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Research Article

A Prospective Study of Antimicrobial Utilisation and Cost Pattern Analysis in the Treatment of Neonatal Sepsis in a Tertiary Care Hospital

Kumar M D[1], Adiga S[2*], Lewis L E[3], Tripathy A[4]

[1]*Department of Pharmacology PK Das Institute of Medical Sciences(PKDIMS), Vaniamkulam, Kerala- 682522.*
[2]*Department of Pharmacology, Kasturba Medical College, Manipal University, Manipal, Karnataka- 576104.*
[3]*Department of Neonatology, Department of Pharmacology, Kasturba Medical College, Manipal University, Manipal, Karnataka- 576104.*
[4]*Department of Pharmacology, Department of Pharmacology, Kasturba Medical College, Manipal University, Manipal, Karnataka- 576104.*

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ABSTRACT

Neonatal sepsis is one of the most common reasons for admission to neonatal units. The present study, a prospective observational one, was carried out to find the antimicrobial utilisation and the various costs involved in the treatment of neonatal sepsis. Data pertaining to demographic characteristics, type of sepsis, various investigations, treatment details, costs and clinical outcome were noted at baseline and discharge. 65% of the neonatal sepsis cases were seen in male infants. Bacterial infection was the cause of sepsis in 65% of all the neonates, *Klebsiella pneumoniae* being the most commonly implicated micro-organism. The two initial antimicrobial regimens which were commonly preferred were ampicillin with amikacin (60%) and a combination of piperacillin plus tazobactam and amikacin (40%). 74% of neonates who were diagnosed with sepsis recovered completely from their ailment. Supportive measures, including cardiac monitoring and respiratory care, had the highest mean cost component/patient of INR 9819.05 ± 8608.61. In comparison to it, supportive drug therapy, with intravenous fluids and drugs, formed the lowest cost component (INR 3918.98± 2684.06/patient) in the study group. Treatment of gram negative sepsis and late onset sepsis was comparatively more expensive. Hence early diagnosis and appropriate antibacterial therapy could prevent the monetary burden of this dreadful disease.

Keywords:

INTRODUCTION

Neonatal sepsis is one of the most common reasons for admission to neonatal units in developing countries and it remains a significant cause of neonatal morbidity and mortality. According to the data from National Neonatal Perinatal Database (NNPD, 2002-03), the incidence of this condition in our country is 30 per 1000 live births[1,2]. Sepsis in neonates is a clinical syndrome characterized by signs and symptoms of infection with or without accompanying bacteremia in the first month of life[2]. This syndrome can be classified into two major categories depending on the onset of symptoms: a) *Early onset sepsis (EOS)* which presents within the first 72 hours of life and b) *Late onset sepsis (LOS)* presenting after 72 hours of birth. The source of infection can either be nosocomial (hospital-acquired) or community-acquired and clinical presentation varies from septicemia to pneumonia and meningitis[2]. Microbes causing neonatal sepsis in developing countries are different from those seen in developed countries, the most common among them being *K. pneumoniae*, *E. coli*, *Pseudomonas* and *Salmonella* species, *Staph. aureus*, Coagulase negative *Staphylococci*, *S. pneumoniae* and *S. pyogenes*[3]. Despite a positive blood culture with sensitivity of the isolated organism being the best guide to antimicrobial therapy, empirical antimicrobial therapy, based on the probable source of infection, is often initiated, because of the neonate's relative immunodeficient state[2]. Once the pathogen has been identified, appropriate antimicrobial therapy, based on the culture sensitivity report, is started. An alarming trend that has emerged recently is the prevalence of highly resistant organisms which are sensitive only to newer and more expensive antimicrobials like vancomycin, monobactams and carbapenems. Though the economic burden of neonatal sepsis in our country has hardly been studied, global trends indicate its association with significant use of health care resources. Thus there is a felt need to carry out pharmacoeconomic studies, which would effectively describe and analyse the costs of neonatal sepsis therapy in our health care system. Cost of Illness (COI), which is defined as the value of resources that are expended as a result of health problem, is an effective pharmacoeconomic tool in measuring the economic burden of a disease and thus promoting informed decision making in policy formulation and resource distribution[4,5]. In an era of spiralling health care costs and rampant prescription of antibiotics for the treatment of infections, we found it pertinent to find out the antimicrobial utilisation and the various costs involved in the treatment of neonatal sepsis and hence the study was conducted.

