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CLINICO-BACTERIOLOGICAL PROFILE AND ANTIBIOTIC SENSITIVITY PATTERN OF NEONATAL SEPTICAEMIA- A PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

Context: Neonatal septicaemia is most common cause of morbidity and mortality in NICU in developing countries with emergence of antibiotic resistant organisms. For effective management of neonatal septicaemia cases and to formulate antibiotic policy for NICU, blood culture is most important investigation.

Aims: This study was carried out to study clinical, microbial profile and antibiotic sensitivity pattern of neonatal septicaemia at our institute.

Settings and Design: Present study was a prospective observational study, carried out in the Department of paediatrics, IGGMC Nagpur.

Methods & material: 292 neonates admitted with diagnosis of neonatal septicaemia were included in the study. Diagnostic work up included complete hemogram with peripheral blood smear, CRP, blood culture and sensitivity (C/S) and other relevant investigations according to cases.

Statistical analysis: Obtained data was analysed and presented. 95 % confidence interval values were also calculated.

Results: Out of 292 cases of neonatal septicaemia blood culture was positive in 107(36.64%). Culture positivity in EOS & LOS were 66(34.74%) & 41(40.20%) respectively. In EOS gram negative organisms (83.33%) were common isolates while in LOS gram positive organisms (46.34%) were predominant. Gram positive were sensitive to vancomycin, linezolid while gram negative were sensitive to imipenam, amikacin, piperacillin + tazobactum.

Conclusion: Neonatal septicemia is an important cause of morbidity and mortality. This is due to infection by both Gram positive and gram negative bacteria most of which are multi drug resistant especially in the hospital environment. Acinetobacter spp is one of the emerging causes of neonatal sepsis.

Key Words: Neonatal septicaemia, Early onset septicaemia (EOS), Late onset septicaemia (LOS), Antibiotic sensitivity

Abbreviations: Early onset septicaemia (EOS), Late onset septicaemia (LOS)

INTRODUCTION

The term neonatal sepsis used broadly in clinical context encompasses the diagnosis of septicaemia, meningitis, pneumonia, arthritis, osteomyelitis and urinary tract infection in newborn. This excludes local infection of newborn such as omphalitis, pyoderma and conjunctivitis. Prompt recognition, appropriate antimicrobial therapy and judicious supportive care are the key determinants of positive outcome in this serious paediatric emergency[1]. It is estimated that almost 20% of all neonates develop infection and approximately 1% die of serious systemic infection. Not surprisingly, sepsis is the commonest admitting diagnosis among neonates at referral facilities[1].

The detection of microorganisms in patient's blood has a great diagnostic and prognostic significance. Many infections in the neonatal and paediatric age group can only be established on the basis of etiologic agent recovered from blood.

In the major 16 hospitals of our country, the incidence of neonatal sepsis was 38 per 1000 live births as per the report of National Neonatal Perinatal database[2]. This is in

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contrast with the reported incidence of 1 to 10 per1000 live births in developed countries[1]. Over the last few decades, various studies have been conducted to find out causative organisms & their sensitivity patterns in neonatal septicaemia. The results obtained vary from place to place & from period to period in which the studies were conducted [3,4,5].

Hence it is important to study neonatal septicaemia in different hospital settings and geographical areas to pin point the microbial aetiology and determine the antimicrobial susceptibility of the microbial isolates for effective management of the cases. It also helps to develop rational antibiotic policy for the NICU. So the present study was undertaken to know the clinicoetiological profile and antibiotic sensitivity pattern of neonatal septicaemia.

MATERIAL & METHODS

This prospective observational study was carried out in the neonatal unit of tertiary care teaching hospital in central India during the period of August 2011 to September 2013 after acceptance from institutional ethical committee. Aims of the study were to study the microbial profile of neonatal septicemia at our institute & to study the antimicrobial resistance & sensitivity pattern of bacterial isolates. Both outborn as well as inborn neonates admitted with diagnosis of neonatal septicemia were included in study after informed written parental consent. As per the criteria by Vergnonoet al[5] all the neonates were included in the study. Septicemia was classified into Early onset septicemia (EOS) and late onset septicemia (LOS) as per standard guidelines[6].

