiting for culture results.

The judicious use of antibiotics can be life-saving; however, broad-spectrum antimicrobials and prolonged treatment with empiric drugs can lead to the development of antimicrobial resistance [5] and adverse outcomes such as necrotizing enterocolitis, late-onset sepsis, and death [6]. Periodic surveillance of the microbial aetiology and antibiotic use patterns in NS will be useful in the rational selection of empirical therapy [5].

While a large number of drug utilisation studies are available for adults and the geriatric age group [7-9], only a few studies provide information on drug use patterns in paediatrics and even fewer in neonates [10,11]. It has been shown that the pattern of antimicrobial usage in neonatal intensive care is changing, with limited current data available [12].

Hence, the present study was conducted to evaluate the antimicrobial drug usage pattern and assess ADRs among patients with NS in the NICU of the tertiary care teaching hospital. This information can be used to assess the quality of care provided and facilitate the rational use of antimicrobials in this population.

MATERIALS AND METHODS

The present prospective observational study was conducted in the NICU of the paediatric department at a tertiary care teaching hospital, PDU Medical College and Civil Hospital, Rajkot, Gujarat, India, from January 2021 to December 2021. The study protocol was approved by the Institutional Ethics Committee (IEC) (Approval letter

no. PDUMCR/IEC/25/2021). Before collection of the data, informed written consent from the patients' parents/guardians was obtained.

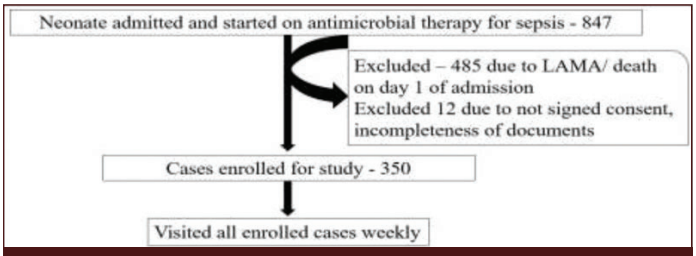
Inclusion criteria: Diagnosed cases of NS according to the AIIMS protocols in neonatology in 2019 [13] were included, with non-specific clinical features such as hypothermia or fever, lethargy, poor perfusion, poor feeding, hypotonia, brady/tachycardia, respiratory distress, and specific clinical features such as bulging anterior fontanelle and seizures indicative of meningitis were included in the study.

Exclusion criteria: Neonates whose parents/guardians were not willing to provide written consent were excluded. Neonates admitted to the NICU for less than 1 day due to death or Leave Against Medical Advice (LAMA) were also excluded.

Sample size: The sample size was calculated using the formula Z^2pq/d^2. The prevalence of sepsis in neonates is 35.34% [14], so with a Z score at a 95% confidence interval of 1.96 and a margin of error of 5%, 350 cases of neonates with NS were analysed during the study period.

Study Procedure

The patients' parents/guardians were provided with a patient information sheet to understand the study procedures. The flowchart in [Table/Fig-1] shows the data collection and enrollment process of 350 cases after excluding LAMA or death cases within one day of admission. During the study, the investigator visited the NICU daily for data collection. No interventions were conducted by the investigator as part of the study; only the treatment given to NS cases in the NICU, prescribed by the pediatrician based on the diagnosis and their choice, was recorded.



[Table/Fig-1]: Flow chart of data collection.

The demographic data regarding age, gender, and birth weight distribution, clinical data regarding gestational age, type and place of delivery, immunisation status, type of sepsis, C-Reactive Protein (CRP positive if the value is >10 mg/L, as it is a non-specific marker of inflammation and an important investigation to determine the length of AMA use in culture-negative NS) [15], culture-sensitivity status, and therapeutic data regarding the name of antimicrobials used, the number of antimicrobials used per case, dose, duration, and frequency were collected from the patients' case files and treatment charts. Data on suspected ADRs were collected and reported to the ADR monitoring center. Causality, preventability, severity, and probability assessment of ADRs were conducted according to the WHO causality assessment scale [16], Modified Schumock and Thornton Preventability scale [17], Modified Hartwig's severity assessment scale [18], and Naranjo ADR probability score [19], respectively.

