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Original Article

Paediatrics Section

"Neonatal Sepsis": Bacteria & their Susceptibility Pattern towards Antibiotics in Neonatal Intensive Care Unit

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ABSTRACT

Background: Neonatal sepsis is one of the most common causes of neonatal mortality and morbidity, particularly in the developing countries. Its causative bacteria and their respective sensitivity patterns are different in each hospital and region. The objective of this study was to determine the causative bacteria and pattern of susceptibility to antibiotics in NICU of a tertiary care centre, which in turn may help in implementation of empirical therapy.

Material and Methods: This prospective study was carried out at a medical college during the period from 1st April 2011 to 31st March 2013. A total of 364 cases of suspected sepsis were admitted in our NICU during the mentioned period. Out of which, 137 cases were positive for culture. All the neonates of suspected sepsis were screened by using a panel consisting of CRP, ANC, I/T ratio, micro ESR and culture and sensitivity.

Results: A total of 137 cultures were found to be positive out of 364 cases. The most common organism isolated was *Staphylococcus aureus* (37.22%) followed by *Klebsiella* pneumoniae (27.01%) and *Escherichia coli* (19.70%). Other organisms were much less in number, which included pathogenic *Streptococci,* Coagulase negative *Staphylococci* (CoNS), *Pseudomonas, Acinetobacter* and *Enterobacter* species. The gram positive organisms except *Streptococci* displayed a high degree of resistance to most penicillins and ciprofloxacin but were sensitive to vancomycin, amikacin and cefepime. There was a high incidence of resistance noted with ampicillin, gentamicin and ciprofloxacin amongst most gram negative organisms' where-in cefepime, amikacin and meropenem were effective in most cases.

Conclusion: There is an increasing trend of antibiotic resistance to the commonly used first line drugs. Continuous surveillance for antibiotic susceptibility is needed to ensure proper empirical therapy.

Keywords: Neonates, Empirical therapy, Early onset sepsis, Late onset sepsis, Antimicrobial sensitivity

INTRODUCTION

Sepsis is one of the commonest causes of neonatal morbidity and mortality. It is responsible for about 30-50% of the total neonatal deaths in developing countries [1,2]. In the year 2010, an estimated 7.7 million childhood deaths occurred among which 3.1 million occurred in the neonatal period [3]. India contributes to around one-quarter of all neonatal deaths in the World and more than half (52%) of these are estimated to occur due to infections [4]. Sepsis related mortality is largely preventable with rational anti-microbial therapy and aggressive supportive care. The risk factors and the clinical presentations of neonatal sepsis are much varied, depending not only on the age of onset, but also on the responsible organism.

It encompasses various systemic infections of the newborn such as septicemia, meningitis, pneumonia, arthritis, osteomyelitis, and urinary tract infections. Superficial infections like conjunctivitis and oral thrush are not usually included under neonatal sepsis [5]. According to the data from National Neonatal Perinatal Database (NNPD, 2002-03) the incidence of neonatal sepsis is 30 per 1000 live births and sepsis to be one of the commonest causes of neonatal mortality contributing to 19% of all neonatal deaths [5]. Neonatal sepsis is of two types; early onset sepsis and late onset sepsis Early Onset Sepsis (EOS) presents within first 72 hours of life. In severe cases, the neonate may be symptomatic at birth. Infants with EOS usually present with respiratory distress and pneumonia. The source of infection is generally the maternal genital tract [6]. Late onset sepsis usually presents after 72 hours of age. The source of infection is either nosocomial or community acquired and neonates usually presented with septicemia, pneumonia or meningitis [5].

Early diagnosis and proper management can reduce the neonatal mortality but aetiological agent do not remain the same and include a wide variety of both gram positive and gram negative bacteria. One should know the usual aetiologic agent and its antibiotic susceptibility pattern in the community, before commencing empirical therapy.

This study was conducted to determine the bacteriological profile of the suspected cases of neonatal sepsis and to know the pattern of antibiotic susceptibility in the NICU of a tertiary care centre.

