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Original Research Article

A study of infections in neonatal intensive care unit at a tertiary care hospital

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ABSTRACT

Background: As infection is a major cause of morbidity and mortality in neonates, early diagnosis and prompt treatment can prevent its serious consequences. The present study was conducted to determine the prevalence of infections in neonatal intensive care unit (NICU) of a tertiary care hospital and to study their risk factors, causative organisms and antimicrobial susceptibility pattern.
Methods: Appropriate samples were collected from all neonates with clinical signs and symptoms of infections. Isolation of microorganisms, their identification and antimicrobial susceptibility was done according to standard microbiological techniques.
Results: Among 1210 neonates admitted in the NICU, 393 (32.4%) were clinically suspected infections. The prevalence of Septicemia, Pneumonia, and Meningitis were 6%, 1.5%, 0.7% respectively. The predominant organisms causing neonatal infection were Gram negative bacteria followed by fungi and Gram positive bacteria.
Among Gram negative bacteria, the antimicrobial resistance was highest for third generation Cephalosporins [Ceftazidime (81.1%), Cefotaxime (60.3%)]. In Gram positive bacteria highest resistance was observed for Penicillin and Ampicillin (91.3%). Methicillin resistance was observed in 91.6% of Coagulase negative *Staphylococci* (CoNS). All isolates of *Candida parapsilosis* were sensitive to Fluconazole, Voriconazole but resistant to Amphotericin B.
Predominant risk factors were low birth weight (87.7%) and prematurity (75%). Maternal risk factors were pregnancy induced hypertension (13.4%) and premature rupture of membranes (PROM) (10.1%). The case fatality rate was 20.7%.
Conclusions: There is a need of strict infection control measures and rational antibiotic policy to reduce the economic burden of hospital and community due to neonatal infections.

Keywords: Neonatal infection, Meningitis, Pneumonia, Risk factors, Septicemia

INTRODUCTION

Advances in newborn intensive care have allowed the survival of infants but at the same time created risks for hospital acquired infections, which are the major cause of mortality. About 20% of very low birth weight, preterm infants suffer serious systemic infections during their hospital stay.[1]

Neonatal infections occur as early or late infections. Their timing gives clues for determining causative agents. The pattern of organisms causing infections changes from place to place and also in the same place over a period of time. In addition, the emergence of resistance of these organisms to antimicrobial agents has become a major threat. Early treatment and appropriate use of antibiotics would reduce the risk of severe morbidity and mortality due to infections, and also the emergence of multi-drug resistant organisms. For the success of early empiric treatment, periodic evaluation of cases to assess any changing trends in the infecting organisms and their antimicrobial susceptibility is important.

The study was conducted to determine the prevalence of infections in neonatal intensive care unit (NICU) patients and their associated risk factors, to identify pathogens causing infections with their antimicrobial susceptibility pattern.

METHODS

A prospective study was carried out at a Microbiology Department of a tertiary care hospital over a period of one year. All patients admitted in NICU with clinical signs and symptoms of infections like poor feeding, lethargy, hypothermia or fever, sclerema, jaundice, bradycardia or tachycardia, respiratory distress, abdominal distension, vomiting, convulsions, oliguria were included.

Depending upon the time of onset of clinical signs and symptoms the neonates were categorized as, Early onset (0-3 days after birth) and Late onset (>3 days after birth). A detail clinical history was taken including risk factors.

Appropriate samples were collected from patients depending upon clinical symptoms and signs with all aseptic precautions.

1 ml blood was collected into the BD BACTEC™ PedsPlus™/ F culture bottles which were loaded in BACTEC machine as per manufacturer's instructions. Cerebrospinal fluid (CSF) was collected through lumbar puncture with all aseptic precautions in sterile test tube. Tracheal aspirates were collected by suctioning through endotracheal tube of patients who were on mechanical ventilation. In all suspected cases of Pneumonia blood was collected.