Diagnostic workup included complete hemogram with peripheral blood smear, CRP, blood culture and sensitivity (C/S). Chest X-ray, Urine C/S, cerebrospinal fluid (CSF) analysis and fungal C/S were done wherever necessary. All specimens were collected before starting antibiotics.

RESULTS

Over the study period, 292 neonates with neonatal septicemia were included in the study. Amongst them, EOS was seen in 190 (65.07%) cases and LOS in 102 (34.93%) cases. Of the total 292 neonatal septicemia cases, 182 (62.33%) were male and 110 (37.67%) were female.

Of the total 292 cases, 58.91% were delivered in hospital, 14.38% were delivered at home, Lower segment caesarean section (LSCS) was performed in 21.92% cases and instrumentation was done in 4.79% cases.

In the present study, 49 (16.78%) cases have history of maternal fever and mother of 60 (20.55%) cases showed premature rupture of membrane.

In present study, most common risk factor observed in neonates in neonatal septicemia was low birth weight (69.18%), followed by prematurity (28.08%). Neonatal resuscitation, lack of breast feeding, superficial skin infection including umbilical sepsis and meconium aspiration were observed in 25.34%, 13.70%, 13.01% and 5.48% neonates respectively.

In the present study, most common manifestation observed in neonatal septicemia cases were lethargy (72.60%) and poor sucking (72.60%) while least common were bulging fontanel (8.90%) and convulsions (9.93%). Other manifestations were decreases capillary refill time (21.92%), hypothermia (42.12%) and tachypnea (23.97%).

Table 1 shows blood culture positivity in EOS and LOS cases.

Amongst total 292 cases of neonatal septicaemia, in 107 (36.64%) cases blood culture was positive, whereas in 185 (63.36%) cases blood culture was negative. Of the total 292 cases of neonatal septicemia, early onset septicemia cases were 190 and late onset septicemia cases were 102. Of the 190 early onset neonatal septicemia cases, blood culture was positive in 66 (34.74%) cases. Similarly, out of 102 late onset neonatal septicemia cases, blood culture was positive in 41 (40.20%) cases.

Table 2 shows the microbial isolates from blood culture of neonatal septicemia cases.

Table 2 shows that, in the present study, gram negative bacilli were found to be commonest cause of neonatal septicemia (68.22%). Gram positive organisms were found in 28.04% cases. Klebsiella pneumoniae (19.62%), Pseudomonas aeruginosa (16.82%) and Acinetobacter baumannii(15.89%) were the commonest isolates from neonatal septicemia cases.

In blood culture positive early onset neonatal septicemia cases (66), gram negative bacilli (83.33%) were common aetiological agents as compared to gram positive cocci (16.67%). Among gram negative bacilli, Klebsiella pneumoniae(31.82%), Acinetobacter baumannii(21.21 %) and Pseudomonas aeruginosa (15.15%) were the common isolates. Among gram positive organisms Enterococcus fecalis(10.61%) was the commonest organism.

In blood culture positive late onset neonatal septicemia cases (41), both gram negative bacilli (43.90 %) and gram positive cocci (43.90 %) were isolated in equal number of cases while Candida albicans and Streptomyces spp were isolated in 4 (9.76%) and 1 (2.44%) cases each. S.epidermidis (24.39%) followed by P. aeruginosa (19.51%) formed the common bacterial isolates in LOS.

Table 3 shows the antimicrobial sensitivity of enterobacteriaceae isolates from blood culture of neonatal septice-

mia cases. It shows that all the enterobacteriaceae isolates (except S. Typhi, where imipenem sensitivity is not advised) are sensitive to imipenem. Except S. Typhi all the isolates were resistant to ampicillin.

As many as 93.93% isolates of enterobacteriaceae were sensitive to piperacillin + tazobactam while only 33.33% were sensitive to piperacillin. Among aminoglycosides enterobacteriaceae isolate showed maximum sensitivity to amikacin (60.60%) fallowed by netilmicin (39.39%).

