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Audit of Antibiotic Prescription in Suspected Neonatal Sepsis at an Indian Tertiary Care Hospital

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Abstract

Neonatal sepsis is one of the most typical causes of neonatal morbidity and mortality in the developing world. Rational use of antibacterial is a priority to prevent the emergence of resistance and to reduce the burden of treatment failure. This study was a prospective, cross-sectional study that collected data from 148 records of clinically suspected neonatal sepsis in a tertiary care hospital between January to December 2017. The isolated organisms, prescribing patterns, approval status, and list of antibacterial in WHO Essential Medicines List/NLEM were analyzed and presented as percentages, mean and standard deviations using appropriate tables and graphs. Of the 430 antibacterials examined, single-drug formulations were most commonly prescribed [400(93.02%)]; 298(69.30%) and 427(99.30%) were approved by DCGI and USFDA, respectively; 275(63.95%) antibacterials were included in both WHO and NLEM. The most common isolated organisms were gram-negative (64.1%). The most common class of antibacterial prescribed was beta-lactams (ATC class: J01D and J01C) [251(58.37%)] followed by aminoglycosides (ATC class: J01G) [124(28.84%)] irrespective of culture and sensitivity and their generic names prescribed almost 50% (216) of drugs. Regarding outcome, 87.16% of cases recovered well. In conclusion, the rationality of antibacterial drug usage in suspected cases of neonatal sepsis was followed the majority of times, leading to better patient care and outcome.

Keywords: Prescribing Patterns; Antibacterial; Neonatal Sepsis

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Introduction

Neonatal sepsis is one of the common causes of neonatal mortality and is responsible for 30-50% of the total neonatal deaths in developing countries.[1] It refers to an infection involving the bloodstream in infants less than 28 days old.[2] The causes of neonatal sepsis were complications of preterm birth (28.58%), birth asphyxia (22.45%), neonatal infection (18.36%), meconium aspiration syndrome (9.18%), respiratory distress syndrome (7.14%), and congenital malformation (4.08%).[3]

The clinical symptoms of neonatal sepsis are nonspecific. The sensitivity and positive predictive value of biomarkers at the onset of symptoms are suboptimal. Therefore, clinical suspicion frequently leads to empirical antibiotic therapy in uninfected infants.[4] Thus, in the suspected case of neonatal sepsis, two or three days of empirical antibacterial treatment should begin immediately after cultures have been obtained without awaiting the results.

Routinely, extended-spectrum antibiotics or combinations of two or more antibacterial are used initially with clinical diagnosis.[5] It is important to select the appropriate drug and optimal duration of antibacterial therapy to treat infants with genuine infection adequately. At the same time, those without infection would not be over-treated. Potential adverse effects of unnecessary antibacterial usage include short-term (e.g., pain, infiltration) and long-term complications (e.g., necrotizing enterocolitis, hearing impairment, resistance development). Inappropriate use of antibacterial led to the development of drug-resistant strains.[6] It is estimated that around 25% of antibacterial prescriptions in tertiary care hospitals are inappropriate.[7]

Promoting rational usage of drugs is a prime priority, and regular drug audits are thus essential.[8] Drug utilization studies are an important tool to study the clinical use of drugs in populations and their impact on the healthcare system.[9] Hence this study was planned to know the pattern of antibacterial usage in neonatal sepsis and their rationality in a tertiary care hospital.

Methods

This was a prospective, cross-sectional study; the relevant data were collected from records of patients with clinically suspected neonatal sepsis admitted from January 2017 to December 2017 in the central part of Karnataka. Before conducting the study, prior permission from the higher authorities and Institutional Ethics Committee clearance were obtained.

All the records of patients admitted to Neonatal Intensive Care Unit (NICU) with suspected neonatal septicemia by a neonatologist were noted. Supportive findings in routine or special investigations were taken into account for diagnosis by the clinician. Predesigned proforma containing relevant details such as demographics (age, sex), duration of hospital stays, clinical diagnosis, and laboratory parameters (Complete blood counts, Platelets, C-Reactive protein, culture, and sensitivity) were recorded to evaluate the drug prescribing pattern. Antibacterial prescribed (generic/ brand name) concerning dosage, route, frequency, duration of administration, and treatment outcome were recorded as per proforma.

