Trends in Incidence of Neonatal Sepsis and Antibiotic Susceptibility of Causative Agents in Two Neonatal Intensive Care Units in Tehran, I.R Iran

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─── ABSTRACT ───

Background: Neonatal sepsis is a worldwide problem that presents a management challenge to care groups for neonates and infants. Early diagnosis and management can considerably decrease the risk of sepsis, and improve the outcome. **Aim:** The aim of the present study was to determine the incidence, causative pathogens, and the antibiotic sensitivity pattern for neonatal sepsis in Iran. **Materials and Methods:** A historical cohort study was conducted on 84 patients with neonatal sepsis who were admitted to the neonatal intensive care unit (NICU) wards of Baqiyatallah and Najmieh University hospitals in Tehran, between 2003 and 2006. Clinical, demographic and laboratory data was collected from medical records. **Results:** Among all the comprised neonates, 44 patients were diagnosed with early-onset sepsis, 23 cases with late-onset sepsis and others with nosocomial sepsis. The most common isolated pathogen in all groups was *Enterobacter*, and was responsible for 31.4%, 47.8% and 41.2% of the episodes of sepsis, according to the sepsis type mentioned above, respectively. Susceptibility of common sepsis related pathogens to imipenem and gentamycin gradually reduced over the years between 2003 and 2006. Total mortality and morbidity rates due to neonatal sepsis were estimated at 27.4% and 89.3%, respectively. Mortality following sepsis was found more in boys (Odds Ratio (OR)=4.897, Conifdence Interval (CI)=95%, *P*=0.031), and those with low birth weight (OR=4.406, CI: 95%, *P*=0.011). Higher sepsis related co-morbidity was found in neonates following cesarean delivery (OR=6.280, CI: 95%, *P*=0.025). **Conclusion:** It seems that the mortality rate in this study was lower than similar studies in Iran and other developing countries. This difference between the mortality rates of the centers in our study and others could be due to the high occurrence of *Enterobacter* infections in the latter and also high resistance of these pathogens to commonly used antibiotics such as β-lactams and aminoglycosides reported in other studies.

Key words:
Antibiotics, neonatal sepsis, neonatal intensive care unit, resistance, susceptibility

INTRODUCTION

Neonatal sepsis (NS) is a worldwide problem that presents a management challenge to care groups for neonates and infants. It has been explained that neonates are at the highest risk for bacterial sepsis, with the prevalence at 1 to 10 per 1000 live births worldwide.[1,2] Existing published data have suggested that sepsis causes about 10% of all maternal, and 26% of all neonatal deaths.[3] Mortality due to sepsis has increased by approximately 13.7% each year over the past 2 decades.[4] Furthermore, the incidence of sepsis in the developing countries is much higher than in the developed world, and in some of these countries, sepsis-related mortality rate was estimated as high as 50% for those infants who are not treated. Thus, this formed a major cause of infant fatality during the first month of life. Advances in diagnosis and management of sepsis can considerably decrease the sepsis complications and improve its outcome, especially in preterm infants.[5] NS incidence increased during the recent years, it may be due to the more common use of invasive procedures and the development of

resistant organisms. Bacterial resistance to commonly used antibiotics has emerged and complicated the management of NS.

Neonatologists who supervise neonatal intensive care unit (NICU) always face a challenge in managing the neonatal infections due to the changing patterns of the microbial flora and their antibiotic sensitivity. A gradual decrease in susceptibility to routine antibiotic is more highlighted in

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infants with lower birth weight and premature infants.[6,7] A few studies were conducted to evaluate the changing trend of the incidence and the antibiotic susceptibility of NS, especially in premature or low birth weight infants in Iran. The aim of the present study was to determine the incidence, causative organisms, antibiotic susceptibility patterns and also the antibiotic sensitivity/specificity patterns for neonatal sepsis among Iranian infants, who were cared for, during a 4-year period (from 2003 to 2006) in two NICUs in Tehran, Iran.

MATERIALS AND METHODS

Study design and patients

The investigation had a retrospective historical cohort plan, which enrolled all neonates with signs of sepsis (blood culture of these infants yielded any microorganism), between March 2003 and July 2006 at the NICU of Baqiyatallah and Najmieh University hospitals in Tehran, Iran.

Inclusion criteria for the study were as follows:
- Only singleton pregnancies;
- Four weeks or younger in age;
- Infants that showed clinical manifestations of NS with atleast one positive blood culture.

Pregnancies complicated by any of the following conditions were excluded from the study:
- Major congenital anomalies;
- Fetal growth restriction;
- Oligohydramnios;
- Suspected chorioamnionitis;
- Antepartum or Intrapartum fever.

The study protocol was approved by the Institutional Review Board and ethic committee of Baqiyatallah University of Medical Sciences, Iran. Besides, all case's parents signed informed consent after explaining the study protocol.