All the isolates of Klebsiella pneumonia and Klebsiella aerogens were sensitive to piperacillin + tazobactam and imipenem. Klebsiella isolates in our study showed complete resistance to ampicillin, amoxyclav, 1st and 2nd generation cephalosporins. Among aminoglycosides amikacin showed maximum sensitivity to Klebsiella pneumoniae(47.62%) and Klebsiella aerogens(50%).

Among the six isolates of E. coli complete sensitivity was seen with imipenem and amikacin. All the six isolates were resistance to ampicillin. Two isolates each of Citrobacter fruendii and Enterobacter aerogens showed complete resistance to ampicillin, amoxyclav, 1st and 2nd generation cephalosporins, kanamycin and aztreonam.

In the present study, two strains of S. Typhi were isolated. Both were sensitive to ampicillin, cefotaxime & ciprofloxacin.

Antimicrobial sensitivity of Acinetobacter spp. and Pseudomonas aeruginosa is shown in table 4. It shows that maximum isolates of Acinetobacter baumannii(88.24%), Acinetobacter woffii(100%), and Pseudomonas aeruginosa(88.89%) were sensitive to imipenem. As many as 82.35% strains of Acinetobacter baumannii were sensitive to Piperacillin + tazobactam while 70.59% to ciprofloxacin. Only 25.52% strains were sensitive to ceftazidime, cefotaxime and cefepime. None of the isolate of Acinetobacterl woffii showed sensitivity to ceftazidime, cefotaxime, cefepime, piperacillin, gentamicin and tobramycin. Pseudomonas aeruginosa isolate showed good sensitivity to Piperacillin + tazobactam (66.67%), Ciprofloxacin (66.67%) and Amikacin (61.11%). These isolates showed poor sensitivity to ceftazidime (27.78%), cefotaxime (16.67%) and cefepime (27.78%).

Table 5 shows the antimicrobial sensitivity of gram positive cocci isolates from blood culture of neonatal septicemia cases. It shows that gram positive cocci isolates were 100% sensitive to linezolid, vancomycin and pristinomycin.

Methicillin resistance was 100% in Staph.aureus and Staph. Hemolyticus while it was 58.33% in Staph. epidermidis. Among the aminoglycosides amikacin showed a maximum sensitivity in Staph. aureus (100%) and Staph. hemolyticus (100%). As many as 8 strains (66.67%) of Staph. Epidermidis were sensitive to amikacin, tobramycin and netilmicin.

Table 6 shows mortality of neonate as per positivity of blood culture.

Table 6 shows that mortality of neonates in blood culture positive cases was more (46.73%) than the culture negative cases (11.35%). It was found to be statistically significant (p= 0.0000).

DISCUSSION

Neonatal septicemia remains a challenging and important problem even with modern drug therapy. It is associated with considerable morbidity and mortality. It is difficult to diagnose the neonatal infection, because of its non-specific clinical signs and symptoms. Microorganism detection has its value as a strong diagnostic method for neonatal septicemia. For the effective management of neonatal septicemia cases, study of bacteriological profile with their antibiotic sensitivity pattern plays a significant role[7].

In present study, maternal pyrexia was seen in 16.78% cases. A similar finding was seen by Soman et al[8] (18.6%) and Saxena et al[9] (17.34%). In the present study, 20.55% of cases had history of premature rupture of membranes for more than 24 hours. A similar finding was seen in Roy et al[10] (28.9%), Hossain et al[11] (29.2%) & Kuruvilla et al[12] (12.8%).

Most important neonatal factor predisposing to infection is prematurity. Preterm infants have a 3-10 fold higher incidence of infection than full term normal weight infants.LBW is a well accepted risk factor for neonatal septicaemia[13,14]. Khatua et al[15] and Mondal et al[16] stated that LBW infants have low IgG and they are more susceptible to infections.

There is little correlation between clinical manifestations and etiological agents[4,17,18,19] . Lethargy (72.6%) was most common manifestation in present study similar to Guha et al[20] (66.25%), Mishra et al[21] (62.52%) & Gupta et al[22] (66.7%). Ahmed et al[23] (40%) & Buetow et al[24] (31.01%) found lethargy in less number of cases.