Further processing and identification of growth was done according to standard microbiological techniques.[2]

Antibiotic susceptibility testing was done by Kirby-Bauer disc diffusion technique, as per the Clinical and Laboratory Standards Institute (CLSI) guidelines.[3] For Staphylococcus *spp*. Vancomycin E strips were used for determination of minimal inhibitory concentration (MIC) as per CLSI guidelines[3].All the isolates of *Klebsiella pneumoniae* and *E. coli* were screened for extended spectrum beta lactamase (ESBL) production and the confirmation was done by combined disk diffusion test as per CLSI guidelines.[3] All the non-fermenters were screened for metallo beta lactamse (MBL) production and confirmed by combined disk diffusion test.[4]

All Candida isolates were tested for Fluconazole (25µg), Voriconazole (1µg) susceptibility by disc diffusion test and for Amphotericin B by E strip (Himedia) as per CLSI guideline.[5,6]

Data was analyzed by using Graft Pad Prism Version 5.01. Comparison between different groups of bivariate qualitative data was done by Chi-square test. The p value <0.05 was considered statistically significant.

RESULTS

During the study period 1210 neonates were admitted in NICU. Of these, 393 (32.4%) neonates had clinical signs and symptoms suggestive of infections.

Infections were more common in male (56.7%), preterm (75%) and low birth weight (<2500 gm) babies (87.7%). Majority of the infected babies were inborn (74.5%) and born vaginally (81.9%) (Table 1).

Table 1: Demographic details of neonates (n=393).

Characteristics		No of neonates (%)
Gender	Male	223 (56.7%)
	Female	170 (43.2%)
Gestational age	Preterm	295 (75%)
	Full term	98 (24.9%)
Birth weight	<2500 gms	345 (87.7%)
	>2500 gms	48 (12.2%)
Type of delivery	Vaginal delivery	322 (81.9%)
	Caesarean section	71 (18 %)
Place of delivery	Inborn	293 (74.5%)
	Out born	100 (25.4%)

Septicemia was most common infection followed by Pneumonia and Meningitis. Out of the 393 neonates, 101 (25.6%) neonates were culture positive (Table 2).

Table 2: Confirmed infections in the neonates.

Type of infection	Clinically suspected cases	Culture positive cases (%)
Septicemia	268	73 (27.2%)
Pneumonia	78	19 (24.3%)
Meningitis	47	9 (19.1%)
Total	393	101 (25.6%)

As we couldn't get tracheal aspirates from each clinically suspected pneumonia case, confirmation of Pneumonia was done on the basis of isolation of pathogen from blood culture.

The prevalence of culture proven septicemia, Pneumonia and Meningitis were 6% (73/1210), 1.5% (19/1210) and 0.7% (9/1210) respectively.

The predominant risk factors were low birth weight (87.7%) and prematurity (75%) (Table 3).

Birth asphyxia, PROM and Pregnancy induced hypertension were statistically significant.

Table 3: Risk factors in neonatal infections.

Parameters		Total (%)	Culture positive (n=101)	Culture negative (n=292)	Statistical significance (Chi Square Test)
Neonatal factors					
Gestation	<37 weeks ≥ 37 weeks	295(75%) 98(24.9%)	83 18	212 80	P >0.05 Not Significant
Birth weight	<2.5 kg ≥ 2.5 kg	345 (87.7%) 48(12.2%)	93 8	252 40	P >0.05 Not Significant
Birth asphyxia	Yes No	79 (20.1%) 314(79.8%)	11 90	68 224	P <0.05 Significant
Mechanical ventilation	Yes No	68(17.3%) 325(82.6%)	13 88	55 237	P >0.05 Not Significant
Maternal factors					
PROM	Yes No	40(10.1%) 353(89.8%)	16 85	24 268	P <0.05 Significant
Meconium stained liquor	Yes No	37(9.4%) 356(90.5%)	7 94	30 262	P >0.05 Not Significant
Pregnancy induced hypertension	Yes No	53(13.4%) 340(86.5%)	7 94	46 246	P <0.05 Significant

Table 4: List of all organisms isolated from neonatal infections.

