



ISSN: 0976-3031

Available Online at <http://www.recentscientific.com>

CODEN: IJRSFP (USA)

International Journal of Recent Scientific Research
Vol. 8, Issue, 9, pp. 20290-20294, September, 2017

**International Journal of
Recent Scientific
Research**

DOI: 10.24327/IJRSR

Research Article

CLINICO-BACTERIOLOGICAL PROFILE OF NEONATAL SEPTICEMIA IN A TERTIARY CARE HOSPITAL; SOUTH INDIA

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DOI: <http://dx.doi.org/10.24327/ijrsr.2017.0809.0866>

ARTICLE INFO

Article History:

Received 05th June, 2017
Received in revised form 21st
July, 2017
Accepted 06th August, 2017
Published online 28th September, 2017

Key Words:

Antimicrobial susceptibility, EOS, LOS,
Neonatal septicemia

ABSTRACT

Introduction: Neonatal sepsis is the most common cause of neonatal mortality. It is more common in developing countries compared with developed countries. Depending on the onset of symptoms, it can be classified into early onset sepsis within 72 h of life and late onset sepsis usually after 72 h of age. The spectrum of organisms that cause neonatal septicemia varies in different countries, and sometimes changes from one center to another within the same country. The management of these infections is complicated by the emergence of antibiotic resistance. The aim of this study was to determine the etiology, clinical characteristics and outcome of neonatal septicemia cases. **Materials and Methods:** One and half year study was conducted on 250 neonates admitted in the neonatal intensive care unit with clinically suspected septicemia Early onset septicemia (EOS) within 72 h of age and late onset septicemia (LOS) >72 h of age). Blood culture was performed by using BacT/Alert and detects organisms metabolic changes by fluorescence based methods which facilitates identification of microorganisms along with antibiotic susceptibility. **Results:** There were 210 (84%) isolates from EOS cases, while 40 (16%) were from LOS illness. In suspected as well as in culture-proven sepsis, the majority were male as compared with female. Cesarean delivery, pre term and low birth weight babies were more as compared with normal vaginal delivery, term and normal birth weight babies. Hypothermia, respiratory distress, neonatal jaundice and shock with DIC were the most common clinical presentations, and prematurity was the major risk factor in both the groups. Blood culture reports were positive in 16 (6.4%) cases of which Gram-negative bacilli and Gram positive cocci accounted for 13 (5.2%) and 2 (0.8%) respectively, in the remaining one case Candida growth was seen. Among Gram-negative bacilli, Klebsiella pneumoniae (44%) was the most common organism isolated and among Gram-positive, Enterococcus species (12%) was the commonest, followed by Burkholderia, Enterobacter, Moraxella and candida. Among Gram-positive bacteria, enterococcus species (12.5%) was the only isolate which was exhibiting MDR as well as vancomycin resistance (Strains with Van A). Strains carrying Van A genes are highly resistant to vancomycin and teicoplanin. **Conclusion:** Gram-negative organisms (Klebsiella, Burkholderia) were the leading cause of neonatal sepsis and multidrug resistant. Therefore, an effective infection control programme, regular antibiotic susceptibility surveillance and evaluation, and the enforcement and periodic review of the antibiotic policy of the hospital as well as the encouragement of rational antibiotic use will reduce the rates of acquiring nosocomial infections and development of bacterial resistance.

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INTRODUCTION

When pathogenic organisms gain access into the blood stream, they may cause an overwhelming infection without much localization (septicemia), or may get predominantly localized to the lung (pneumonia) or the meninges (meningitis). Systemic bacterial infections are known by the generic term neonatal sepsis, which incorporates septicemia, pneumonia and meningitis^{1,2}. It is more common in developing countries compared with developed countries. Neonatal sepsis is the

most common cause of neonatal mortality³. Studies have recorded an incidence of neonatal sepsis, varying between 11 and 24.5 per 1000 live births in some Asian countries³. It is responsible for about 30-50% of the neonatal deaths. Majority (56%) of under 5 deaths occur in the neonatal period, and the neonatal mortality accounts for 70% infant deaths¹.