Definitions

Suggestive criteria of sepsis were the following: Fever (rectal temperature >38°C), hypothermia (rectal temperature <36°C), metabolic acidosis (base deficit of ≥4 meq/L), white blood cell (WBC) count ≥30,000/mm or <5,000/ mm, or >25% of immature cells, hypotension (mean blood pressure continues to be less than patient's gestational age after receiving 20 mL/kg of normal saline bodyweight and patient needs ionotropic support) and respiratory symptoms such as tachypnea (>60 breaths/min), oxygen requirement, or need for mechanical ventilation.[8] Early-onset neonatal sepsis (EOS) was characterized as sepsis recognized within the first 72 hours of life and late-onset neonatal sepsis (LOS) was characterized as those that occurred after 72 hours of life.[9] Premature neonate

was defined as near-term (35-37 weeks gestational age) and pre-term was defined as neonate with gestational age lesser than 35 weeks. Furthermore, Nosocomial infection was defined as an infection occurring at any site, which was acquired during hospitalization and resulted from an organism inoculation that was not present in the patient at the time of admission.[10]

Laboratory methods and susceptibility testing

The blood cultures were processed in a conventional 2-bottle broth blood culture system (BACTEC; Becton Dickinson, MD, United States of America). All of the isolates were identified using standard procedures as described by the National Committee for Clinical Laboratory Standards (NCCLS) guidelines. Routine susceptibility testing was performed by the disk diffusion method.[11]

Data collection

Clinical, demographic and laboratory data was collected from the medical records. Maternal data including gestational age at delivery based on last menstrual period, mode of delivery, and prolonged rupture of membranes (PROM) (that was considered as rupture of membranes for more than 18 hours before delivery) was listed on a standardized data collection sheet.[6] Neonatal data including sex, birth weight and composite neonatal morbidity (defined as the presence any of the following: respiratory distress syndrome, poor feeding, jaundice, cyanosis or hypoglycemia) was recorded. Information related to the death in relation to sepsis was also obtained.

Statistical analysis

Summary of measures was reported as mean±standard deviation (SD) for quantitative variables and percentages for categorical variables. The differences in distribution were evaluated using the one-way analysis of variance (ANOVA) test, or Kruskal-Wallis test for continuous variables, and the chi-square test or Fisher's exact test for categorical variables. We used independent T-Test and Chi square (and its non-parametric equal test such as Mann-Whitney U and Fisher Exact) for the analysis, and then based on the results, we included the variable with significance level less than 0.2 into multivariate analysis. Odds Ratio (OR) and 95% Confidence Interval for OR was also calculated. A. value ≤0.05 was considered statistically significant. All the statistical analysis were performed using Statistical Package for Social Sciences (SPSS) version 16.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

During the four year study period, the number of recorded births at the centers of the study was 19,573. 1800 (9.1%) neonates were hospitalized with clinical signs of sepsis.

Eighty-four infants who were admitted to the NICU ward of Baqiyatallah (31 neonates) and Najmieh (53 neonates) university hospitals, were enrolled in the study. Of these 84 infants, 38 (45.2%) were female, and 46 (54.8%) were male. Forty-seven out of 84 patients were delivered as preterm and 37 patients as full-term. Among all comprised neonates, 44 (52.3%) patients were diagnosed with EOS, 23 (27.4%) patients with LOS and others (20.2%) with nosocomial sepsis. The mean of gestational age and birth weight was 35.23±3.34 weeks, and 3.09±1.25 kg, respectively. There were no significant differences between the three groups regarding the maternal and neonatal baseline data [Table 1]. In all the groups, more than half of neonates were pre-term, and chief complaint of 55.0%, 75% and 73.3% of patients in the EOS, LOS and Nosocomial infection groups was respiratory distress, respectively. The most commonly isolated pathogen in the three study groups was *Enterobacter spp.*, which was responsible for 34.1%, 47.8%, and 41.2% of the episodes of EOS, LOS and Nosocomial infections, respectively [Table 2]. However, no significant differences were found in the type and frequency of isolated pathogens between the groups. The trends for the resistance rates of isolated pathogens responsible for NS within these four years showed that, for the cephalosporins' subgroups, although changes was observed in resistance rates, the sensitivity rate was significantly reduced only for cefalotin [Figure 1]. Furthermore, among other common used antibiotics, sensitivity of common pathogens against ciprofloxacin was gradually increased, and susceptibility to imipenem and gentamycin antibiotics gradually reduced within the years [Figure 2] of study.