Organisms (Total No.)	Septicemia			Pneumonia			Meningitis		
Gram negative bacteria (n=53)	30			18			5		
	Early onset	Late onset	Total	Early onset	Late onset	Total	Early onset	Late onset	Total
K. pneumoniae (n=20)	10	4	14	5	1	6	0	0	0
A. baumannii (n=16)	1	5	6	0	8	8	0	2	2
P. aeruginosa (n=11)	2	4	6	1	2	3	0	2	2
E. cloacae (n=3)	2	1	3	0	0	0	0	0	0
E. coli (n=2)	1	0	1	1	0	1	0	0	0
C. koseri (n=1)	0	0	0	0	0	0	0	1	1
Fungi (n=25)	25			0			0		
Candida parapsilosis (n=25)	3	22	25	0	0	0	0	0	0
Gram positive bacteria (n=23)	18			1			4		
CoNS (n=12)	2	10	12	0	0	0	0	0	0
E. faecalis (n=9)	3	2	5	1	0	1	2	1	3
S. aureus (n=2)	1	0	1	0	0	0	0	1	1
Total	25	48	73	8	11	19	2	7	9

Among 73 culture confirmed septicemia, 25 (34.2%) neonates had early onset while, 48(65.7%) neonates had late onset septicemia.

Gram negative bacteria [n=30, (41%)] were the predominant pathogen causing septicemia followed by fungi [n=25, (34.2%)] and Gram positive bacteria [n=18, (24.6%)]. The most common pathogen causing EOS was *K. pneumoniae* [n=10, (40%)], however in LOS, *Candida parapsilosis* [n=22, (45.8%)] and *CoNS* [n=10, (20.8%)] were predominant pathogens.

Out of 9 culture confirmed meningitis, 2 neonates had early onset while, 7 had late onset meningitis. *A. baumanni*, *P. aeruginosa* and *E. faecalis* were the predominant organisms causing late onset meningitis.

Out of 78 clinically suspected pneumonia cases, 19 neonates had blood culture confirmed pneumonia including 8 (42.1%) early onset and 11 (57.8%) late onset pneumonia. *A.baumannii* [n=8, (42.1%)] was predominant pathogen followed by *K.pneumoniae* [n=6, (31.5%)].

Table 5: Organisms isolated from tracheal aspirates.

Organisms	No. (%)
Acinetobacter baumannii	13 (54.1%)
Klebsiella pneumoniae	5 (20.8%)
Pseudomonas aeruginosa	2 (8.3%)
Enterobacter cloacae	1 (4.1%)
Citrobacter koseri	1 (4.1%)
Escherichia coli	1 (4.1%)
Enterococcus faecium	1 (4.1%)
Total	24

Out of the 27 tracheal aspirate cultures, 20 had significant growth.

24 pathogens were isolated from 20 tracheal aspirates culture. 4 neonates had polymicrobial infection (2 organisms) (Table 5).

5 neonates had both tracheal aspirate and blood culture positive. 4 of them had similar pathogens grown from blood culture and tracheal aspirate culture.

Among Gram negative bacteria, overall, highest resistance was observed for, third generation Cephalosporins [Ceftazidime (81.1%) and Cefotaxime (60.3%)].

Out of the 20 isolates of *K. pneumoniae*, 9 (45%) isolates were ESBL producers. Out of the 27 nonfermenters [*A. baumannii* (n=16) and *P. aeruginosa* (n=11)] 3 (11.1%) isolates were MBL producers. All isolates were sensitive to Colistin and Polymixin B (Table 6).

Among the Gram positive bacteria, overall, the highest resistance was observed for Penicillin (91.3%) and Ampicillin (91.3%).11 (91.6%) isolates of *CoNS* were Methicillin resistant. All isolates were susceptible to Vancomycin and Linezolid (Table 6).