Selection Criteria of the Patients[10]

Inclusion Criteria:

The patients with neonatal sepsis were admitted to NICU with the following infections:

- Major infections- septicemia, pneumonia, diarrhea and meningitis
- Minor infections- umbilical sepsis, pyoderma, conjunctivitis.

Exclusion Criteria:

- Patients were discharged against medical advice
- Neonates with fungal and viral infections.
- The records with incomplete data

Data Analysis

- The data were subjected to descriptive analysis using Microsoft Excel version 2010
- The utilization of different drugs and individual drugs was analyzed and presented as percentages.
- The approval status of the drugs by drug regulatory bodies [Drug Controller General of India (DCGI) and the United States Food and Drug Administration (USFDA)] was checked on the official website of Central Drugs Standard Control Organisation (CDSCO), Directorate General of Health Services, India[11] and Drugs FDA: FDA Approved Drug Products.[12]
- The prescribed antibacterial was listed in the WHO essential medicines list and National List of Essential Medicines (NLEM) was found from the WHO Model List of essential medicines for Children 2015 and NLEM India 2011.[13,14]
- Drugs were classified into different groups based on World Health Organisation (WHO)/ Anatomical Therapeutic Chemical (ATC) classification.

Results and Discussion

Septicemia is a vital basis for neonatal morbidity and mortality. Blood culture has been considered as the benchmark evidence of sepsis, and antibiotics should be reassessed when the results of the culture and sensitivity tests are available. Because of the nonspecific nature of neonatal sepsis, antibiotics should not be stopped, although cultures are negative. The duration of therapy depends on the initial response to the appropriate antibiotics.[1] Antibacterials resistance in NICU affects the management of neonatal sepsis by affecting the initial choice of empirical antibacterial. This leads to multiple antibacterial prescriptions, increases drug interactions and adverse drug reactions, and reduces future antibacterial selection.

It also prolongs the intensive care stay and increases the cost burden of treatment. Auditing antibacterial usage and their sensitivity pattern guides the development of early resistance and helps select appropriate antibacterial.[6] The present study analyzed the isolated organisms, the prescribing patterns of antibacterial agents admitted with the clinical diagnosis of neonatal sepsis, and their approval status in NLEM, DCGI, and USFDA over one year.

We analyzed 148 patients' records with clinically suspected neonatal sepsis. About 95 (64.19%) were male babies, and 53 (35.81%) were females. Sepsis was more common in term (56%) than in pre-term (44%) neonates, and 8.12% were low birth weight (LBW)/ intrauterine growth retardation (IUGR), compared to 48.1% of LBW babies in a study by Rasul HC et al.[10]

Among 148 patients, culture and sensitivity were conducted in 130 patients. In them, >1 sample (blood, urine, cerebrospinal fluid, pus, endotracheal tube) was collected in 28 patients and the average number of samples from each patient was 1.24. Therefore, a total of 161 samples from 130 patients were available, of which only 39 (24%) samples showed growth of microorganisms, which was less compared to the results obtained by Patel et al. (46.03%).[15]

Blood was the most commonly used specimen, showing 22 (17.2%) cultures with organism growth compared to 32% of

Table 1. Particulars of Isolated Organisms

Sl no.	Organism	Number among positive cultures (n=39)	Percentage
1	*Acinetobacter* species	12	30.77
2	*Citrobacter* species	4	10.26
3	*Klebsiella*	3	7.69
4	*Pseudomonas*	3	7.69
5	*E coli*	1	2.56
6	*Enterococci*	2	5.13
7	*Staphylococcus aureus*	7	17.95
8	Coagulase negative *staphylococci*	6	15.38
9	Gram positive bacilli	1	2.56

Table 2. Antibacterial Prescription Characteristics

Sl no.	Particulars	No. (n=430)	Percentage
1	Single drug formulations	400	93.02
2	Fixed dose combinations	30	6.98
3	Drugs approved by DCGI	298	69.30
4	Drugs approved by FDA	427	99.30
5	Drugs prescribed listed in WHO essential drug list	293	68.14
6	Drugs prescribed listed in NLEM	324	75.35
7	Parenteral dosage forms prescribed (injectable)	414	96.28
8	Oral route administered	16	3.72
9	Drugs prescribed in generic name	216	50.23
10	Drugs prescribed by brands	214	49.77