Poor feeding (71.925) was second most common manifestation in present study, a finding similar to Guha et al[20] (66.25%), Mishra et al[21] (62.52%). Buetow et al[25] (19.62%) found that poor feeding was less common.

In the present study, blood culture positivity in neonatal septicemia cases was 107 (36.64%), whereas in 185 (63.36%) of cases there was no growth. Culture positivity for aerobic organisms in neonatal sepsis varies widely (19.20% to 76.8%) among different studies[7,26,27,28] .

These wide variations might be due to the fact that most of the patients receive the antibiotics before they come to the tertiary care hospital. Further, self medication is

very common as the medicines are easily available at the counter[29]. It can also be explained by technique & volume of blood sample collection, methods used for bacterial isolation or presence of anaerobic infection.

The negative cultures were presumed to be due to anaerobic infections or antibiotic usage before collection of samples for culture or clinically overdiagnosing the bacterimias as a prelude to avoid the risk of missing any true bacterimias[7].

In the present study, the percentage of gram negative septicemia is 68.22% and that of gram positive is 28.04% (Table 1). Observation made by various workers is given in Table 7. The increased susceptibility of neonates to the gram negative bacteria may be explained by the fact that the antibodies against these organisms are primarily IgM type, which do not transfer passively through placenta and are at very low level in blood (about 5% of adult value) at birth, and reaches the adult level by 2 years of age. This is in contrast with IgG type, which are passively transferred to placenta and are almost at adult level at birth and falls gradually reaching lowest level around 3 to 4 months of age after which they start to rise again gradually. Adequate IgG (except IgG 2-subtype) levels at term, afford protection against several gram positive bacteria[30].

In the present study (Table 1), it was observed that gram negative organisms causing EOS (83.33%) outnumbered gram positive organisms (16.67%). In contrast in LOS gram positive organisms isolates (46.34%) were more common than gram negative organisms (43.90%).

The bacteriological profile differs in EOS and LOS and it also differs in developing and developed countries. In developed countries gram positive organism is predominant in both EOS and LOS but Group B streptococci is found more in EOS. In developing countries gram negative organism are predominant in EOS & LOS both.[23]

Kaushik et al[13] had reported that gram negative bacilli predominated in EOS (62.5%) whereas gram positive organisms accounted for majority of LOS cases (58.33%). Chugh et al[3] reported 90.31% gram negative bacilli in EOS and 29% positive organisms in LOS. Stoll et al[14] stated that majority of EOS 60.7% were caused by gram negative organisms.

Antimicrobial sensitivity showed that all the enterobacteriaceae isolates (except S. Typhi) were sensitive to imipenem. Except S. Typhi all the isolates were resistant to ampicillin. As many as 93.93% isolates of enterobacteriaceae were sensitive to piperacillin + tazobactam while only 33.33% were sensitive to piperacillin. Among aminoglycosides enterobacteriaceae isolate showed maximum sensitivity to amikacin (60.60%) followed by netilmicin (39.39%). Twenty three Klebsiella isolates and two isolates each of Citrobacter fruendii and Enterobacteraerogens showed complete resistance to ampicillin, amoxyclav, 1st and 2nd generation cephalosporins, cephamycin and tetracycline. Two strains of S. Typhi were sensitive to ampicillin, cefotaxime, ciprofloxacin and chloramphenicol.

There were 21 isolates of Staphylococcus spp., with 5 S. aureus, 12 S. epidermidis and 4 S. hemolyticus. All the 21 Staphylococcus isolates showed 100% sensitivity for vancomycin, linezolid and pristinomycin. For S. aureus and S. hemolyticus maximum resistance (100%) was seen in penicillin G, cefoxitin and erythromycin. All the 7 strains of Enterococcus fecalis were sensitive to vancomycin, linezolid, pristinomycin whereas all were resistant to penicillin G and erythromycin. One isolate of Streptococcus pneumoniae was found to be 100% sensitive to all the drugs (penicillin G, erythromycin, vancomycin, pristinomycin, linezolid, chloramphenicol and tetracycline) tested.