All Antimicrobials (AMA) used for sepsis in this set-up were compared with the WHO Essential Medicine List (EMLc)-2021 [20], Essential Medicine list by the Government of Gujarat-2021 [21], and the National list of essential medicine for children issued in 2011 [22]. Additionally, the drug dosages given in the present study were compared to the recommended doses by the Indian Academy of Paediatrics (IAP) Standard Treatment Guidelines (STG) [23].

STATISTICAL ANALYSIS

The recorded data were analysed using descriptive statistics such as percentages, means, medians with standard deviation, and interquartile range in Microsoft Office Excel 2019.

RESULTS

In the present study, the mean gestational age and birth weight were 35±3.6 weeks and 2±0.7 kg, respectively. There were 273 cases (78%) of Early Onset Neonatal Sepsis (EONS), which were higher than the 77 cases (22%) of Late Onset Neonatal Sepsis (LONS) [Table/Fig-2]. Empirical antimicrobial therapy was initiated in all cases of NICU admissions. Seventeen different antimicrobial agents were used, with 221 neonates (63.14%) started on two Antimicrobial Agents (AMA). 115 cases (32.85%) were receiving 3-5 AMAs, and 14 cases (4%) were receiving 6-8 AMAs. All AMAs were administered intravenously.

Variable	n (%) (Total N=350)
Gender	
Male	172 (49.15%)
Female	178 (50.85%)
Place of delivery	
Institutional	329 (94.00%)
Domiciliary	21 (06.00%)
Type of delivery	
Normal vaginal	248 (70.85%)
Caesarean section	102 (29.15%)
Birth weight	
Mean±SD=2.0±0.7 kg	
Low Birth Weight (LBW)	242 (69.15%)
Normal birth weight	108 (30.85%)
Gestational age	
Mean±SD=35±3.6 weeks	
Term	
Preterm	197 (56.27%)
Full term	153 (43.73%)
Type of sepsis	
Early Onset Neonatal Sepsis (EONS)	273 (78.00%)
Late Onset Neonatal Sepsis (LONS)	77 (22.00%)
Others	
Immunised	344 (98.28%)
C-Reactive Protein positive (CRP)	203 (58.00%)

[Table/Fig-2]: Baseline demographic data and patient's characterstics.
Data presented in number, percentage and mean±SD (N=350)
CRP positive if CRP is >10 mg/L

The commonly used regimens for empirical therapy were Piperacillin-Tazobactam Fixed Dose Combination (FDC)+Amikacin and Meropenem+Amikacin. Piperacillin-Tazobactam combination was used in EONS, while Meropenem combination was used in LONS as the most common empirical agent [Table/Fig-3].

Only 48 blood cultures (13.71%) were positive, with *Coagulase-negative staphylococcus* being the most common isolated organism in 15 cases (4.2%). In EONS, the most common isolated organism was *Klebsiella Pneumoniae* in 13 cases (3.7%), while in LONS, *Coagulase-negative staphylococcus* was the most common in seven cases (2%) [Table/Fig-4].

Out of the 17 AMAs used for sepsis in the present setup, 12 are included in the WHO EMLc-2021, 13 in the EML by the Government

S. No.	Name of antimicrobial	No. of case in EONS	No. of case in LONS
1	Piperacillin+Tazobactam	173*	26
2	Gentamycin	111	22
3	Amikacin	109*	27†
4	Levofloxacin	95	21
5	Ampicillin+Sulbactam	59	9
6	Meropenem	51	40†
7	Amoxicillin+Clavulonic Acid	51	13
8	Metronidazole	22	16
9	Polymyxin B	13	16
10	Vancomycin	12	16
11	Cefotaxime	11	10
12	Clindamycin	9	4
13	Fluconazole	6	3
14	Linezolid	4	6
15	Ampicillin	4	0
16	Tigecycline	2	2
17	Netilmycin	1	0

[Table/Fig-3]: Antimicrobial used and number of cases.
*Piperacillin-Tazobactam (FDC)+Amikacin were most common AMAs for initiation of empirical therapy in EONS; †Meropenem+Amikacin were most common AMAs for initiation of empirical therapy in LONS

