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Original Article

Neonatal sepsis bacterial isolates and antibiotic susceptibility patterns at a NICU in a tertiary care hospital in western Nepal: A retrospective analysis

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Abstract

Background: Neonatal sepsis is one of the commonest causes of neonatal mortality in the developing world. The neonatal intensive care units (NICUs) today face one common problem of tackling sepsis and neonatologists remain constantly baffled by the changing patterns of microbial flora and their sensitivity patterns. With the neonatal services coming of age in Nepal this retrospective analysis spread over a period of six years has become very pertinent.

Materials and methods: We conducted a retrospective study over a period of six years to study the prevalence of different organisms causing septicaemia in the community and at our hospital and the antibiotic susceptibility pattern. In all 265 cases of suspected sepsis were screened using a panel consisting of CRP, ANC and I/T ratio and subsequently confirmed by cultures. The cases were early onset (n=44), late onset (n=56) and nosocomial groups (n=40). The data for the intramural (n=32) and extramural (n=68) cases was analysed separately.

Results: One hundred nineteen cultures out of the 131 positives were obtained from blood (44.92%) and the remaining were isolated from urine (6.11 %) and CSF (4.58 %). The most common organism to be isolated was staphylococcus aureus (42.75%) followed by *klebsiella pneumoniae* (18.32%)and *escherechia coli* (12.21%). Staphylococcus was isolated from 36.84%, 45.16% and 31.81% of the cultures obtained from neonates in the in-born, out-born and the nosocomial groups respectively while *klebsiella pneumoniae* [18.32 %] was seen in 21.05 %, 17.39 % and 36.36 % in each of the three groups. *Pseudomonas aeruginosa* [6.11 %] was isolated from 13.64 % of the nosocomial cultures compared to 8.7 % of the out-borns while it was not seen in the in-borns. Other organisms isolated were much less in number, included - pathogenic streptococci, *acinetobacter* and *enterobacter* species. Coagulase negative staphylococci (CoNS) was seen in 4.39 % [n=4] and 9.09 % [n=4] of the same groups respectively. The gram positive organisms displayed a high degree of resistance to most penicillins and cephalosporins but glycopeptides and monobactams were effective in them. There was a high incidence of resistance noted with most third generation cephalosporins and aminoglycosides amongst most gram negative organisms where-in cefepime and imepenem were effective in most cases.

Conclusions: Staphylococcal sepsis is not only common in community acquired infections but also in nosocomial sepsis. There is an emerging resistance to cephalosposrins probably attributable to extended spectrum betalactamases. Further large-scale multicentre studies are required to generalise the data for the whole country.

Key words: neonatal sepsis, culture and susceptibility patterns.

Neonatal sepsis is one of the commonest causes of neonatal mortality in the developing world accounting for 30 -50 percent of 5 million neonatal deaths per year.[1] The incidence of neonatal septicaemia is 1 to 10 per thousand live births.[2] However the incidence of the latter varies with the geographical area, the socio-economic structure and various customs and practices in the perinatal period.[3] The neonatal intensive care units (NICUs) today face one common problem of tackling sepsis. A strictly endorsed aseptic measures policy is the best hope for the solution to the latter. Nevertheless, neonatologists remain constantly baffled by the changing patterns of microbial flora and their sensitivity patterns, making neonatal septicaemia a difficult problem to tackle. There are a number of studies of the microbial flora and sensitivity patterns in neonates from other parts of the world but none so far in Nepal. With the neonatal services coming of age in Nepal this retrospective analysis spread over a period of six years has become very pertinent.