Depending on the onset of symptoms, it can be classified into early onset sepsis (EOS) within 72 h of life and late onset sepsis (LOS) usually after 72 h of age^{1,2,5}. Knowledge about

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potential risk factors would help in the early diagnosis of sepsis. Early signs of sepsis are frequently non-specific and subtle. The spectrum of organisms that cause neonatal septicemia varies in different countries, and sometimes changes from one center to another within the same country⁴. Group B streptococci (GBS) and E. coli predominate in the USA and Europe, whereas Staphylococci and Gram-negative bacilli are much more common in developing countries⁵. The management of these infections is complicated by the emergence of antibiotic resistance. Multidrug-resistant bacteria are increasingly being reported from intensive care units as well as the community. Because of the different pathogens involved in neonatal sepsis of either onset, appropriate management and care depends on knowledge about the causative organisms and their sensitivity to antibiotics^{6,7}. Sepsis related mortality is largely preventable with prevention of sepsis itself, timely recognition, rational antimicrobial therapy and aggressive supportive care. The aim of this study was to determine the etiology, clinical characteristics and outcome of neonatal septicemia cases.

MATERIALS AND METHODS

This 18 months (from January 2014 to June 2015) study was conducted at the Department of Microbiology and Pediatrics, NRI Medical College, South India; on 250 neonates admitted in the neonatal intensive care unit with clinically suspected septicemia. Neonates with at least one of the clinical signs and symptoms, including poor feeding and lethargy, respiratory problems such as respiratory rate >60/min, apnea, grunting, cyanosis and retraction, temperature instability such as hyperthermia or hypothermia, gastrointestinal problems including vomiting, abdominal distension, diarrhea and abnormal gastric residual and central nervous system symptoms such as convulsion, hypotonia and irritability, were enrolled in the study. The neonates with septicemia were divided into EOS <72 h of age and LOS >72 h of age^{1,2,3}. Demographic data, clinical manifestations and outcomes for both EOS and LOS were recorded. 2ml of blood was collected from all neonates aseptically bedside and inoculated into pediatric blood culture bottles which are provided with CO₂ sensitive chemical sensor and transported immediately to the microbiology laboratory. The bottles were incubated in BacT/Alert [automated and computerized blood culture system] which works on the principle of detection of CO₂ liberated from the growing microorganisms. Once the system detects growth of the aerobic organism in the blood culture bottle, it generates alert sign. Positive bottles were removed, sub cultured onto solid media and incubated. Further processing [identification and antibiotic susceptibility testing] was carried out in VITEK-2 compact system [Biomarieux, France] according to manufactures instructions. This system detects organisms metabolic changes by fluorescence based methods which facilitates identification of microorganisms along with antibiotic susceptibility.

RESULTS

Of the 250 neonates, 205 were inborn and 45 were outborn cases. There were 210 (84%) isolates form EOS cases, while 40 (16%) were from LOS illness. In suspected as well as in culture-proven sepsis, the majority were male as compared

with female. Cesarean delivery, pre term and low birth weight babies were more as compared with normal vaginal delivery, term and normal birth weight babies. Hypothermia, respiratory distress, neonatal jaundice and shock with DIC were the most common clinical presentations, and prematurity was the major risk factor in both the groups [Table 1].

Table 1 Demographic characteristics of suspected and culture-positive neonatal sepsis cases

Characteristics	Suspected cases (234) Number (%)	Culture positive cases (16) Number (%)
Gender		
Male	115 (49%)	4 (25%)
Female	119 (51%)	12 (75%)
Type of delivery		
NVD	104 (44.4%)	6 (37.5%)
LSCS	130 (55.6%)	10 (62.5%)
Gestational age		
>37W	38 (16%)	6 (37%)
<37W	196 (84%)	10 (62.5%)
Birth weight		
>2.5Kg	96 (41%)	7 (44%)
<2.5Kg	138 (59%)	9 (56%)
Risk Factors		
Prematurity	196 (84%)	10 (62.5%)
Delayed cry	61 (26%)	6 (37.5%)
Meconium stained liquor	19 (8%)	2 (12.5%)
Leaking P/V	38 (16.4%)	4 (25%)
Maternal fever/UTI	23 (10%)	2 (12.5%)
Clinical Signs And Symptoms		
Hypothermia	103 (44%)	8 (50%)
Fever	5 (2%)	2 (12.5%)
Respiratory distress	153 (65%)	12 (75%)
Apnoea	61 (26%)	8 (50%)
Poor feeding	19 (18%)	4 (25%)
Seizures	38 (16%)	2 (12.5%)
Feed intolerance	38 (16%)	4 (25%)
Neonatal jaundice	115 (49%)	4 (25%)
Hypoglycemia	15 (6.4%)	2 (12.5)
Shock	103 (103%)	8 (50%)
Anemia	57 (57%)	6 (37.5%)
DIC/Thrombocytopenia	54 (23%)	6 (37.5%)
IVH	8 (3.4%)	0