MATERIAL AND METHODS

A Prospective study was conducted at the neonatal intensive care unit, Department of Paediatrics and Department of Microbiology, Rama Medical College, Kanpur, India, after due permission of the ethical committee of our institute. In this analysis, we analysed the data of culture and sensitivity pattern of cases of neonatal sepsis from 1st April 2011 to 31st March 2013. Neonates with clinical features of sepsis were included in the study with age 0-28 days. Details of obstetric history, maternal risk factors, and physical examination were recorded meticulously. All the cases of suspected sepsis were screened by using C-reactive protein, TLC, ANC, I/T ratio, micro ESR and blood culture. The CRP was done after 24 hours of life in case of intramural babies with risk factors (with or without symptoms) and also for extramural babies. Blood culture was done by standard microbiological techniques (BACTEC Method) in all the cases. CSF analysis as well as culture was done only in suspected cases of meningitis and the late onset sepsis. Urine examination and culture were performed only for selected cases.

Neonates with congenital anomalies, acute bilirubin encephalopathy, grade III perinatal asphyxia, neonates on antibiotics or those whose mothers have received antibiotics before delivery, were

excluded from the present study. Empirical antibiotics were started after taking blood for culture and sensitivity and then changed accordingly.

RESULTS

A total of 364 neonates were included in the present study, 226 (62.08%) were male and 138 (37.92%) females (M: F ratio 1.63:1). Amongst them 205 (56.32%) were aged < 72 hours (early onset) and 159 (43.68%) were aged >72 hours (late onset).

All the cases were screened for sepsis; 254 (69.78%) were positive for sepsis but only 137 (37.63%) yielded positive cultures.

Among the culture positive neonates, 48 were delivered at hospital and the rest elsewhere. Culture positivity rate was high among preterm babies (47.04%) as compared to term babies (35.84%) [Table/Fig-1].

Out of these 137 bacterial isolates, 76 (55.48%) were gram negative organisms and the rest were gram positive bacteriae, mostly comparising of *Staphylococcus aureus*. This is followed by *Klebsiella* pneumoniae 37 (27.01%) & *Escherichia coli* 27 (19.70%). All other pathogen were responsible for less than 16% of cases [Table/Fig-2].

All isolates showed low sensitivity to *ampicillin*, *ciprofloxacin* and gentamicin, good sensitivity to cefotaxime, and maximum sensitivity to *amikacin, cefepime, meropenem* and *vancomycin*. *Staphylococcus aureus* was absolutely resistant to penicillin but showed 100% sensitivity to vancomycin. A good sensitivity to cefotaxime (76.47%) and amikacin (82.35%) was seen but very low sensitivity to other commonly used antibiotics [Table/Fig-3].

	Culture positive	Culture negative	Total
Age < 72 hours (EOS*)	77 (37.56%)	128 (62.44%)	205 (56.32%)
Age > 72 hours (LOS**)	60 (37.74%)	99 (62.26%)	159 (43.68%)
Mature	97 (35.66%)	175 (64.34%)	272 (74.73%)
Premature	40 (43.48%)	52 (56.52%)	92 (25.27%)

[Table/Fig-1]: Culture positivity with respect to age and maturity
EOS* - Early Onset Sepsis. LOS** - Late Onset Sepsis

S. No.	Bacterial Isolates	Number	Percentage
1.	*Staphylococcus aureus*	51	37.22%
2.	*Klebsiella* pneumoniae	37	27.01%
3.	*Escherichia coli*	27	19.70%
4.	*Pseudomonas*	6	04.38%
5.	*Staphylococcus epidermidis (CoNS)*	6	04.38%
6.	*Streptococcus sp*	4	02.92%
7.	*Acinetobacter*	3	02.19%
8.	*Enterobacter*	3	02.19%

[Table/Fig-2]: Bacterial isolates causing neonatal sepsis (n=137)
CoNS – Coagulase Negative *Staphylococcus*

The *klebsiella* isolates were 100% sensitive to meropenem, while the cefepime as well as amikacin were also quite effective. *E. coli* displayed 100% sensitivity to not only meropenem but also to cefepime & amikacin. *Pseudomonas* aeruginosa isolated from cases were also 100% sensitive to *Amikacin, Cefepime* and *Meropenem*. The sensitivity pattern of *acinetobacter* and *enterobacter* was similar with a few minor differences. All isolates of *enterobacter* were sensitive to amikacin as against 66.67% of *acinetobacter*. *Acinetobacter*, however, displayed 66.67% sensitivity to gentamicin but all the isolates of *enterobacter* were resistant.