Isolated organism in EONS (n=33)		
Isolated organism	**No. of case**	**Percentage**
Klebsiella Pneumoniae	13	3.7%
E.coli	8	2.28%
Coagulase negative staphylococcus	8	2.28%
Candida tropicalis	1	0.28%
Acinetobacter	1	0.28%
Staphylococcus Aureus	1	0.28%
MRSA	1	0.28%
Isolated organism in LONS (n=15)		
Isolated organism	**No. of case**	**Percentage**
Coagulase negative staphylococcus	7	2.00%
MRSA	5	1.42%
Streptococcus	1	0.28%
Escherichia coli	1	0.28%
Acinetobacter	1	0.28%

[Table/Fig-4]: Microorganisms isolated from blood culture data presented in number and percentage (N=48).

of Gujarat-2021, and only five in the National list of essential medicine for children issued in 2011. Drugs not included in the WHO list are Levofloxacin, Tigecycline, Netilmycin, Ampicillin, and Ampicillin-Sulbactam FDC. In the EML of the Gujarat government, Tigecycline, Netilmycin, Ampicillin, and Ampicillin-Sulbactam are not included. The National list of essential medicine only includes Metronidazole, Gentamycin, Amoxicillin-Clavulonic acid, Fluconazole, Ampicillin, and misses the rest of the AMAs [Table/Fig-5].

Variations in dose, frequency, and duration were observed. The total dose of Amikacin, Metronidazole, Amoxicillin-Clavulanic acid, Gentamycin, Piperacillin-Tazobactam, Levofloxacin, and Ampicillin-Sulbactam were higher compared to the recommended doses by the IAP STG [Table/Fig-5].

Amikacin, Gentamycin, and Levofloxacin were administered in divided doses in 2 (0.57%), 1 (0.28%), and 36 (10.28%) cases, respectively. Meropenem, Piperacillin-Tazobactam, and Vancomycin were given as once-daily doses in 3 (0.85%), 1 (0.28%), and 3 (0.85%) cases, respectively. Six Adverse Drug Reactions (ADRs) were reported, and according to the WHO causality assessment scale, all were probably related to the suspected antimicrobial agents. According to the Naranjo ADR probability score, all ADRs were considered probable. According to the Modified Schumock and Thornton Preventability scale, all reported ADRs were definitely preventable as the treatment of ADRs is known. According to the modified Hartwig's severity scale, two were mild, three were moderate, and one was severe, which was an anaphylactic reaction due to vancomycin [Table/Fig-6].

DISCUSSION

A total of 350 neonates were included for evaluation. A comparison of demographic and clinical data from the present study with similar studies is shown in [Table/Fig-7]. In the present study, neonates with Low Birth Weight (LBW) were more associated with sepsis. This observation is similar to studies by Behera N and Behera J [24] and Subash KR and Shanmugapriyan S [4], as LBW is one of the predisposing factors for Neonatal Sepsis (NS) [15]. Preterm babies were more affected by sepsis than term babies, a finding that is consistent with studies conducted in Maharashtra, Tamil Nadu, Odisha, and West Bengal [4,5,24,25]. This finding may be attributed to the lower immunity in preterm babies.

The incidence of Early Onset Neonatal Sepsis (EONS) cases was higher (78%) than Late Onset Neonatal Sepsis (LONS), which is similar to the findings of Behera N and Behera J [24]. LONS can either be a healthcare-associated infection or community-acquired.

S. No.	Name of drug (Injections only)	AMA included in 8th WHO EMLc	AMA included in 1st Indian EMLc	AMA included in EML given by state government	Dose (mg/kg)	Duration (Days)	Total Dose used/Day (mg/day)	Median and IQR of total dose	Recommended dose in mg/day by IAP
1	Cefotaxime	+	-	+	50	2-10	110-480	270 (225-360)	100-900
2	Amikacin	+	-	+	15	2-16	10.5-75‡	30 (10.5-38)	7.5-63
3	Metronidazole	+	+	+	10	2-24	20-144‡	55.5 (39-75)	12-95
4	Meropenem	+	-	+	40	1-24	25-450	180 (117-242)	30-500
5	Linezolid	+	-	+	10	2-12	24-90	39 (30-60)	20-90
6	Amoxicillin+ Clavulonic Acid	+	+	+	50	1-12	18-540‡	210 (170-300)	50-420
7	Gentamycin	+	+	+	7.5	1-16	5-32‡	13.2 (10-18)	2.5-21
8	Tigecycline	-	-	-	1	4-20	2-9	2.8 (2.6-4.35)	2-16
9	Fluconazole	+	+	+	6	2-14	6-24	8 (7.8-17)	3-25.2