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Materials and methods

We conducted a retrospective analysis of the cases admitted to the neonatal intensive care unit (NICU) of Manipal Teaching Hospital, Manipal College of Medical Sciences, Pokhara, Nepal and studied the culture and sensitivity pattern of neonatal sepsis during the period starting from 1st January 2000 to 31st December 2005. The management of the cases was according to the written standard protocols in the unit. The neonates who presented with signs and symptoms of septicaemia, with/without pneumonia and/or meningitis were studied in retrospect and a detailed record of the maturity, age at onset, sex, birth weight (weight on admission for home deliveries), symptoms and signs along with the maternal risk factors was made. The cases with suspect sepsis were screened using C-reactive protein (CRP, quantitative nephalometric test), the total leucocyte (WBC) count, absolute Neutrophil count (ANC) and the presence of toxic granules in the WBC's. The CRP was done after four hours of life in case of in-born babies with risk factors with or without symptoms and on admission for out-born babies. Blood culture (1 ml blood in 5 ml liquid broth, followed by inoculation in the appropriate culture media) was done in all the cases while cerebrospinal fluid (CSF) was analysed only in those neonates with suspected meningitis and the ones with late onset septicaemia. Urine microscopy and cultures were done routinely for all neonates. Other investigations were done as required. The cases with suspect sepsis were started empirically on antibiotics, which were changed according to the sensitivity pattern (Kirby-Bauer method) once the culture report was available or stopped after two days if both the screen and cultures were negative, while in case of a positive screen with negative cultures the antibiotics were given for seven days. Meanwhile the clinical status of the neonate was closely observed. Deteriorating clinical picture or no response to antibiotic therapy over a reasonable period warranted repeat cultures. A note of whether, repeated isolation of same or different organism or for that matter polymicrobial isolates in the same case, was taken into consideration, when calculating the incidence of septicaemia. The results were categorized into intramural or in-born babies, extramural or out-born babies, early onset (culture positive within 7 postnatal days) late onset (culture positive after 7 postnatal days) and nosocomial sepsis (defined as a organism being isolated after the fourth day of admission, wherein the initial screen and culture was negative). The data for the in-born and the out-born babies was analysed separately. We observed a vast differences in the presentation and the culture sensitivity pattern in between the groups, namely intramural, extramural and the nosocomial. The skin contaminants were disregarded. The following aspects were studied:

1. The prevalence of different organisms causing septicaemia in the community and at our hospital.
2. The antibiotic susceptibility pattern.

Observation and results

In all 265 neonates (male: female = 1.86:1) were screened for sepsis, out of which 183 (69.06 %) resulted a positive screen. Out of these 183 neonates, 117 neonates had positive cultures, but when the contaminants/skin commensals (B. subtilis, micrococcus spp. etc) were excluded,100 (54.64 %) nenates had pathogenic organisms. The total number of organisms isolated was 131. Table 1 summarises the comparison of various patient characteristics, isolation parameters and the outcome in the three categories viz. in-born, out born and the nosocomial sepsis. Among the culture positive neonates, 32 were in-house deliveries, and the rest were out-born There were obvious significant differences in the mean age on admission, maturity , birth weight and the day of life on culture isolation between the in-born group and the other two groups ($p < 0.001$). There was no significant difference in the parameters used for septic screening in either of the groups (Table 1). Except the fact that the mean (± SD) day of admission in the nosocomial group, the same in the other two groups, was comparable. In all there were 131 isolates, amongst 100 subjects, from blood, cerebrospinal fluid (CSF) and urine, out of which 38 (29.0%) were in the in-born babies. Nosocomial sepsis accounted for 44 (33.59 %) of the isolates out of both the in and out-born babies combined. There was evidence of meningitis (microbiological/biochemical proof) in 17 (25.8%) of the out-born babies with a positive blood culture, which was higher than that in the other two categories (Table 1).

However the incidence of an organism actually being isolated from the CSF was only one out 32 in the in-born neonates (3.13 %) compared to 4.41 % (n=3) and 5.0 % (n=2) out-borns and nosocomials respectively. Early onset sepsis accounted for 49.62 % [n=66] of the isolates with the mean age at presentation of 3.96 days (95 % CI = ± 0.97) (Table 2). The frequency of late onset sepsis was also similar with a mean age at onset being 13 days (95% CI = ±1.96) [range = 8 to 25 days.

One hundred nineteen cultures were obtained from blood (44.9% - that is 119 out of the 265 screened): One hundred nineteen cultures were obtained from blood (44.9% - that is 119 out of the 265 screened). 4 of them had simultaneous polymicrobial isolates while 13 had a repeat different organism isolated on a different date. The remaining were isolated from urine [n=7] (6.11 %) and CSF [n=5] (4.58 %). The most common organism to be isolated was staphylococcus aureus (42.75%), followed by *klebsiella pneumoniae* (18.32%) and *escherechia coli* (12.21%) (Fig 1). *Staphylococcus* was isolated from 36.84%, 45.16% and 31.81% of the cultures obtained from neonates in the in-born , out-born and the nosocomial groups respectively. The second most frequent organism to be isolated was *klebsiella pneumoniae* [18.32%] (21.05%, 17.39% and 36.36% in each of the three groups). *Escherechia coli* consisted of 12.21 % of the organisms over all, and was seen in 21.05% of the in-born neonates. *Pseudomonas aeruginosa* was isolated from 13.64% of the nosocomial cultures compared to 8.7% of the out-borns while it was not seen in the in-borns. Pathogenic streptococci (*streptococcus pyogenes*, Group B streptococcus) were seen in 10.5% of the isolates from the in-borns compared to only 2.2% of their out-born counterparts. *Acinetobacter* species accounted for 6.52% and 13.64% of the out-born and nosocomial isolates respectively while the coagulase negative staphylococci (CoNS) was seen in 4.39 % and 9.09 % of the same groups respectively. *Enterobacter* species was seen in 5.26% and 6.52% of the in and out-born isolates (Fig 1). One case of *neisseria gonorrhoeae* was reported in the blood from among the in-born babies whose mother had a history of sexual promiscuity (high vaginal swab also positive). No anaerobic organism or fungemia was reported. No anaerobic organism or fungemia was reported.