The *streptococcal* species were sensitive to most penicillins, cephalosporins, ciprofloxacin and erythromycin with a comparatively high degree of resistance to aminoglycosides (50% to 100%). The four cases of Coagulase Negative *Staphylococcus* (CoNS) were resistant to all antibiotics except vancomycin.

None of the gram negative organisms were resistant to meropenem and negligible resistance was seen with cefepime and amikacin. All the gram positive organisms were sensitive to vancomycin.

DISCUSSION

Blood culture has remained the gold standard for the confirmation of sepsis [7]. In our study culture positivity rate was 37.63% while that in Shah AJ et al., [8] (2012) study was 31.75%, Shaw CK et al., [9] (2007) study was 54.64%, Bhattacharjee et al., [10] study was 32%. In advanced centres, blood culture is positive in 80% of genuine sepsis [11]. Thus culture positivity rate is highly variable from place to place.

The rate of admission of early and late onset sepsis as well as the prevalence of organisms and their sensitivity patterns were much similar [Table/Fig-4]. This may be due to the fact that not only the vertical transmission but also the horizontal spread of infection may play a part in the early onset of sepsis in hospitalized neonates [12,13]. A male predominance was found in our study which is found in almost all the studies of sepsis in newborn [8,9].

The most common organism identified in our study was *staphylococcus aureus* (37.22%) [n=51] which is very similar to recent study of Shaw CK et al., [9]. The other gram positive organisms to be isolated were *streptococcal* species and coagulase negative *staphylococcus*. Most of the studies have found a preponderance of gram negative organisms like *klebsiella*, *pseudomonas*, and *enterobacter species* [14-17]. However, *staphylococcus* was the commonest gram positive organism to be isolated in most of the studies [14,18]. In western countries,

Antibiotics	Disc conc. (mic.gr.)	Staph. N = 51	CoNS N = 6	Strept. N = 4	Kleb. N = 37	*E. coli* N = 27	Pseud. N = 6	Acinet. N = 3	Entero. N = 3
Penicillin	10 U	0	0	2 (50)	NT	NT	NT	NT	NT
Gentamicin	10	8(15.69)	0	0	12(32.43)	12(44.44)	4(66.67)	2(66.67)	0
Co- trimoxazole	23.75/1.25	16(31.37)	0	3(75)	NT	NT	NT	NT	NT
Tetracycline	30	7(13.73)	NT	NT	0	0	NT	NT	0
Erythromycin	15	15(29.41)	0	3(75)	NT	NT	NT	NT	NT
Vancomycin	30	51(100)	6(100)	4(100)	NT	NT	NT	NT	NT
Cefepime	30	NT	NT	4 (100)	30(81.08)	27(100)	6(100)	3(100)	3(100)
Ampicillin	10	7 (13.73)	0	3 (75)	0	0	0	0	0
Amikacin	30	42(82.35)	0	2 (50)	30(81.08)	27(100)	6(100)	2(66.67)	3(100)
Cefotaxime	30	39 (76.47)	0	4(100)	16(43.08)	13(48.15)	4(66.67)	2(66.67)	2(66.67)
Piperacillin-Tazobactam	100/10	NT	NT	NT	NT	NT	4(66.67)	2(66.67)	NT
Ciprofloxacin	5	8(15.69)	0	4(100)	12(32.43)	9(30)	0	0	0
Polymixin - B	300 U	NT	NT	NT	NT	NT	4(66.67)	NT	NT
Meropenem	10	NT	NT	NT	37(100)	27(100)	6(100)	3(100)	3(100)