**Author for Correspondence: drshaliadiga@gmail.com*

Table 1: Gender wise distribution of neonatal sepsis patients and their mean birth weight.

Gender	No. of patients (n)	Birth weight in kg (Mean±SD)	Early Onset Sepsis (EOS) Number of neonates n (%)	Late Onset Sepsis (LOS)	
				Community acquired infections n (%)	Nosocomial infections n (%)
Male	65	2.25±0.73	33(68.75)	20(62.5)	12(60)
Female	35	2.1±0.70	15(31.25)	12(37.5)	08(40)
Total	100	2.215±0.73	48(100)	32(100)	20(100)

Table 2: Clinical signs/symptoms and their corresponding duration of hospital stay

Clinical signs and symptoms	Percentage of patients (%)	Mean duration of hospital stay in days
Feeding difficulty/Vomiting/Poor cry only	22	13.09
Respiratory distress/Grunting only	13	8.40
Fever/Hypothermia only	13	12.23
Respiratory distress+ Fever/Hypothermia	13	11.50
More than two clinical signs/symptoms	12	15.50
Feeding difficulty/Vomiting/Poor cry+ Fever	10	12.10
Jaundice only	06	15.75
Miscellaneous	06	25.85
Respiratory distress+ Feeding difficulty/Poor cry	05	8.83
Total	100	13.15

Table 3: Enumeration of the various microbes identified in culture positive blood samples.

Isolated micro organism	Number of patients n (%)
Klebsiella pneumoniae	18 (27.69)
Miscellaneous	12 (18.46)
Burkholderia capecia	09 (13.85)
Staph.aureus	07 (10.8)
MRSA (Methicillin Resistant Staphylococcus Aureus)	06 (9.2)
CONS (Coagulase negative staphylococcus)	05 (7.7)
Enterococcus species	03 (4.6)
Other gram negative bacillus	03 (4.6)
Streptococcus species	02 (3.1)
Total	65 (100)

MATERIALS AND METHODS

This was a prospective observational study which was carried out over a period of twelve months in a tertiary care centre in Karnataka.

Subject Selection

Inclusion criteria

Confirmed or suspected cases of neonatal sepsis based on clinical features, risk factors, and laboratory findings, with or without culture positive results.

Exclusion criteria

Neonates who have contracted transplacental infections by organisms such as *Toxoplasma gondii*, Rubella, Cytomegalovirus, Varicella Zoster virus, Herpes Simplex virus, Human Immunodeficiency Virus, Hepatitis B virus, *Treponema pallidum*, and Human parvovirus B19. Neonates with coexisting morbidities like malignancy, inborn errors of metabolism, congenital heart disease, and necrotizing enterocolitis. After obtaining the institutional ethical clearance, neonates fulfilling the study criteria, were enrolled, after obtaining a prior informed consent from their parent/guardian. Data from these patients, who were admitted to Neonatal Intensive Care Unit (NICU), between December 2012 and November 2013, was collected under the following headings:

- Demographic characteristics (age, gender, birth weight).
- Risk factors (maternal, preterm/low birth weight, perinatal asphyxia).
- Type of sepsis (EOS/LOS).
- Chief complaints and clinical findings.
- Concomitant diseases if any.
- Investigations like haematocrit, C Reactive Protein (CRP), blood culture and antibiotic sensitivity, CSF examination, X ray, neurosonogram, CT, etc. and their individual costs.
- Treatment details, including antimicrobial regimens, and their corresponding monetary charges.
- Other costs incurred during the course of treatment.
- Clinical outcome.