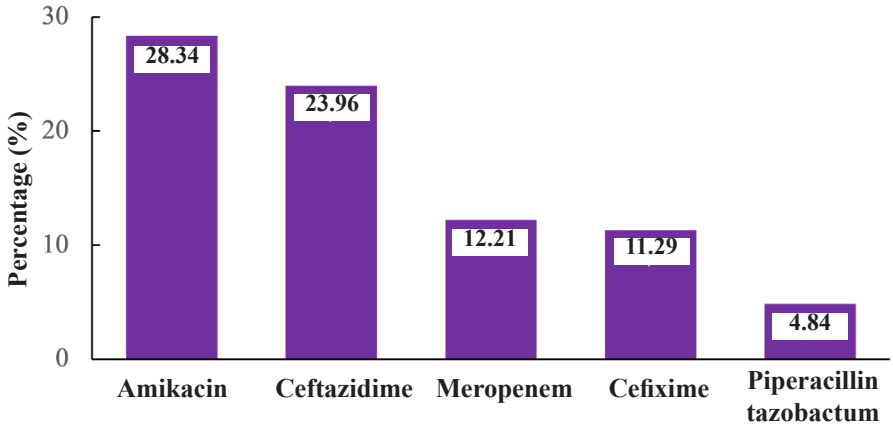

Figure 1. Most Common Antibacterial Prescribed

Gandhi S et al.[1] and 46.2% of Desai KJ et al.[16] The most common organisms isolated in the present study were gram-negative (64.1%) (Table 1), similar to the findings of Gandhi S et al. (58%)[1] and 46.2% of Desai KJ et al.[16] The most frequently isolated organisms in the NICU are likely to be varying with time and hospital settings.

While analyzing the prescription patterns, the average number of overall drugs prescribed per patient was 862 (5.82 ± 2.93), of which 430 (2.94 ± 1.34) were antibacterials. The mean duration of antibacterial usage was 5.39 ± 2.89 days. The duration of prescription was based on the clinical improvement of the patients regardless the choice of antibacterial. Moreover, single-drug formulations and parenteral (IV) forms were commonly used (93% and 96%). Nearly 50% of drugs were prescribed by their generic names (Table 2).

The most common antibacterial prescribed were amikacin, ceftazidime, meropenem, cefixime, and fixed dose combination (FDC) of piperacillin + tazobactum (Figure 1). This treatment approach is more appropriate for organisms commonly isolated in our setting, especially gram-negative organisms. Beta-lactams act like third-generation cephalosporins that have wider gram-negative coverage.

The combination of an aminoglycoside (amikacin) with penicillins is the fair rational approach, since beta-lactams and other beta-lactam antibacterial increase the activity of aminoglycosides.[17] Additionally, we observed that the combination of amikacin with another beta-lactam antibacterial (mostly third-generation cephalosporins) was started as empirical therapy that is indicated as the standard protocol for treating sepsis in many studies.[18,19] However, amikacin causes more hearing loss. Thus, we may suggest the use of gentamicin because it is more potent, less toxic, and cheaper than amikacin.[20]

Table 3 and 4 show the single and FDC antibacterial characteristics of Anatomical Therapeutic Chemical (ATC) classification with their mean duration of prescriptions. The antibacterial prescribed based on culture and sensitivity reports DCGI disapproved azithromycin, ceftazidime, netilmicin, and vancomycin. Whereas FDA disapproved azithromycin and ceftriaxone + tazobactam.

The antibacterial aztreonam, cefepime, cefixime, meropenem, netilmicin, and the FDCs ceftriaxone+tazobactum and piperacillin+tazobactum used were not enlisted in the WHO Essential Medicines List for children and NLEM (Table 5).