The sensitivity pattern of various organisms was also studied in retrospect (Table 3). *Staphylococcus aureus* was 100% resistant to penicillin while a 10 to 25% rate of resistance was also seen with most of the other penicillins and cephalosporins. They were however 100% sensitive to vancomycin and imepenem-cilastin. Among the aminoglycosides amikacin had the highest sensitivity (92%) while 25% of the staphylococci were resistant to gentamycin. A high rate of resistance was also seen with most ciprofloxacin and erythromycin in case of the staphylococcal isolates. The *klebsiella* isolates were 100% sensitive to imepenem-cilastin, while the third and fourth generation cephalosporins as well as ciprofloxacin and ofloxacin were also quite effective. (Table 3) *E. coli* displayed a high resistance to most of the third generation cephalosporins while cefepime fared much better, likewise 87.5% of them were sensitive to amikacin, ofloxacin and aztreonam. High rates of resistance were seen with netlimycin and gentamycin and most of the penicillins with *E. coli*. The graphic representation of the sensitivity pattern of the three most common organisms isolated is shown in Fig 2. *Pseudomonas aeruginosae* isolated in the cases were highly resistant to ceftazidime and piperacillin, however they were more sensitive to amikacin, cefepime and the monobactams. The sensitivity pattern of *acinetobacter* and *enterobacter* was similar with a few minor differences like all isolates of *enterobacter* being sensitive to piperacillin as against 14.3% sensitivity with *acinetobacter*, while *acinetobacter* displayed a better sensitivity to ampicillin, amikacin and netlimycin (71.4% vs. 25%, 71.4% vs. 62.5% and 100% vs. 25% respectively). The streptococcal species (Group A and B) (n=7) were all sensitive to most penicillins, cephalosporins and erythromycin with a comparatively high degree of resistance to aminoglycosides (28.6% to 85.7%). The four cases (3.05%) of coagulase negative staphylococcus (CoNS) were resistant to all antibiotics except vancomycin. The only case of gonococcal isolate was sensitive to all penicillins and cephalosporins. None of the organism were resistant to imepenem-cilastin combination. There was a negligible resistance seen with aztreonam and cefepime.

Table 1: The patient parameters and isolation characteristics of organisms among the various categories in the study

Parameters	In-born (n=32)	Out born (n=68)	Nosocomial (n=40)
Age on admission (days)	2.13 ±1.75	9.38 ± 5.51	5.43 ± 3.21
Birth wt. / wt. on adm. (gms.)	2471.9 ± 653.3	2709.7 ± 821.5	2672 ± 788.4
Maturity (weeks)	36.3 ± 2.8	38.3 ± 3.2	38.8 ± 3.4
DOL (mean ± S.D.)	3.2 ±1.9	10.2 ± 5.6	11.71 ± 5.9
DOL (min)	1	1	3
DOL (max)	7	25	16
DOA (mean ± S.D.)	2.3 ± 1.7	2.4 ± 3.1	5.1 ± 2.4
DOA (min)	1	1	3
DOA (max)	6	13	25
Isolation rates			
Blood %	32 (100%)	66 (97.06%)	36 (90.0%)
CSF * (% of blood c/s + ve)	n=3 (9.38 %)	n=17 (25.76 %)	n=6 (16.67 %)
Urine	1 (3.13%)	6 (8.82%)	4 (10.0%)

DOL = Day of life on isolation of organism.
DOA = Day of admission on isolation of organism.
** Biochemical and/or microbiological proof of meningitis.*

Table 2: The distribution (%) of organisms in early and late onset sepsis in the study