Their clinical progress was periodically evaluated and monetary charges incurred at every stage of the treatment was meticulously noted down from the bills and analysed later. Only the direct medical costs, in rupees, from the payer's perspective, was considered for cost of illness (COI) study. Descriptive and inferential statistics was used for analysis of data. A p-value of less than 0.05 was considered as statistically significant. Data was analysed using Statistical Packages for Social Sciences (SPSS) software version 20.

RESULTS

Demographic and Baseline Characteristics

During the study period, there were 100 neonates who were diagnosed with sepsis, with the majority of them being males as shown in table 1. Majority of these sepsis patients were either low birth weight (LBW) i.e. 31% or extremely low birth weight (ELBW) i.e. 23%. It was possible to ascertain a positive history of risk factors in

Table 4: Culture and sensitivity directed antimicrobial regimens (definitive therapy).

Initial antimicrobial regimen	Second line regimen	Number of patients n (%)
Piperacillin+Tazobactam and Amikacin	Nil	18 (27.7)
Piperacillin+Tazobactam and ciprofloxacin	Nil	12 (18.5)
Miscellaneous	Nil	11 (16.9)
Vancomycin/Meropenem	Nil	10 (15.4)
Betalactam, aminoglycoside and metronidazole	Nil	05 (7.7)
Piperacillin+Tazobactam and Amikacin	Amphotericin/Fluconazole	03 (4.6)
Betalactam,aminoglycoside and metronidazole	Vancomycin/Meropenem	03 (4.6)
Piperacillin+Tazobactam, amikacin and ciprofloxacin	Nil	02 (3.1)
Piperacillin+Tazobactam and ciprofloxacin	Amphotericin/Fluconazole	01 (1.5)
Total		65 (100)

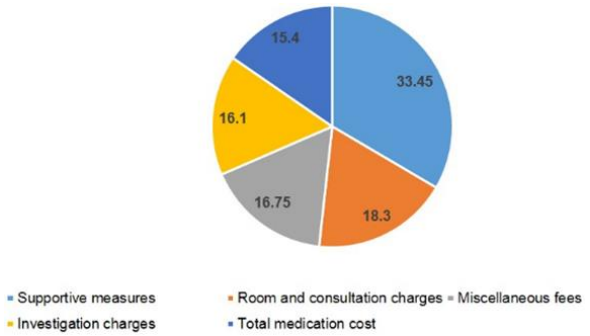

Figure 1: Share of individual components (%) in total treatment expenditure.

54% of cases with prematurity (alone or in combination with maternal risk factor) being noted in 38 neonates and maternal risk factors (alone or in combination with prematurity) posing a threat in 24 patients.

The commonest signs and symptoms presented by the neonates has been described in Table 2. Feeding difficulty, vomiting and poor cry were the commonest symptoms encountered at admission (22%). Jaundice was responsible for the longest duration of hospital stay (15.75 days) amongst all the other clinical features.

Culture Report and Sensitivity Pattern

Sixty five culture reports turned out to be positive in neonates suspected to have sepsis. The remaining 35 reports were either negative (27) or unidentified (8). While 66.7% of EOS were confirmed by culture reports, 63.5% of LOS cases were substantiated by blood culture results. There was a predominance of gram negative sepsis in the study population with 39 of the total 65 cases being ascribed to gram negative microbes. Majority of the culture positive EOS cases (21 out of 32), were attributed to gram negative organisms. Table 3 enlists the various microbes which were isolated from our study samples. While it was found that 46.1% of the total 65 culture positive samples showed resistance to aminoglycosides, the occurrence of penicillin and fluoroquinolone resistance in our study population were seen to be 24.6% and 10.77% respectively.