Table 3. Single Drug Formulation of Antibacterial Characteristics

Sl no	Drug	ATC code	Number (%) of prescriptions	Duration (days) of antibacterial prescribed (Mean ± S.D.)
ATC class: J01G; Drug class: Aminoglycoside antibacterial				
1	Amikacin	J01GB06	123(30.75)	5.22 ± 2.89
2	Netilmicin	J01GB03	1(0.25)	10
ATC class: J01D; Drug class: Other Beta-lactam antibacterial				
3	Cefepime	J01DE01	4(1)	9 ± 3.08
4	Cefixime	J01DD08	49(12.25)	4.41 ± 2.91
5	Ceftazidime	J01DD01	104(26)	4.52 ± 2.89
6	Imipenem	J01DD04	5(1.25)	7.6 ± 3.03
7	Meropenem	J01DC02	53(13.25)	7.38 ± 2.88
8	Aztreonam	J01DH02	6(1.5)	5.83 ± 2.95
ATC class: J01M; Drug class: Quinolone antibacterial				
9	Ciprofloxacin	J01MA02	1(0.25)	6
10	Levofloxacin	J01MA16	8(2)	6 ± 3.05
ATC class: J01F; Drug class: Macrolides				
11	Azithromycin	J01FF01	7(1.75)	4.71 ± 2.96
ATC class: J01X; Drug class: Other antibacterial				
12	Linezolid	J01XX08	5(1.25)	3.4 ± 3.13
13	Metronidazole	J01XX08	19(4.75)	7.44 ± 2.91
14	Vancomycin	J01XD01	14(3.5)	5.5 ± 2.96

Table 4. Fix-dose Combination of Antibacterial Characteristics

Sl no	Drug	ATC code	Number (%) of prescriptions	Duration (days) of antibacterial prescribed (Mean±S.D.)
ATC class: J01C; Drug class: Beta-lactam antibacterial, Penicillins				
1	Amoxicillin + Clavulanic acid	J01CR02	6(20)	4 ± 2.92
2	Piperacillin + Tazobactam	J01CR05	21(70)	5.48 ± 2.91
ATC class: J01D; Drug class: Other Beta-lactam antibacterial				
3	Ceftriaxone + Tazobactam	J01DD54	3(10)	5 ± 3.13

Table 5. Antibacterial drug approval status and listing in WHO / NLEM

Sl no	Drug	Approved by		Listed in essential medicines list	
	Single Drug Formulations	**DCGI**	**FDA**	**WHO**	**National**
1	Amikacin	Y	Y	Y	Y
2	Amoxicillin	Y	Y	Y	Y
3	Azithromycin	**N**	Y	Y	Y
4	Aztreonam	**N**	Y	**N**	**N**
5	Cefepime	Y	Y	**N**	**N**
6	Cefixime	Y	Y	**N**	Y
7	Ceftazidime	**N**	Y	Y	Y
8	Ciprofloxacin	Y	Y	Y	Y
9	Imipenem	Y	Y	Y	**N**
10	Levofloxacin	Y	Y	Y	**N**
11	Linezolide	Y	Y	Y	**N**
12	Meropenem	Y	Y	**N**	**N**
13	Metronidazole	Y	Y	Y	Y
14	Netilmicin	**N**	Y	**N**	**N**
15	Vancomycin	**N**	Y	Y	Y
	Fixed Dose Combinations	**DCGI**	**FDA**	**WHO**	**National**
1	Amoxicillin + Clavulanic acid	Y	Y	Y	Y
2	Ceftriaxone + Tazobactum	Y	**N**	**N**	**N**
3	Piperacillin + Tazobactum	Y	Y	**N**	**N**

Cefixime, meropenem, and piperacillin + tazobactum may be considered for entering the Essential Medicines List based on their approval status and the frequency of the prescription. In the present study, the majority of the neonates (87%) showed improvement at the end of the treatment period, indicating a good treatment outcome.

Conclusion

In the present study, gram-negative organisms were most commonly isolated, and drugs like beta-lactams and aminoglycosides comprised the major classes of antibacterial prescribed. Hence, the rationality of antibacterial drug usage in suspected cases of neonatal sepsis was followed the majority of times, leading to better patient care and outcome. To minimize the uncertainty with the choice of the antibacterial agents, through our study, we suggest that similar studies be conducted at various health care levels concerning the causative agent and their antibacterial susceptibility pattern.