Table 6: Antimicrobial resistance pattern of Gram negative bacteria (GNB).

Antibiotics	*K. pneumoniae* (n=20)	*A. baumannii* (n=16)	*P. aeruginosa* (n=11)	*E. cloacae* (n=3)	*E. coli* (n=2)	*C. koseri* (n=1)	Total No of GNB (N=53)
Ceftazidime	16	12	11	2	1	1	43(81.1%)
Cefotaxime	15	13	NT	2	1	1	32(60.3%)
Gentamicin	10	9	9	1	0	0	29(54.7%)
Cotrimoxazole	12	12	NT	2	0	0	26(49%)
Piperacillin- Tazobactum	5	9	6	1	0	0	21(39.6%)
Amikacin	3	8	7	1	0	0	19(35.8%)
Ciprofloxacin	5	10	2	1	0	0	18(33.9%)
Meropenem	0	7	4	0	0	0	11(20.7%)

NT: Not tested

Table 7: Antimicrobial resistance pattern of Gram positive cocci (GPC).

Antibiotics	*CoNS* (n=12)	*Enterococcus faecalis* (n=09)	*S.aureus* (n=2)	Total No. of GPC (n=23)
Penicillin	12	8	1	21 (91.3%)
Ampicillin	12	8	1	21 (91.3%)
Amoxicillin-clavulanic acid	11	8	0	19 (82.6%)
Ciprofloxacin	2	6	0	8 (34.7%)
Cotrimoxazole	3	NT	01	4 (17.3%)
Gentamicin	3	NT	0	3 (13%)

NT: Not tested

All isolates of *Candida parapsilosis* were sensitive to Fluconazole, Voriconazole but were resistant to Amphotericin B (MIC-1.5 µg/ml).

The case fatality rate was 20.7%. It was higher in late onset infection (22.7%) as compared to early onset infection (17.1%) (Table 8).

Table 8: Outcome of neonates with confirmed infection.

	Early onset infection	Late onset infection	Total
Cured	29 (82.8%)	51 (77.2%)	80 (79.2%)
Died	6 (17.1%)	15 (22.7%)	21(20.7%)
Total	35	66	101

DISCUSSION

Neonates are immunocompromised individuals who are prone to infection with significant morbidity and mortality. When pathogenic bacteria gain access into the blood stream, they may cause overwhelming infection without much localization (Septicemia) or may get predominantly localized to the lung (Pneumonia) or the meninges (Meningitis).[7] The pattern of organisms causing infections varies from place to place, even in same place over a period of time due to the changing pattern of antibiotic use.

In present study 393 (32.4%) neonates had clinical signs and symptoms suggestive of infections. Shah et al and Mehar et al from India have reported the rate of infections in NICU as 21.22% and 50.9% respectively.[8,9] The frequency of infections in NICUs varies from 6% to 25% in the United States and from 8% to 10% in Europe.[10] These differences could be a reflection of the different population characteristics and varying predisposing factors.

In our study, infections were more common in male (56.7%), LBW (87.7%) and preterm (75%) neonates. Similar predominance of infections has been reported in other studies.[9,11] Male preponderance in neonatal septicemia may be linked to X-linked immune regulatory genes resulting in susceptibility to infections in males.

Preterm and low birth weight neonates are more susceptible to infection due to underdeveloped innate immunity and their fragile, easily damaged skin. These neonates are dependent for survival on therapeutic interventions and thus acquire infections.[12] Majority of infected neonates were born vaginally (81.9%) indicating vertical transmission from maternal genital tract. Majority of neonates were inborn (74.5%). Our hospital is a tertiary care referral hospital for both obstetrics and pediatric cases and it has many late referral cases with adverse intrapartum and neonatal risk factors.