Empirical and Definitive Therapy

The two initial antimicrobial regimens which were commonly preferred was ampicillin with amikacin (sixty patients) and a combination of piperacillin plus tazobactam and amikacin (forty patients). Due to inadequate response, second line therapy with fluoroquinolone and a combination of piperacillin plus tazobactam had to be initiated in three cases. Table 4 elucidates the various definitive regimens utilised in neonatal sepsis therapy. All the patients who received piperacillin plus tazobactam combination with amikacin recovered completely with the mean duration in definitive therapy being 8.57±2.38 days and the mean antibiotic acquisition cost 529.80 ± 384.47 rupees. 90% of neonates who were administered vancomycin/meropenem as initial definitive therapy had a favourable outcome with the mean duration of drug therapy being 8±3.27 days. However, its mean acquisition cost was on the higher side i.e.1076.20±1044.06 rupees.

Clinical Outcome and Cost of Illness

It was seen that 74% of neonates who were diagnosed with sepsis recovered completely from their ailment. The remaining 26% of cases resulted in either death/got discharged against medical advice or only had a minimal improvement in their clinical condition. A staggering 90% of sepsis patients who were unable to survive had coexisting morbidities, among which gastro intestinal and CNS disorders dominated (66.67%). The total treatment cost of neonatal sepsis has been highlighted in Figure 1. Supportive measures, including cardiac monitoring and respiratory care, had the highest mean cost component/patient of INR 9819.05 ± 8608.61. In comparison to it, supportive drug therapy, with intravenous fluids and drugs, formed the lowest cost component (INR 3918.98± 2684.06/patient) in our study group.

DISCUSSION

A male preponderance of 65% was seen in our study, which was in line with almost all the national and international studies, where in the gender distribution was seen to be similarly skewed in favour of males in the range of 50% to 70%[1,6]. Out of the 100 patients in our study, 48 neonates contracted the disease within the first 72 hours of life (EOS) and the remaining 52 developed LOS. Though the data from the Indian sub- continent reflected similar patterns[6,7], van den Hoogen *et al*[8]. and Morioka I *et al*[9]. showed a higher incidence of LOS (91.9% and 82.4% of the total cases respectively) in their studies. This could be partly explained by the lack of uniformity in the classification of sepsis, gross variations in sample size, and a lower incidence of sepsis, in general, and EOS in particular, in countries with state of the art health facilities. But when it comes to clinical signs and symptoms, our