10	Piperacillin+ Tazobactam	+	-	+	100	1-14	130-1110‡	400 (280-520)	100-840
11	Vancomycin	+	-	+	15	1-20	25-165	94.5 (56.25-123.75)	12-189
12	Levofloxacin	-	-	+	10	1-14	5-84‡	23 (14-32.25)	5-42
13	Clindamycin	+	-	+	10	2-21	10-81	33 (22-42)	10-90
14	Netilmycin	-	-	-	4	4	4.4	-	4-16.8
15	Ampicillin	-	+	-	50	3-5	70-220	135 (115-160)	25-420
16	Ampicillin+ Sulbactam	-	-	-	50	1-14	94-525‡	174 (129.75-212.5)	20-420
17	Polymyxin B	+	-	+	25000 IU/kg	1-24	25000-375000 IU/day	75000 (55000-87500)	75000-630000 IU/day

[Table/Fig-5]: AMA included in essential drug list for paediatrics, dose, duration, total dose/day and recommended dose by IAP.
‡indicates total dose exceed than dose recommended by IAP guidelines for NS
Data of total dose per day is presented in median with interquartile range
EMLc: Essential medicine list for children; AMA: Antimicrobial agents; IAP: Indian academy of paediatrics

S. No.	Adverse drug reaction	Suspected drug	WHO causality assessment scale	Naranjo ADR probability score	Modified Schumock and Thornton Preventability scale	Modified Hartwig's severity scale	Management
1	Hyperbilirubinemia	Cefotaxime	Probable	Score-5	Definitely preventable	Level-4	Suspected drug withdrawal and shifted to Amoxicillin+Clavulonic acid
2	Diarrhoea	Amoxicillin+ Clavulonic acid	Probable	Score-5	Definitely preventable	Level- 2	Suspected drug dose was not changed, Treatment of dehydration
3	Hyperbilirubinemia	Cefotaxime	Probable	Score-5	Definitely preventable	Level-4	Suspected drug withdrawal and shifted to Amoxicillin+Clavulonic acid
4	Red men syndrome	Vancomycin	Probable	Score-5	Definitely preventable	Level-3	Suspected drug dose was not changed, Injection Pheniramine 0.1 mg/kg stat, slow infusion of Vancomycin was administered again by using infusion pump
5	Diarrhoea	Ampicillin	Probable	Score-5	Definitely preventable	Level-2	Suspected Drug withdrawal and shifted to Amoxicillin+Clavulonic acid
6	Anaphylactic reaction	Vancomycin	Probable	Score-5	Definitely preventable	Level-5	Suspected drug stoppage, Injection Pheniramine 0.1 mg/kg stat, Injection Dexamethasone 0.6 mg/kg stat and Injection Adrenaline 0.01 mg/kg 1:1000 strength subcutaneously was kept ready in case if anaphylactic shock occurs

[Table/Fig-6]: Causality, preventability and severity analysis of reported ADRs and their management (n=6).
WHO causality assessment scale-Certain, Probable, Possible, Unlikely
Naranjo probability score-≥9=definite ADR, 5-8=probable ADR, 1-4=possible ADR, 0=doubtful ADR
Modified Schumock and Thornton Preventability scale-Definitely preventable, Probably preventable, Not preventable
Modified Hartwig's severity scale- Mild=level 1 and 2, Moderate=Level 3 and 4, Severe= Level 5,6 and 7

Observations	Present study	Behera N and Behera J, [24]	Subash KR and Shanmugapriyan S, [4]	Tank PJ et al., [6]
Sample size (n)	350	204	250	320
Variables				
Gender				
Male	172 (49.15%)	150 (73.5%)	42.38%	170 (53.2%)
Female	178 (50.85%)	54 (26.5%)	57.62%	150 (46.8%)
Place of delivery				
Institutional	329 (94.00%)	80 (39%)	-	307 (96%)
Domiciliary	21 (06.00%)	124 (61%)	-	13 (4%)
Type of delivery				
Normal vaginal	248 (70.85%)	161 (79%)	-	160 (50%)
Caesarean section	102 (29.15%)	33 (16%)	-	160 (50%)