Organism	Early onset (n = 65) [%]	Late onset (n = 66) [%]
Staphylococcus aureus	43.08	42.42
Klebsiella pneumoniae	15.38	21.21
Escherechia coli	12.31	12.12
Pseudomonas aeruginosa	6.15	6.06
Enterobacter spp.	9.23	3.03
Acinetobacter spp.	4.62	6.06
Streptococcal Spp.	7.69	3.03
CoNS *	0	6.06
Neisseria gonorrhoeae	1.54	0

** CoNS = Coagulase negative Staphylococcus.*

Table 3: The antibiotic sesitivity of some of the organisms isolated in all the cases

Organisms (% sensitive) / Drugs	S. aureus [n=56] (%)	E. coli [n=8] (%)	K. pneumoniae [n=25] (%)	P. aeruginosa [n=8] (%)	Enterobacter spp. [n=8] (%)	Acinetobacter spp. [n=7] (%)	Sterptococcus [n=7] (%)
Penicillin	0	0	0	0	0	0	71.4
Ampicillin	0	12.5	58.3	0	25	71.4	71.4
Amox-clav	92.9	-	58.3	-	-	-	100
Cloxacillin	64.3	-	-	-	-	-	100
Piperacillin	36.9	75	58.3	25	100	14.3	-
Cephalhexin	92.9	-	-	-	-	-	100
Cefuroroxime	85.8	50	83.3	75	0	14.3	100
Cefotaxime	78.6	37.5	83.3	75	37.5	14.3	100
Cephazolin	78.6	37.5	75	-	0	-	100
Ceftriaxone	85.8	50	50	25	25	14.3	100
Ceftazidime	-	62.5	58.3	0	75	42.9	-
Cefepime	-	100	83.3	100	100	100	100
Amikacin	96.4	87.5	75	100	62.5	71.4	42.9
Netlimycin	85.6	75	66.7	75	25	100	71.4
Gentamycin	75	62.5	58.3	25	0	100	14.3
Ciprofloxacin	57.4	62.5	91.7	0	25	14.3	100
Ofloxacin	28.6	87.5	91.7	75	87.5	71.4	100
Erythromycin	42.9	-	-	-		-	71.4
Imepenem-cil	100	100	100	100	100	100	100
Aztreonam	-	87.5	83.3	100	100	100	-
Vancomycin	100	-	-	-	-	-	100
Methicillin	11.4	-	-	-	-	-	-

0 = resistant

Fig 1: The distribution of different organisms in the in-born, out-born and nosocomial groups