101 (25.6%) neonates had culture confirmed infections in present study. The prevalence of culture confirmed septicemia in our NICU was 6%. Movahedian AH et al and Kuruvilla et al reported the prevalence of neonatal septicemia as 6.6% and 4.4%.[13,14] In developed countries the estimated incidence of pneumonia in full term neonates is less than 1%. However in low birth weight neonates the incidence may be closer to 10%.[15] In developing countries, almost 8, 00,000 neonatal deaths occur each year from acute respiratory infection, mostly pneumonia.[16] In our study the prevalence of pneumonia was 1.5%.

The prevalence of meningitis in our NICU was 0.7% which is comparable to study by Bentlin et al (0.6%).[17] The study from Africa and Asia reported incidence of meningitis ranging from 0.8 to 6.1 per 1000 live births.[18]

Neonatal risk factors observed in our study were low birth weight (87.7%), prematurity (75%), birth asphyxia (20.1%), mechanical ventilation (17.3%). Similar risk factors were observed by Tallur et al and West BA et al.[19,20] Other neonatal risk factors reported are umbilical catheterization, and formula feeding.[21]

Maternal risk factors observed were, pregnancy induced hypertension (13.4%), PROM (10.1%), and meconium stained amniotic fluid (9.4%). Similar maternal risk factors were reported by Shah et al, and West BA et al.[8,20]

Among these risk factors, Birth asphyxia, PROM and Pregnancy induced hypertension were statistically significant ($P<0.05$).

Majority of septicemia cases were of late onset (65.7%) which was also shown by Gosalia et al.[21] Ibrahim et al reported more number of EOS cases.[22] The reason for high percentage of LOS cases may be due to high exposure of premature, low birth weight babies to invasive procedures like Intravenous catheters and endotracheal intubation.

The predominant organisms causing neonatal septicemia in our study were Gram negative bacteria (41%) followed by fungi (34.2%) and Gram positive bacteria (24.6%). Movahedian et al and Desai et al also reported Gram negative bacteria as a predominant pathogen in neonatal septicemia.[13,23] However Ballot et al have reported Gram positive bacteria as predominant cause of neonatal septicemia.[24]

The microbial profile of neonatal septicemia is constantly changing with advances in early diagnosis and treatment of septicemia. In the preantibiotic era the most common organisms causing septicemia were Gram positive cocci like *Streptococcus pyogenes* and *Pneumococci*. With the introduction of antimicrobial agents, Gram negative bacteria like *E. coli*, *Pseudomonas* and *Klebsiella* became the major threat to the ill, fragile and debilitated newborns in the NICU.[25]

In our study most common pathogen in early onset septicemia was *Klebsiella pneumoniae* (40%). Most of the studies in India have reported *K. pneumoniae* as a predominant pathogen in EOS.[19,21,26] In Western countries *GBS (Group B Streptococcus)* is the most frequently isolated organism in EOS. Schuchat et al reported *GBS* as the most common etiological agent of EOS.[27]

The most common pathogens causing late onset septicemia were *Candida parapsilosis* (45.8%) followed by *CoNS* (20.8%). Similar predominance of *CoNS* and *Candida spp.* in LOS was reported by Ahmed et al.[28]

Common use of broad spectrum antibiotics, presence of central line catheters, endotracheal intubation, prematurity, respiratory distress syndrome and prior

fungal colonization are the risk factors for neonatal Candidemia.[29] Though *Candida albicans* is the most common species isolated there is increase in prevalence of non-albicans Candida septicaemia.[30] This could be due to increasing use of triazole antifungal agents.

The increased frequency of *CoNS* nosocomial infection is concurrent with the advances in neonatal medicine and technology. There are now more premature infants surviving at younger gestational ages and at lower birth weights.