Birth weight				
Mean±SD	2.00±0.7 kg			
Low Birth Weight (LBW)	242 (69.15%)	128 (63%)	>90%	162 (50.62%)
Normal birth weight	108 (30.85%)	76 (37%)	-	158 (49.38%)
Gestational age				
Mean±SD (weeks)	35±3.6			
Term				
Preterm	197 (56.27%)	152 (74.5%)	232 (92.85%)	160 (50%)
Full term	153 (43.73%)	52 (25.5%)	18 (7.15%)	160 (50%)
Type of sepsis				
Early onset (EONS)	273 (78.00%)	126 (62%)	>90%	297 (92.8%)
Late onset (LONS)	77 (22.00%)	78 (38%)		23 (7.2%)
M/C Isolated organism	*Coagulase negative staphylococcus*	*Staphylococcus aureus*	*Klebsiella Pneumoniae*	-
Average no. of AMAs/encounter	2.9	2.4	-	-
M/C used antimicrobial	Piperacillin-Tazobactam	Ampicillin+Amikacin	Piperacillin-Tazobactam	Penicillin+Gentamycin
No. of ADR reported	06	Not reported	Not reported	Not reported
Immunised	344 (98.28%)	-	-	-
C-reactive protein positive (CRP)	203 (58.00%)	-	-	-

[Table/Fig-7]: Comparison of demographic data, patient's characteristics and clinical data of present study with similar studies.
CRP positive if CRP is >10 mg/L, M/C: Most common; AMA: Antimicrobial agent; ADR: Adverse drug reaction
Data presented in number, percentage and mean±SD (N=350)

In the present study, 13.71% of blood cultures had isolated organisms, whereas in the study by Behera N and Behera J, 77% of cultures had isolated organisms, which included cerebrospinal fluid and pus samples for culture in addition to blood culture [24]. Blood culture is considered the gold standard for the diagnosis of sepsis and should be performed in all cases of suspected sepsis before starting antibiotics. The most common isolated organism was Coagulase-negative *Staphylococcus*, which differs from the study by Behera N and Behera J, where *Staphylococcus aureus* was the most commonly isolated organism [Table/Fig-7] [24].

Neonatal Sepsis (NS) is rapidly progressive and has a high mortality rate (21%) [26]. Timely administration of the first dose of antibiotics is life-saving for a septic infant, and any unintended delay in treatment initiation while waiting for investigation results should be avoided.

Empirical therapy should be tailored to the specific unit and determined by the prevalent spectrum of etiological agents and their antibiotic sensitivity patterns. In the present study, most neonates (221 cases, 63.14%) were prescribed at least two Antimicrobial Agents (AMA) as Empirical antimicrobial therapy, while in the study by Das M et al., the majority of neonates received at least three AMAs [5]. Decisions to change regimens were based on clinical deterioration or if a different organism was isolated from the blood culture than the suspected one.

Piperacillin-Tazobactam was the most commonly prescribed antimicrobial in Early Onset Neonatal Sepsis (EONS), which is consistent with findings from some similar studies [5,24]. Meropenem was the most commonly prescribed antimicrobial in Late Onset Neonatal Sepsis (LONS), although Meropenem is a reserved drug for empirical therapy [27]. For empirical therapy in LONS, a combination of Ampicillin or Cloxacillin with Gentamycin or Amikacin may be used [13]. Amikacin or Gentamycin was the preferred choice for empirical therapy in both EONS and LONS. Ampicillin was only used in four cases of EONS, as it no longer covers 70% of hospital-isolated organisms [15]. Polymyxin-B was used in 13 cases of EONS and 16 cases of LONS. Polymyxin-B is used in cases of culture-negative septicaemia based on descending order of utilisation [28]. The anti-fungal agent Fluconazole was used in six cases of EONS and three cases of LONS, following either high C-Reactive Protein (CRP) levels, culture-confirmed fungal infection, or in neonates who were not responding satisfactorily to AMAs. The actual choice of therapy varies across institutions depending on the susceptibility profile of prevalent sepsis pathogens. Thus, a single empirical regimen cannot be universal; it varies depending on the time and place [15].