[Table/Fig-3]: Antibiotics sensitivity pattern of blood cultures in neonates presenting with sepsis
Staph. = *Staphylococcus aureus*, Strept. = *Streptococcus species*, CoNS = Coagulase Negative Stapphylococcus, Kleb. = *Klebsiella* pneumoniae, *E. coli* = *Escherichia coli*, Pseud. = *Pseudomonas*, Acinet. = *Acinetobacter*, Entero. = *Enterobacter*

S. No.	Organism	Early onset (n= 77)%	Late onset (n= 60)%
1.	*Staphylococcus* aureus	31 (40.26%)	20 (33.33%)
2.	*Klebsiella pneumoniae*	18 (23.38%)	19 (31.67%)
3.	*Escherichia coli*	17 (22.08%)	10 (16.67)
4.	*Pseudomonas*	3 (3.9%)	3 (5.0%)
5.	*Staphylococcus* epidermidis (CoNS)	0 (0.0)	6 (10.0%)
6.	*Streptococcus sp*	3 (3.9%)	1 (1.67%)
7.	*Acinetobacter*	3 (3.9%)	0 (0.0)
8.	*Enterobacter*	2 (2.6%)	1 (1.67%)

[Table/Fig-4]: The distribution of organisms in early and late onset sepsis in the study

Group B *streptococcus* is mainly responsible for neonatal sepsis but this is not observed in this part of the world [19]. CoNS are usually associated with indwelling catheters or central lines. In our study, CoNS was isolated only in late onset sepsis group. All of them were sensitive to vancomycin only. Similar findings were reported by a study in Nepal [9].

Klebsiella pneumoniae was the most common gram negative organism (27.01%) and the second most frequent after *staphylococcus aureus* in the study. This finding is not in accordance with NNPD 2002 – 03 data, where the most common organisms causing neonatal sepsis was *klebsiella pneumoniae* followed by *staphylococcus aureus* and *pseudomonas* [3]. In this study, culture positivity rate was found to be high among preterm neonates as compared to term (43.48% Vs.35.66%), suggesting prematurity to be a risk factor associated with neonatal sepsis. This finding was similar to the study by Monjur F et al., [20].

In our study, all the isolates were resistant to penicillin. Ampicillin, gentamicin & ciprofloxacin had lowest sensitivity to all bacterial isolates. Highest sensitivity was recorded with meropenem and vancomycin followed by amikacin and cefepime. Vancomycin and meropenem showed sensitivity of 100%. As far as cephalosporins are concerned, moderate sensitivity was observed for third generation cephalosporins i.e., cefotaxime while higher sensitivity was documented for fourth generation cephalosporins i.e. cefepime. Low sensitivity of commonly used antibiotics and fair sensitivity to amikacin was also observed by other authors [16,21,22] Tallur et al., [22] concur with us that most isolates were resistant to ampicillin, gentamicin and cotrimoxazole.

Almost all the isolates in our study were sensitive to either cefotaxime or amikacin and hence a co-prescription of these two antibiotics appear prudent as the initial choice while awaiting for the blood culture reports. This combination has given us the best results in our neonatal intensive care unit.

CONCLUSION

Neonatal sepsis is a leading cause of neonatal admissions, morbidity and mortality in developing countries. Bacterial spectrum for sepsis could be different in different regions. Sensitivity pattern also differs accordingly. The antibiotic susceptibility pattern in our study suggested that, initial empirical choice of cefotaxime in combination with amikacin was the most appropriate as maximum isolates were sensitive to either cefotaxime or amikacin. A low susceptibility to commonly used antibiotics like ampicillin and gentamicin is a cause for concern. The knowledge of prevailing strains and the antibiotic sensitivity patterns in the region is mandatory for each center due to temporal changes in the causative organisms and their antibiotic susceptibility. Periodic evaluations not only reveals the recent trend of increasing resistance to commonly used antibiotics but also helps in implementation of a rational empirical therapy.

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