During the study period, a total of 250 neonates with clinical suspicion of septicemia were admitted into NICU. Blood culture reports were positive in 16 (6.4%) cases of which Gram-negative bacilli and Gram positive cocci accounted for 13 (5.2%) and 2 (0.8%) respectively, in remaining one case Candida fungi growth was seen. Among Gram-negative bacilli, Klebsiella pneumoniae (44%) was the most common organism isolated and among Gram-positive, Enterococcus species (12%) was the commonest, followed by Burkholderia, Enterobacter, Moraxella and candida (Table 2).

Table 2 Bacteriological profile of neonatal septicaemia in NRI Hospital

Gram Negative isolates (5.2%)	Gram positive Isolates (0.8%)	Fungi (0.4%)
K.pneumoniae (44%)	Enterococcus faecium (6.25%)	Candida krusei(6.25%)
B.Caepaecia (25%)	Enterococcus faecalis (6.25%)	
E.cloacae (6.25%)		
M.non-liquefaciens(6.25%)		

Antibiotic resistance pattern among Gram-positive organisms Table 3		
Drug	Enterococcus faecium	Enterococcus faecalis
Benzyl penicillin	Sensitive	Resistant
Ciprofloxacin	Resistant	Resistant
Highlevel gentamycin	Resistant	Resistant
Levofloxacin	Resistant	Resistant
Erythromycin	Resistant	Resistant
Clindamycin	Resistant	Resistant
Linezolid	Resistant	Resistant
Teicoplanin	Resistant	Resistant
Vancomycin	Resistant	Resistant
Ticoplanin	Resistant	Resistant
Tetracycline	Resistant	Resistant
Tigecycline	Resistant	Sensitive
Nitrofurantoin	Resistant	
Daptomycin		Sensitive

Antibiotic susceptibility in Gram-positive and Gram-negative isolates were analysed (Table 3 and Fig 1). High level of resistance was observed in Gram-Negative isolates for cephalosporins, penicillins, carbapenems and co-trimoxazole [Table 3, Fig 1]. Eighty six percent of Klebsiella isolates were either ESBL or AMP or Carbapenemase producers. Maximum sensitivity for Nalidixic acid, Fluoroquinolones, tetracyclines and colistin was exhibited by Klebsiella. Burkholderia was sensitive to Nalidixic acid, cotrimoxazole and cefepime.

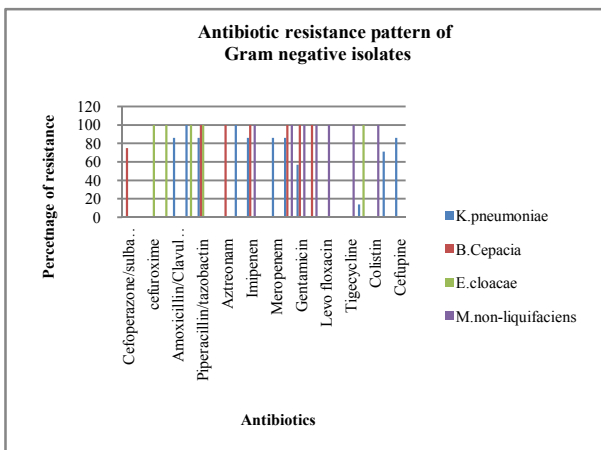


Fig 1 Antibiotic resistant pattern of Gram-negative isolates

Among Gram-positive bacteria, enterococcus species (12.5%) was the only isolate which was exhibiting MDR as well as vancomycin resistance (Strains with Van A). Strains carrying Van A genes are highly resistant to vancomycin and teicoplanin.

DISCUSSION

Septicemia remains a significant cause of morbidity and mortality in the newborn. The correct and timely identification of infectious agents and their antibiotic sensitivity patterns are essential to guide the clinicians regarding both the empirical and definitive treatment.

The bacteriological profile of septicemia keeps changing with the passage of time from region to region and hospital to hospital in the same city or country. The emergence of resistant bacteria in NICU settings leads to failure in the treatment of neonatal septicemia. To supplement the management of septicemia in neonates, study of bacteriological profile along with antimicrobial sensitivity pattern plays a note worthy

role^{8,9,10}. Out of the 250 clinically suspected cases of sepsis in our study, 16 were culture positive with a blood culture positivity rate of 6.4%. The incidence of Gram negative and Gram- positive organisms was 5.2% and 0.8% respectively. There were 210 (84%) isolates from EOS cases, while 40 (16%) were from LOS illness.