In the study by Behera N and Behera J, all antimicrobials used were included in the Essential Medicines List (EML) provided by the Government of Odisha [24], whereas in this study, 76.47% of antimicrobials were included in the EML given by the Government of Gujarat [21]. Amikacin, Piperacillin-Tazobactam, and Vancomycin are considered essential medicines for Neonatal Sepsis (NS), but they are not included in the list of essential medicines for children in India-2011 [22] compared to the WHO 8th Essential Medicines List for Children-2021 [20].

All babies were treated as full-term babies, with the same mg/kg dose regardless of the gestational age of the babies, which could adversely affect preterm babies. There was a variation in the total dose given per day compared to the recommended dose. It is important to determine the optimal dose of the antibiotic for the patient and the dosing schedule that maximises the antimicrobial effect. The dose of seven Antimicrobial Agents (AMAs) exceeded the recommended dose according to the Standard Treatment Guidelines (STG) provided by the Indian Academy of Paediatrics [23], which could lead to drug toxicity. The frequency of drug administration was not appropriate in 46 cases based on the killing effect of the drug. Amikacin, Gentamycin, and Levofloxacin have concentration-dependent killing, and a single daily dose is recommended, while Meropenem, Piperacillin-Tazobactam, and Vancomycin have time-dependent killing, so administration in divided doses is recommended. This inappropriate dosing may lead to treatment failure or drug toxicity. In neonates, a comprehensive understanding of factors influencing dosing will enhance accurate and effective drug therapy and may help identify the cause of treatment failure or therapy-related toxicity [28].

The reported Adverse Drug Reactions (ADRs) were probably related to the suspected antimicrobial agents according to the WHO causality assessment scale [16] and the Naranjo ADR probability score [19]. All ADRs were deemed preventable according to the Modified Schumock and Thornton Preventability scale [17]. According to the modified Hartwig severity assessment scale, one ADR was classified as severe (anaphylactic reaction) [Table/Fig-6] [18].

In this Neonatal Intensive Care Unit (NICU), newborn care is conducted properly with aseptic precautions to prevent hospital-acquired sepsis, although the use of antimicrobials is on the higher side [23]. The dose, duration, and frequency of antimicrobials should adhere to the STG. They should be dosed according to whether the baby is full-term, preterm, or low birth weight to prevent unnecessary exposure and toxicity. Blood samples should be collected before initiating empirical therapy so that Culture and Sensitivity (CS) testing can be performed, and based on the CS report, antimicrobial de-escalation can be implemented. Such practices can have an impact on preventing resistance and rationalising the use of antimicrobials.

Limitation(s)

This is a tertiary care hospital where most cases are referred from the periphery. Unfortunately, the history of antimicrobials received by patients from outside the institute before admission could not be evaluated due to the unavailability of records.

CONCLUSION(S)

Neonates are a vulnerable group due to developing body functions. The average antimicrobial use per patient is 2.9 in the NICU. The most commonly used antimicrobial agents were Piperacillin + Tazobactam in Early-onset Neonatal Sepsis (EONS) and Meropenem in Late-onset Neonatal Sepsis (LONS). The doses of seven antimicrobial agents exceeded the recommended dose according to the Standard Treatment Guidelines (STG) provided by the Indian Academy of Paediatrics (IAP). In 46 cases, the frequency of antimicrobial agent use was inappropriate based on their killing effect, which may lead to drug toxicity. Six Adverse Drug Reactions (ADRs) were reported, with one ADR being a serious anaphylactic reaction due to Vancomycin. The ADRs were detected and managed well. To ensure rational use, antimicrobials in neonates must be effective, safe, have the proper spectrum, correct dosage, and should be easily available. Similar studies conducted at regular intervals can reflect the changing pattern of antimicrobial prescribing, helping authorities to plan and ensure necessary antimicrobials are available.