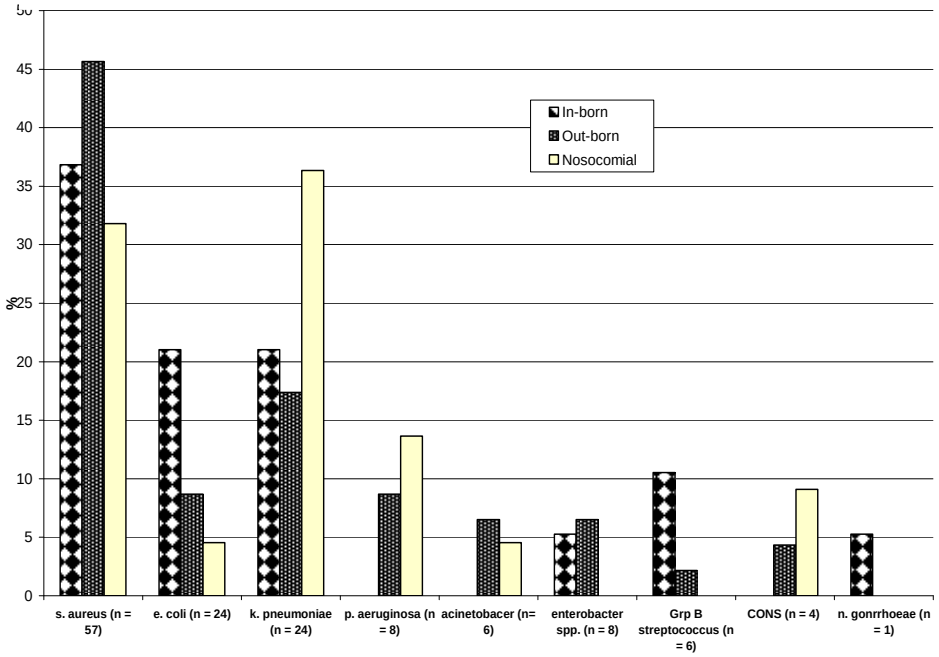
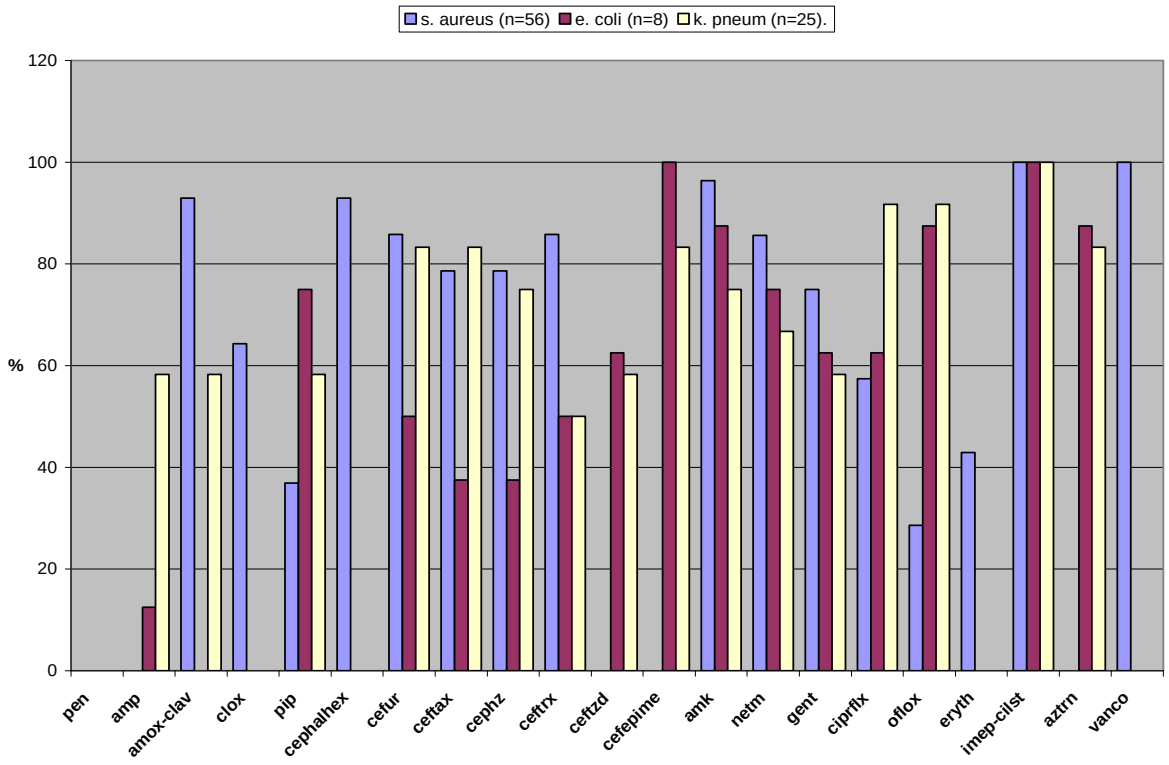


Fig 2: Graphic depiction of the overall sensitivity pattern of the common organisms in



Discussion

Sepsis is one of the important causes of neonatal morbidity and mortality. The risk factors and the clinical presentations of neonatal sepsis are myriad, with differences in the early and late onset types as are the usual organisms responsible for each type**.**[2]

Blood culture is the gold standard for the confirmation of sepsis.[4] In advanced centres, blood culture is positive in 80% of genuine sepsis.[5] However isolation rates vary from 6.7 % to 55.4%.[6,7] Our centre (isolation rate = 44.9%) being a tertiary care, referral hospital in the region, the rate of out-born admissions was higher than that of in-borns Which precludes the calculation of the exact incidence of neonatal sepsis per live births whether early or late-onset. Besides, most of the out-born

babies had received prior antibiotics which made the isolation rates lower than expected. This may also explain the paucity of organisms seen in the CSF study despite a high incidence of other evidence of meningitis viz. leucocytosis and/or hypoglycorrhachia hypoglycorrhachia. Various factors affect the rate of isolation of organisms from the blood.[8,9] These include the degree of bacteraemia/prior antibiotic therapy (false negatives), presence of fastidious organisms (false negatives) the collection process (false positives), the ratio of the volumes of the amount of blood collected and liquid broth, the storage/delay prior to plating (false negative) to mention a few. Catheter tips[10,11], tracheal aspirates[12,13] and urine[14] are other sources of isolation of organism in case of a negative blood culture.