Limitations

- As the incidence of neonatal sepsis is large, the sample size included and the duration of the study may not be sufficient to extrapolate the results to a larger population.
- Since many patients' culture and Sensitivity (C/S) data were not available, the actual incidence of the organisms colonizing Neonatal sepsis cases could not be ascertained. Among the available C/S reports, many samples did not show the growth of organisms. This could be the paradox of the presentation of neonatal sepsis.
- Data on adverse drug reactions of the antibacterial prescribed was not available.
- Direct and indirect costs related to the antibacterial prescribed could not be calculated (pharmacoeconomics)

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Conflict of Interest
None declared

References

1. Gandhi S, Ranjan KP, Ranjan N, Sapre N and Masani M. Incidence of neonatal sepsis in tertiary care hospital: an overview. *International Journal of Medical Sciences Public Health.* 2013; 2: 548-52.
2. Seale AC, Blencowe H, Manu AA, Nair H, Bahl R, Qazi SA et al. Investigator Group. Estimates of possible severe bacterial infection in neonates in sub-Saharan Africa, South Asia, and Latin America for 2012: a systematic review and meta-analysis. *Lancet Infectious Diseases.* 2014; 14(8): 731-41.
3. Desalew A, Sintayehu Y, Teferi N et al. Cause and predictors of neonatal mortality among neonates admitted to neonatal intensive care units of public hospitals in eastern Ethiopia: a facility-based prospective follow-up study. *BMC Pediatrics*. 2020; 20: 160.
4. Klingenberg C, Kornelisse RF, Buonocore G, Maier RF, Stocker M. Culture-Negative Early-Onset Neonatal Sepsis - At the Crossroad Between Efficient Sepsis Care and Antimicrobial Stewardship. *Frontiers in Pediatrics.* 2018; 6: 285.
5. Tamma DP, Cosgrove ES and Maragakisb LL. Combination Therapy for Treatment of

Infections with Gram-Negative Bacteria. *Clinical Microbiology Reviews*. 2012; 25: 450-70.
6. Chauhan I, Yasir M, Kumari M, Verma M. The pursuit of rational drug use: Understanding factors and interventions. *Pharmaspire*. 2018; 10(2): 48-54.
7. Atif M, Azeem M, Saqib A, Scahill S. Investigation of antimicrobial use at a tertiary care hospital in Southern Punjab, Pakistan using WHO methodology. *Antimicrobial Resistance and Infection Control*. 2017; 28: 41.
8. Kar SS, Pradhan SH, Mohanta PG. Concept of Essential Medicines and Rational Use in Public Health. *Indian Journal of Community Medicine*. 2010; 35: 10-3.
9. Sachdeva PD and Patel BG. Drug Utilization Studies- Scope and future perspectives. *International Journal of Pharmaceutical and Biological Research*. 2010; 1: 11-7.
10. Rasul HC, Hassan AM and Habibullah M. Neonatal Sepsis and use of antibiotic in a Tertiary care Hospital. P*akistan Journal of Medical Sciences*. 2007; 23(1): 78-81.
11. List of Drugs Approved for Marketing in India. Available at: *http://cdsco.nic.in/listofdrugapprovedmain.html.* [Accessed June 16, 2018].
12. Drugs@FDA:FDA Approved Drug Products. Available at: *http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm.* [Accessed June 16, 2018].
13. WHO Model List of Essential Medicines for Children. World Health Organization. 2015: 1–38. Available at: *http://www.who.int/medicines/publications/essentialmedicines/en/index.html.* [Accessed June 19, 2018].
14. National List of Essential Medicines of India. 2011: 1-123. Available at: *http://cdsco.nic.in/NationalListofEssentialMedicine-finalcopy.pdf*. [Accessed June 19, 2018].
15. Patel TK, Sheth KV and Tripathi CB. Antibiotic sensitivity pattern in neonatal intensive care unit of a tertiary care hospital of India. *Asian Journal of Pharmaceutical and Clinical Research*. 2012; 5(3): 46-50.
16. Desai KJ and Malek SS. Neonatal Septicemia: Bacterial Isolates & Their Antibiotics Susceptibility Patterns. *National Journal of Integrated Research in Medicine*. 2010; 1(3): 12-5.
17. Satoskar RS, Rege NN, Tripathi KR, Bhandarkar SD. P*harmacology and pharmacotherapeutics*. 25th ed. New Delhi: Elsevier; 2017: 686-90
18. Aggarwal R, Sarkar N, Deorari AK and Paul VK. Sepsis in the Newborn. *AIIMS protocols in Neonatology*. CBS Publishers, Delhi 2014; 1-19.
19. Sivanandan S, Soraisham SA and Swarnam K. Choice and Duration of Antimicrobial Therapy for Neonatal Sepsis and Meningitis. *International Journal of Pediatrics*. 2011:712150.
20. Tripati KD. *Essentials of Medical Pharmacology*. 8th ed. New Delhi: Jaypee; 2019: 797-9.