Acknowledgement

The authors are thankful to Dr. Pankaj Buch sir, head of department of paediatrics for helping in study designing, data points to be collected and permitting quality data collection. Also, thankful to Dr. Hemal Dholakia, Assistant professor for helping in protocol designing.

REFERENCES

[1] Shane AL, Sachez PJ, Stoll BJ. Neonatal sepsis. Lancet. 2017;390:1770-80. Doi: 10. 1016/S0140-6736(17)31002-4. PMID: 28434651.
[2] Newborn Infections. Available from: https://www.who.int/teams/maternal-newborn-child-adolescent-health-and-ageing/newborn-infection. [Last accessed Janury 12, 2023].
[3] Gupta P, Menon PSN, Ramji S, Lodha R. Neonatal sepsis. In: PG textbook of Paediatrics. 2nd ed. New Delhi: Jaypee Brothers Medical Publishers(P) Ltd., 2018, Pp. 596-97.
[4] Subash KR, Shanmugapriyan S. A study on prescription of antibiotics utilization in neonatal intensive care at a tertiary care center. Int J Med Res Heal Sci. 2015;4(2):265-68.
[5] Das M, Pal N, Dolui SK, Choudhury S. Pattern of antimicrobial usage in neonatal septicaemia at neonatal intensive care unit of a tertiary care hospital in Kolkata. J Nat Sci Biol Med. 2019;10(2):178.
[6] Tank PJ, Omar A, Musoke R. Audit of antibiotic prescribing practices for neonatal sepsis and measurement of outcome in new born unit at Kenyatta National Hospital. Int J Pediatr. 2019;2019;7930238. Doi: 10.1155/2019/7930238. PMID: 31182965; PMCID: PMC6512059.
[7] Rakesh Kumar T, Shahina S, Shobha JC, Naidu MUR, Usha Rani P, Vijay T. Drug utilization in geriatric population in tertiary care centre. J K Sci. 1999;1(3):118-20.
[8] Shah RB, Gajjar B, Desai SV. Drug utilization pattern among geriatric patients assessed with the anatomical therapeutic chemical classification/defined daily dose system in a rural tertiary care teaching hospital. Int J Nutr Pharmacol Neurol Dis. 2012;3(3):258-65.
[9] Jhaveri BN, Patel TK, Barvaliya MJ, Tripathi CB. Drug utilization pattern and pharmacoeconomic analysis in geriatric medical in-patients of a tertiary care hospital of India. J Pharmacol Pharmacother. 2014;5(1):15-20. Doi: 10.4103/0976-500X. 124411. PMID: 24554905; PMCID: PMC3917160.
[10] Sawalha A, Al-Bistawi G, Al-Khayyat L, Sweileh W, Ramahi R, Jaradat N. Pattern of parenteral antimicrobial prescription among pediatreic patients in Al-Watani government hospital in Palestine. An-Najah Univ J Res. 2006;20:193-207. Doi: 10.35552/anujr.a.20.1.594.
[11] Baidya S, Hazra A, Datta S, Das AK. A study of antimicrobial use in children admitted to pediatric medicine ward of a tertiary care hospital. Indian J Pharmacol. 2017;49(1):10-15. Doi: 10.4103/0253-7613.201034. PMID: 28458416; PMCID: PMC5351220.
[12] Al-Turkait A, Szatkowski L, Choonara I, Ojha S. Review of drug utilization studies in neonatal units: A global perspective. Int J Environ Res Public Health. 2020;17(16):5669. Doi: 10.3390/ijerph17165669. PMID: 32764503; PMCID: PMC7459677.
[13] Agarawal R, Deorari AK, Paul VK, Sankar MJ, Sachdeva A. Sepsis in the newborn. In: AIIMS Protocols in Neonatology. 2nd ed. New Delhi: Nobel, 2019.
[14] Assudani HJ, Gusani JK, Mehta SJ, Agravat HH, Kothari K. Bacteriological profiles of septicaemia in neonates at tertiary care hospital, Gujarat, India. J Res Med Dent Sci. 2015;3(2):148-51. Doi: 10.5455/jrmds.20153212.
[15] Eichenwald E, Hansen RA, Martin CR, Stark AR. Cloherty and Stark's Manual of neonatal care. 8th ed. New Delhi: Wolters Kluwer. 2021: Pp. 1124.
[16] The use of the WHO-UMC system for standardised causality assessment [Internet]. Available from: http://www.who-umc.org/graphics/4409.pdf. [Last accessed October 02, 2023].
[17] Schumock GT, Thornton JP. Focusing on the preventability of adverse drug reactions. Hosp Pharm. 1992;27(6):538. PMID: 10118597.
[18] Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. AM J Hosp Pharm. 1992;49(9):2229-32. PMID: 1524068.
[19] Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Robert EA, et al. A method for estimating the probability of advers drug reactions. Clin Pharmacol Ther. 1981;30(2):239-45. Doi: 10.1038/clpt.1981.154. PMID: 7249508.
[20] WHO. WHO model list of essential medicine for children- 8th list 2021 [Internet]. Available from: https://www.who.int/publication/i/item/WHO-MHP-HPS-EML-2021.02. [Last accessed June, 2023].
[21] Essential Drug List/ Drug/Drug Procurement/Gujarat Medicine Services Corporation Limited [Internet]. Available from: https://gmscl.gujarat.gov.in/essential-drug-list.htm. [Last accessed June 2023].
[22] Pediatrics IAP. List of essential medicines for children of India 2011 [Internet]. Available from: https://www.medbox.org/document/list-of-essential-medicines-for-children-of-india#GO (2011). [Last accessed June, 2023].
[23] Santhanam S, Anand P, Mohanty PK. Neonatal Sepsis Standard Treatment Guidelines. 2022 [Internet]. Available from: https://iapindia.org/pdf/STG-Neonatal-Sepsis-005.pdf [Last accessed October 2023].
[24] Behera N, Behera J. Drug utilization pattern of antimicrobials in neonatal sepsis in tertiary care teaching hospital. Indian J Neonatal Med Res. 2017;5(3):01-05.
[25] Suryawanshi S, Pandit V, Suryawanshi P, Panditrao A. Antibiotic prescribing pattern in a tertiary level neonatal intensive care unit. J Clin Diagn Res. 2015;9(11):FC21-24. Doi: 10.7860/JCDR/2015/14764.6807. Epub 2015 Nov 1. PMID: 26672773; PMCID: PMC4668430.
[26] Nyenga AM, Mukuku O, Mutombo AK, Mpoy CW, Luboya ON, Wembonyama SO. Predictors of mortality in neonatal sepsis in a resource-limited setting. J Adv pediatr Child Heal. 2021;4:57-61. Doi: 10.29328/journal.japch.1001034.