In our study, overall mortality rate was 24.31%. Further the mortality in blood culture positive cases of neonatal septicemia was higher (46.73%) as compared to culture negative cases (11.35%) and this difference was statistically significant (p value=0.0000 df=1).

CONCLUSIONS

Overall Gram negative bacilli were found to be commonest cause of neonatal septicemia. In EOS gram negative while in LOS gram positive organisms predominate. In EOS, Klebsiella pneumoniae, Pseudomonas aeruginosa and Acinetobacter baumannii whereas in LOS Staphylococcus epidermidis and Pseudomonas aeruginosa were found to be common.

Acinetobacter spp is one of the emerging cause of neonatal septicaemia because of the high potential of this genus to develop antibiotic resistance, leading to a considerable selective advantage in environments with widespread and heavy use of antibiotic, especially with relation to hospital environment and nosocomial infections. This was evident in the present study with substantial isolation of this organism in cases of neonatal sepsis.

The most effective antibiotic for gram negative isolates was imipenem, while the most effective antibiotic for gram positive isolates was vancomycin. Reserve drugs like linezolid and pristinomycin have not yet developed resistance[42]. Most of the organisms had good sensitivity to amikacin and ciprofloxacin. It is therefore necessary to generate hospital data on antimicrobial sensitivity of common isolates, provide timely sensitivity report and advise them regarding judicious use of antibiotics.

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Table 1: Blood culture positivity in EOS & LOS

Blood Culture	EOS (%)	LOS (%)	Total (%)
Positive	66 (34.74)	41(40.20)	107 (36.64)
Negative	124 (65.26)	61(59.80)	185 (63.36)
Total	190	102	292 (100)

Table 2: Microbial isolates from blood cultures of neonatal septicemia

(n = 107)

Organisms	EOS (%)	LOS (%)	Total
Gram positive organisms	11 (16.67)	19 (46.34)	30 (28.04)
Staphylococcus aureus	01	04	05
Staphylococcus epidermidis	02	10	12
Staphylococcus hemolyticus	00	04	04
Enterococcus fecalis	07	00	07
Streptococcus pneumonia	01	00	01
Streptomyces spp	00	01	01
Gram negative bacilli	55 (83.33)	18 (43.90)	73 (68.22)
E. coli	04	02	06
Klebsiella pneumonia	21	00	21
Klebsiella aerogens	02	00	02
Citrobacter fruendii	02	00	02
Enterobacteraerogens	00	02	02
Salmonella Typhi	02	00	02
Acinetobacter baumannii	14	03	17
Acinetobacter woffii	00	03	03
Pseudomonas aeruginosa	10	08	18
Others		4 (9.76)	04 (3.74)
Candida albicans	00	04	04
Total	66 (61.68)	41 (38.32)	107 (100.00)

Table 3: Antimicrobial sensitivity of enterobacteriacae isolates (n=35)

Drugs	Klebsiellapneumoniae n=21 (%)	Klebsiellaaerogens n=2 (%)	E. coli n=6 (%)	Citro. fruendii n=2 (%)	Entero. aerogens n=2 (%)	S. Typhi n=2 (%)	Total enterobact-eriaceae isolates (n= 35) (%)
Ampicillin	0	0	0	0	0	2(100)	2 (5.71)
Amoxyclav	0	0	2(33.33)	0	0	-	2 (6.06)
Cefuroxime	0	0	2(33.33)	0	0	-	2 (6.06)
Cefoperazone	0	0	2(33.33)	0	0	-	2 (6.06)
Cefotaxime	5(23.81)	0	4(66.67)	1(50)	0	2(100)	12 (34.28)
Piperacillin	5(23.81)	0	4(66.67)	1(50)	0	-	10 (33.33)
Piperacillin + tazobactam	21(100)	2(100)	5(83.33)	1(50)	2(100)	-	31 (93.93)
Imipenem	21(100)	2(100)	6(100)	2(100)	2(100)	-	33 (100)
Aztreonam	5(23.81)	0	2(33.33)	0	0	-	7 (21.21)
Gentamicin	4(19.05)	0	2(33.33)	1(50)	0	-	7 (21.21)
Amikacin	10(47.62)	1(50)	6(100)	1(50)	2(100)	-	20 (60.60)
Tobramycin	7(33.33)	0	4(66.67)	0	0	-	11 (33.33)
Netilmicin	8(38.10)	0	4(66.67)	0	1(50)	-	13 (39.39)
Kanamycin	4(19.05)	0	1(16.67)	0	0	-	5 (15.15)
Ciprofloxacin	10(47.62)	0	3(50)	1(50)	2(100)	2(100)	18 (51.43)