The rate of admission of early (46 %) [n=46] and late onset sepsis as well as the prevalence of organisms and their sensitivity pattern was quite similar, however, there were significant differences between the in-born, out born and the nosocomial groups with respect to the type of organisms and their sensitivity pattern and their respective outcomes. Hence the focus of this retrospective study was in differentiating between these three groups. There are a host of organisms incriminated in neonatal sepsis.[2,5,15] Their relative preponderance varies with the type of onset: early or late. The most common organism to be identified in our study was staphylococcus aureus in all categories except the nosocomial (18.18%) [n=8]**.** The other gram positive organisms to be isolated were streptococcal species and coagulase negative

staphylococcus. The results of our study are very similar with another recent one at Multan, Pakistan.[16] Most of the studies have found a preponderance of gram negative organisms like *klebsiella*, *pseudomonas*, and *enterobacter* species.[16-19] However, the commonest gram positive organism to be isolated was staphylococcus in most of the studies.[16,20] The classical preponderance of group B streptococcus as reported in western literature in early onset sepsis is not observed in this part of the world.[21] CoNS are usually associated with indwelling catheters or central lines[22]. Out of the four cases of CoNS isolated in this study three had exchange transfusions performed on them (nosocomial). All of them were resistant to all antibiotics except vancomycin. Similar report has been provided by a study in Bahrain.[23] In another study, the MRSA/CoNS (most commonly *s. hemolyticus* and *s. epidermidis*), were associated with mecA gene detected by PCR. A PCR assay for detection of the mecA gene in CoNS may be a beneficial adjunct to standard susceptibility testing for timely and reliable detection of methicillin resistance.[24] PCR has been found to be useful in the diagnosis of neonatal sepsis even otherwise.[25,26] In this analysis *klebsiella pneumoniae* was the most common nosocomial organism (36.36%) and the second most frequent in the other two categories. Though the frequency of *klebsiella* was equal to that of e. coli in the in-born category (21.05%), it was more frequently associated with late out born babies (Table 2) Similar results were observed by Kumhar GD et al.[27] The other studies reported *e. coli*, *pseudomonas* and *acinetobacter* species to be common among the gram negative organisms. (Joshi SG et al.)[19]

The gram positive organisms were highly resistant to the penicillins, except for the amoxicillin+clavulanate combination besides being sensitive to monobactams and glycopeptides in our study. Given the large number of methicillin-resistant CoNS, inclusion of vancomycin in empiric therapy for neonates with late-onset septicaemia may be justified.[24] The gram negative organisms were highly resistant to most penicillins because of penicillinase production, but the frequent resistance to most third generation cephalosporins probably attributable to extended spectrum betalactamase (ESBL) production as also observed in another study in neonates.[19] This foretells the use of combination of cephalosporins and "suicide inhibitors" "suicide inhibitors" of ESBL like sulbactam or tazobactam. Cefoperazone + sulbactam or piperacillin + tazobactam combination would be an appropriate choice in most gram negative neonatal sepsis in regions with high prevalence of ESBL.

Neonatal sepsis is associated with high mortality and morbidity. In our study klebsiella and pseudomonas (nosocomial) were associated with high mortality rates (10%). Among the gram positive organisms CoNS was associated with higher mortality rates. Fungemia is not uncommon in nosocomial sepsis with the use of broad spectrum antibiotics and carries a poor prognosis. There were no cases of fungal sepsis reported in the cases studied. Nosocomial sepsis was also associated with higher incidence of meningitis and neurological sequel (7.5%). These results are in concordance with the data available.[28,29]

Conclusion

The cost of treatment in NICU increases manifold with neonatal sepsis and its complications like requirement for prolonged ventilatory support, requirement of newer (costly) antibiotics, intravenous immunoglobulins, colony stimulating factors and blood products. Despite the use of the most modern armamentarium, the combat with neonatal sepsis, more often than not portrays a dismal picture; not to mention the mental, physical and economical burden it lays down on the parents and the government. Thus it should be managed effectively. The knowledge of the prevailing strains and the antibiotic sensitivity patterns in the region is essential to meet the challenge of neonatal sepsis with equal competence and opposing force. The present retrospective study is a step towards achieving the latter; nevertheless large-scale multicentric prospective studies are necessary to identify the changing patterns of the prevailing flora and susceptibility to various antibiotics in the region as the present study had a small study population and yielded a limited variety of pathogens, to really generalise for the whole country. As the age-old adage goes: "prevention is better than cure"- strict asepsis in the NICU is the need of the hour and hand washing still stands out among the other precautions one needs to universally observe inside the NICU!

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