Culture positivity for aerobic organisms in neonates vary from 25% to 60%^{11, 12, 13}. In this study, blood culture positivity rate is 6.4%. This finding is comparable with other reports¹⁴. However, a high blood culture positivity rate in septicemic children (56%) had been reported by Sharma *et al*¹⁵ and Jain *et al*¹⁶.

A low blood culture isolation rate could be due to the possibility of infection with anaerobes. A negative blood culture doesn't exclude sepsis and about 26% of all neonatal sepsis could be due to anaerobes¹⁴. The Pathogens most often implicated in neonatal sepsis in developing countries differ from those seen in developed countries. Overall Gram-negative organisms are more common and are mainly represented by Klebsiella, E.coli, Pseudomonas and Salmonella.

Of the Gram-positive organisms, S.aureus, CONS, S. pneumoniae and S.pyogenes are most commonly isolated¹⁷. Gram-negative and Gram-positive septicemia was encountered in 13 (5.2%) and 2 (0.8%) of the culture positive cases in this study; which is comparable to a study conducted by Agnihotri *et al*¹⁸ which reported that Gram-negative and Gram-positive organisms were responsible for 59% and 41% of the septicemia cases. Similar observations were made by other workers^{19, 20}.

The report of the National Neonatal-Perinatal database showed klebsiella as the predominant (29%) pathogen¹¹. Klebsiella species was the predominant Gram-negative species isolated in this study, which agrees with previous reports^{21, 22}. The second commonest organism was Burkholderia cepacia 4 (25%). Many recent studies have reported the emergence of new emerging organisms as a cause of neonatal septicemia of which one of them is this^{24, 25, 26, 27, 28}. Other Gram-negative organisms isolated were Enterobacter cloacae and Moraxella non-liquifaciens.

Several studies have shown S.aureus as a major pathogen^{17, 23, 24, and 25} of neonatal septicaemia among Gram-positive. In this study Enterococcus species was the commonest. This may be attributed to the fact that bacteriological profile of septicemia keeps changing with the passage of time from region to region²⁴.

An alarming finding in the current study was organisms exhibiting multidrug resistance. High Resistance ranging from 6% to 44% was observed in Gram-negative isolates for cephalosporins, penicillins, carbapenems and co-trimoxazole. Gram-positive isolates had shown the resistance of 6.5% against penicillins, fluoroquinolones, macrolides, lincosamides, glycopeptides and tetracyclines. The greater prevalence of resistance to commonly used antibiotics has also been reported by other studies^{19, 21}. The choice of drug for empiric treatment of suspected neonatal septicaemia is likely to be difficult in the presence of ESBL, AmpC and Carbapenemase producers which often fail to achieve therapeutic goals even after showing invitro susceptibility.

Antibiotic resistance is a global problem today. Reports of MDR bacteria causing neonatal sepsis in developing countries are increasing. The wide availability of over the counter antibiotics and the inappropriate use of broad spectrum antibiotic in the community may explain this situation. It is difficult to compare antibiotic resistance between countries because the epidemiology of neonatal sepsis is extremely variable¹⁷. In our study, candida krusei was also isolated exhibiting sensitivity to voriconazole, Aspofungin, Micafungin, Amphotericin B and resistance to Fluconazole and Flucytosine. In the present study overall mortality was observed in 36 (14.4%) where as Chaudary reported a mortality of 45.5% in their study, which is quite high as compared to our study²⁹. This could be attributed to advancement in medical technology and better neonatal care in NICU.

CONCLUSION

It is evident from this study that Gram-negative organisms (klebsiella, Burkholderia) which are the leading cause of neonatal sepsis are multidrug resistant. Therefore, an effective infection control programme, regular antibiotic susceptibility surveillance and evaluation, and the enforcement and periodic review of the antibiotic policy of the hospital as well as the encouragement of rational antibiotic use will reduce the rates of acquiring nosocomial infections and development of bacterial resistance.

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How to cite this article:

Ananta Rao K *et al.* 2017, Clinico-Bacteriological Profile of Neonatal Septicemia In A Tertiary Care Hospital; South India. *Int J Recent Sci Res.* 8(9), pp. 20290-20294. DOI: <http://dx.doi.org/10.24327/ijrsr.2017.0809.0866>