[27] Cotten CM, Taylor S, Stoll B, Goldberg RN, Hansen NI, Sanchez PJ, et al. Prolonged duration of initial empirical antibiotic treatment is associated with increased rates of necrotizing enterocolitis and death for extremely low birth weight infants. Pediatrics. 2009;123(1):58-66. Doi: 10.1542/peds.2007-3423. PMID: 19117861; PMCID: PMC2760222.

[28] Gumbo T. General Principles of Antimicrobial Therapy. In: Goodman & Gilman's The Pharmacological basis of therapeutics. 13th ed. New Delhi: Mc Graw Hill Education, 2018, pp. 957-66. Available from: https://accessmedicine.mhmedical.com/content.aspx?bookid=2189&sectionid=172483986.

PARTICULARS OF CONTRIBUTORS:
1. Senior Resident, Department of Pharmacology, P.D.U. Medical College and Civil Hospital, Rajkot, Gujarat, India.
2. Head, Department of Pharmacology, P.D.U. Medical College and Civil Hospital, Rajkot, Gujarat, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Riddhi C Parmar,
Department of Pharmacology, P.D.U. Medical College and Civil Hospital,
Jamnagar Road, Rajkot-360001, Gujarat, India.
E-mail: riddhiparmar9060@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Jan 07, 2024
- Manual Googling: Mar 06, 2024
- iThenticate Software: Mar 22, 2024 (8%)

ETYMOLOGY: Author Origin

EMENDATIONS: 7

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes (from parents/guardians)
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Jan 07, 2024**
Date of Peer Review: **Feb 06, 2024**
Date of Acceptance: **Mar 23, 2024**
Date of Publishing: **Jun 30, 2024**