The predominant organism isolated from tracheal aspirate was *A. baumanii* (54.1%) followed by *K. pneumoniae* (20.8%). Tripathi et al reported *Klebsiella spp.* (32.8%), *E. coli* (23.2%) and *Acinetobacter spp.* (17.8%) as the common organisms isolated from tracheal aspirate of neonates with ventilator associated pneumonia.[31]

The most common pathogen responsible for early onset pneumonia was *K. pneumoniae* (n=5) and for late onset pneumonia was *A. baumannii* (n=8). Mathur NB et al from India have also reported *Klebsiella* as predominant pathogens causing neonatal pneumonia.[32] Webber et al reported *group B Streptococci* as predominant pathogen in early onset pneumonia while *Staphylococcus epidermidis* in late onset pneumonia.[33]

Majority of cases of Meningitis were of late onset (n=7 out of total 9 cases). Bentlin et al have also reported (21 out of 22) late onset of neonatal meningitis cases.[17] These low rates of positive culture in early infection may be due to hemodynamic instability which delays lumbar puncture and use of antibiotics before the lumbar puncture which interfere with bacterial growth.[34]

The pathogens causing meningitis in neonates were *Enterococcus faecalis*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Citrobacter koseri*, and *Staphylococcus aureus*. Garges et al reported *Group B Streptococci* and *E. coli* as the major etiologic agents in neonatal meningitis.[34] However, Aletayeb et al reported *Klebsiella pneumoniae* and *Enterobacter spp.* as the most common pathogens involved in neonatal bacterial meningitis.[35]

Among Gram negative bacteria, highest resistance was observed for, third generation Cephalosporins [Ceftazidime (81.1%) and Cefotaxime (60.3%)]. All Gram negative bacteria were sensitive to Polymixin B and Colistin. Aurangzeb et al also showed high resistance to Ceftazidime (71.6%), Cefotaxime (55.2%) and Gentamicin (43.2%).[36]

Out of the 20 isolates of *K. pneumoniae*, 9 (45%) isolates were ESBL producers. Infection caused by ESBL producing organisms are a significant cause of neonatal morbidity and mortality all over the world. The incidence of infections caused by ESBL producing organisms varies considerably in different geographical area and in different institutes. In a study conducted in Nagpur, India ESBL production was shown by 58.3% of *K. pneumoniae* and 50% of *E. coli* isolates. In our study 45% of *K. pneumoniae* were ESBL producers.[37]

11.1% of nonfermenters were MBL producers. Emergence of MBL mediated resistance is of serious concern. Carbapenems are effective therapeutic agents against highly resistant pathogens such as *Pseudomonas aeruginosa* and *Acinetobacter spp.*, so their resistance among these pathogens would have limited the therapeutic options.

Among the Gram positive bacteria, the highest resistance was observed for Penicillin and Ampicillin (91.3%) followed by Amoxicillin-clavulanic acid (82.6%) Methicillin resistance was observed in 91.6% of *CoNS*. All Gram positive bacteria were sensitive to Vancomycin and Linezolid. Shaw et al have reported a high degree resistance to Penicillins and Cephalosporins however glycopeptides and monobactum as effective antimicrobial agents.[38]

All *Candida parapsilosis* isolates were sensitive to Fluconazole and Voriconazole and resistant to Amphotericin B. Pfaller MA et al showed Fluconazole and Voriconazole resistance in *Candida parapsilosis* as 3.6% and 1.9% respectively.[39] The in vitro resistance of *Candida parapsilosis* to Amphotericin B has been reported as 2 to 3%.[40]

The case fatality rate in our study (20.7%) is comparable to other studies.[9,14,22] The case fatality rate was higher in late onset infection (22.7%) as compared to early onset infection (17.1%). Ballot et al have also reported higher case fatality rate in late onset infection (19.6%) as compared to early onset infection (6.3%).[24] However higher mortality rate in early onset infection was reported by Jumah et al.[41]

CONCLUSION

Neonatal infections are associated with high mortality every effort must be taken to prevent, recognize and treat infections. As resistance to multiple antimicrobial agents is a great challenge to the effective management of infections, formulation of rational antibiotic policy is important. Also certain preventive measures like hand hygiene, barrier nursing and restricted entries in NICU should be enforced.

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