Table 4: Antimicrobial sensitivity of Acinetobacter spp. and Ps. aeruginosa (n=38)

Drugs	Acinetobacter baumannii n=17 (%)	Acinetobacter lwoffii n=03 (%)	Pseudomonas aeruginosa n=18 (%)
Ceftazidine	4(25.52)	0	5(27.78)
Cefotaxime	4(25.52)	0	3(16.67)
Cefepime	4(25.52)	0	5(27.78)
Piperacillin	3(17.65)	0	7(38.89)
Piperacillin + tazobactam	14(82.35)	1(33.33)	12(66.67)
Imipenem	15(88.24)	3(100)	16(88.89)
Gentamicin	6(35.29)	0	7(38.89)
Amikacin	10(58.82)	1(33.33)	11(61.11)
Tobramycin	6(35.29)	0	7(38.89)
Ciprofloxacin	12(70.59)	2(66.67)	12(66.67)

Table 5: Antimicrobial sensitivity of gram positive cocci (n= 29)

Drugs	Staph. aureus n=5 (%)	Staph. epider-midis n=12 (%)	Staph. hemolylti-cus n=4 (%)	Entero. fecalis n=7 (%)	Strepto. pneumo-niae n=1 (%)	Total gram positive cocci n=29 (%)
Cefoxitin	0	5 (41.67)	0	--	--	5 (23.81)
Gentamicin	3 (60)	4 (33.33)	2 (50)	3 (42.86)	-	12 (42.86)
Amikacin	5 (100)	8 (66.67)	4 (100)	-	-	17 (80.95)
Tobramycin	2 (40)	8 (66.67)	3 (75)	-	-	13 (61.90)
Netilmicin	2 (40)	8 (66.67)	2 (50)	-	-	12 (57.14)
Ciprofloxacin	2 (40)	10 (83.33)	2 (50)	4 (57.14)	-	18 (64.28)
Vancomycin	5 (100)	12 (100)	4 (100)	7 (100)	1(100)	29 (100)
Pristinomycin	5 (100)	12 (100)	4 (100)	7 (100)	1(100)	29 (100)
Linezolid	5 (100)	12 (100)	4 (100)	7 (100)	1(100)	29 (100)

Table 6: Association of mortality of blood culture positivity with neonatal mortality

Blood culture	Mortality		
	Yes(%)	No(%)	Total
Positive Blood culture	50(46.73)*	57(53.27)	107
Negative Blood culture	21(11.35)*	164(88.65)	185
Total	71 (24.31)	221(75.69)	292

*x^2=46.10, p=0.0000 df=1

Table 7: Gram negative and gram positive isolates in different studies

Authors	Year	Gram negative organisms (%)	Gram positive organisms (%)
Smith et al[31]	1956	80	20
Silverman et al[32]	1969	68	32
Choudhary et al[33]	1975	69	31
Somu et al[34]	1976	64.3	35.7
Singh M[35]	1978	58.2	41.8
Mishra et al[21]	1985	71.7	28.3
Khatua et al[15]	1986	85	15
Mathur et al[36]	1994	87.1	12.9
Kaushik et al[13]	1998	50	50
Ghanshyam et al[37]	2002	60	40
Agnihotri et al[38]	2004	58.5	41.5
Movahedian et al[39]	2006	72.1	27.9
Bhattacharjee et al[40]	2008	73.04	26.96
Guleria s et al[41]		42.8	50.2
Present study		68.22	28.04

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