study results reflected the global scenario where lethargy/poor cry, respiratory distress and alterations in body temperature have been the most prevalent ones[1,10]. Similar to a study result published in Eastern journal of medicine 2007[1], inferential analysis using One-way ANOVA showed that there was no statistically significant difference, in relation to the duration of hospital stay, between the various clinical presentations (p-value>0.05). A closer look on the nature of pathogens causing EOS and LOS showed that gram-ve bacteria were responsible for a majority of these cases with *Klebsiella pneumoniae* turning out to be the most commonly isolated bacteria (27.69%). While these findings were in unison with similar studies conducted in India[6,11], gram positive organisms, namely group B *Streptoccus*, CONS and MRSA continues to be the leading cause of culture positive sepsis in developed nations[1,8]. This could possibly be due to maintenance of aseptic conditions in NICU as well as the prevalence of better hygiene practices among health care professionals in developed countries, which makes the transmission of commensal organisms, particularly gram-ve bacteria, highly unlikely. *Burkholderia capecia*, a gram –ve bacteria, which thrives in moist conditions and medical equipments, is considered as a rare cause of sepsis in neonates. But a recent study in southern Karnataka found out twelve cases of *B.capecia* sepsis, in neonates studied over a period of one year, which is almost in line with our study results[12]. As the empirical management of neonatal sepsis often requires a thorough understanding of the prevalent microbes from a particular area, these findings may help us in deciding the antimicrobial regimen which is best suited for our conditions. Antimicrobial susceptibility patterns have spatial and temporal differences and hence treatment modalities should be reviewed and modified accordingly[13]. Similar to our observations, both Ahmed A *et al*[1], and Parm U *et al.*[14] have reported the usage of betalactam and aminoglycoside combination empirical therapy in an overwhelming manner. But disagreement existed with respect to the selection of aminoglycosides. Here, all the clinically suspected neonates were started on amikacin, rather than gentamicin. In 40% of the study population combination of piperacillin and tazobactam was the preferred betalactam antibiotic, unlike the other two studies, where either Penicillin G or ampicillin was utilised. These two deviations could be due to the increased possibility of multidrug resistant gram-ve infections in our locality, which are more susceptible to amikacin and piperacillin plus tazobactam combination. Even though it is advisable to discontinue empirical antibiotic treatment after 72 hours of initiating the same[13], the mean duration of the two regimens used in our study were higher, reflecting an increasing advent of neonatal sepsis in preterm, LBW, and ELBW infants, who may require a longer duration of drug therapy[13]. Piperacillin/tazobactam with either amikacin or ciprofloxacin were the two most commonly employed definitive regimens (32.3% and 20% respectively). It is not a coincidence that *K. pneumoniae* and *B.capecia* were the most commonly identified microbes, whose susceptibility to these antibiotic combinations are well established[12,15]. The mean duration of these regimens were found to be falling in line with the current recommendation of 7 to 14 days of antimicrobial treatment in culture proven sepsis[13]. The inclusion of vancomycin/meropenem in 20% of our definitive regimens is justified because of their commendable in vivo activity against a variety of pathogens like *MRSA*, *CONS*, and gram –ve bacteria belonging to the *Enterobacteriaceae* family[16]. Four neonates required antifungal medications, as clinical signs were suggestive of opportunistic candida infection. These patients were earlier started on a definitive therapy containing piperacillin plus tazobactam and it has been reported that this antimicrobial agent has the potential to cause candida infection in predisposed individuals[17]. Although the reported mortality rate in neonatal sepsis is about 10%, in reality, it is said to have a much higher incidence[18], as depicted in our study. Generally gram-ve septicemia, and hence LOS, is difficult to manage and thus has a poorer clinical outcome[18]. We found that EOS had a poorer outcome than LOS (41.7% versus 28.85%). This could be because of the existence of comorbid conditions, which can worsen the prognosis in sepsis patients. These cardiovascular and gastro intestinal complications were seen more in the EOS group (22.9%) than in LOS (13.5%). In our study of 100 sepsis patients, the average total treatment expenditure came around 29332 Indian National Rupees (INR), reiterating the fact that it poses a significant financial burden on low income and middle income families. When the two empirical therapies were economically assessed and compared, the mean cost of 'piperacillin containing regimen' (175.80 INR) was more than double that of the commonly used 'ampicillin containing regimen' (79.80 INR). Hence the use of the latter regimen is fully justified in terms of monetary aspects. Similarly, the indiscriminate use of vancomycin/meropenem regimen cannot be economically validated, as its mean cost was about two times more than that of the most commonly used definitive regimen of 'piperacillin/tazobactam with amikacin' (529.80 INR). But, as described earlier, because of its superior pharmacological properties in certain conditions, vancomycin/meropenem had to be administered in 13 cases. Thus it underscores the fact that it is necessary to carry out an economical as well as clinical evaluation before deciding the appropriate antimicrobial regimen for a patient. A higher percentage of utilitarian costs in our study (68.5%) is well supported by other reports and could be indicative of the rising equipment and service charges in patient care[19,20]. However the study is not devoid of limitations. As it was conducted in 100 neonates pertaining to a single institution, the results may not hold true in different clinical settings. Another drawback is only the direct medical costs were considered for Pharmacoeconomic evaluation. The real impact on the family could not be ascertained due to lack of data on the patient's family income.

CONCLUSION

It is indeed indubitable that the success or failure of neonatal sepsis management, relies heavily to a large

extent, on rational antimicrobial therapy and adequate supportive care. Our study results showed that early recognition and appropriate use of antibiotics, based on the prevalent microorganisms, can help in reducing the socio economic burden of this dreadful disease. In conclusion, let us hope that our endeavour serves as the much needed fillip in carrying out studies, promoting targeted and cost effective treatment modalities, in the future.

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