Total mortality rate due to NS was estimated at 27.4%. Sepsis-related mortality in Nosocomial infection group (47.1%) was higher than other groups with EOS (27.3%) and LOS (13.0%); however, the difference was not statistically significant (P=0.058). Although the trend of the incidence of sepsis, as well as the mortality due to sepsis, especially in the EOS variety, seemed to be significant between 2003 and 2006, the trends in the three groups were not statistically significant during this period [Figure 3]. There were no significant differences in the mortality and morbidity rates based on the gender (P=0.058, 0.622, respectively), type of delivery (P=0.544, 0.063), platelet count (P=0.295, 0.347), type of pathogens (P=0.266, 0.803), and resistance to ciprofloxacin (P=0.265,0.185), ceftriaxone (P=0.669, 0.542), ceftizoxime (P=0.180,0.727), cefotaxime (P=0.678, 0.659), Imipenem (P=0.835, 0.065), cephalexin (P=0.652,0.787), gentamicin (P=0.358, 0.287), cefalotin (P=0.421, 0.230), ampicillin (P=0.446, 0.762), chloramphenicol (P=0.589, 0.448), penicillin (P=0.647, 0.941), tetracycline (P=0.239, 0.701), ceftazidime (P=0.732, 0.558), cloxaciline (P=0.600, 0.361). However, the mortality rate was different according to the weight (P<0.001), gestational age (P=.003) and neutrophil count (P<0.001). Further, the morbidity rate was different in terms of the chief complaint (P<0.001) only, and no significant differences were seen in the morbidity rates based on the differences in the weight (P=0.536), gestational age (P=0.624) and neutrophil count (P=0.600).

Table 1: Baseline characteristics and clinical data of neonates with early onset neonatal sepsis, late onset neonatal sepsis and nosocomial infection as seen in the study

	EOS group (%)	LOS group (%)	Nosocomial group (%)	*P* value
Gender				
Male	24 (54.5)	13 (56.5)	9 (52.9)	0.974
Female	20 (45.5)	10 (43.5)	8 (47.1)	
Birth weight				
Normal	20 (45.5)	7 (30.4)	6 (35.3)	0.373
Low birth weight	15 (34.1)	12 (52.2)	5 (29.4)	
Very low birth weight	9 (20.5)	4 (17.4)	6 (35.3)	
Type of delivery				
Normal delivery	17 (38.6)	8 (34.8)	5 (29.4)	0.792
Cesarean section	27 (61.4)	15 (65.2)	12 (70.6)	
Time of delivery				
Term	21 (47.7)	11 (47.8)	5 (29.4)	0.396
Pre-term	23 (52.3)	12 (52.2)	12 (70.6)	
Chief complaint				
Respiratory distress	22 (55.0)	15 (75.0)	11 (73.3)	0.769
Poor feeding	4 (10.0)	2 (10.0)	1 (6.7)	0.929
Jaundice	4 (10.0)	0	0	0.174
Cyanosis	2 (5.0)	0	0	0.411
Hypoglycemia	2 (5.0)	0	1 (6.7)	0.556
Others	10 (15.0)	6 (15.0)	4 (13.3)	0.824

EOS = Early onset neonatal sepsis; LOS = Early onset neonatal sepsis

Multivariable logistic regression analysis showed that mortality was significantly higher among the male gender (OR=4.897, *P*=0.031), and in low birth weight infants (OR=4.406, *P*=0.011) [Table 3]. Morbidity rate in relation
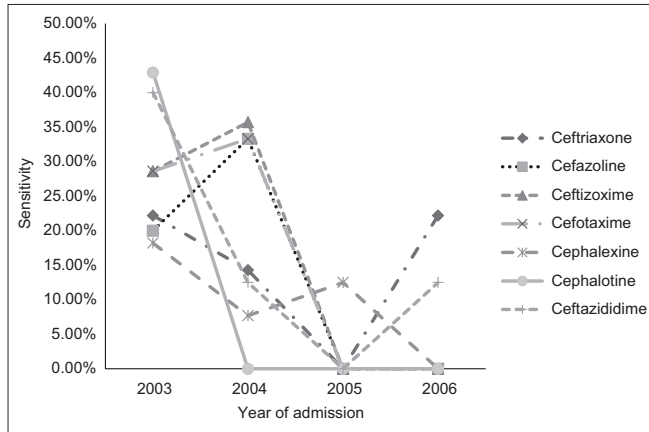

Figure 1: The trend for the resistance rate of isolated pathogens responsible for neonatal sepsis against cephalosporins over the years between 2003 and 2006, as seen in the study
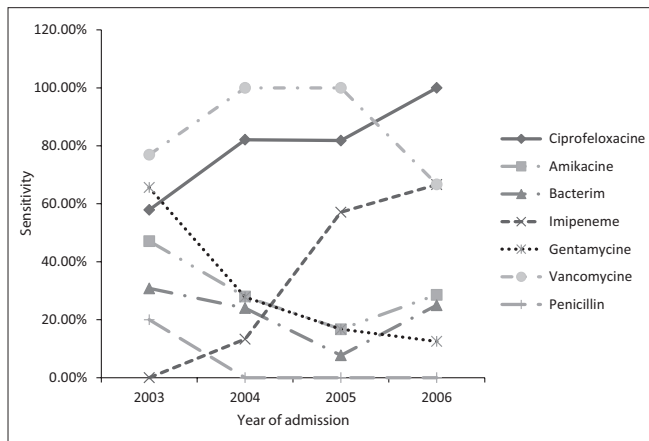

Figure 2: The trend for the resistance rate of isolated pathogens responsible for neonatal sepsis against common antibiotics over the years between 2003 and 2006, as seen in the study
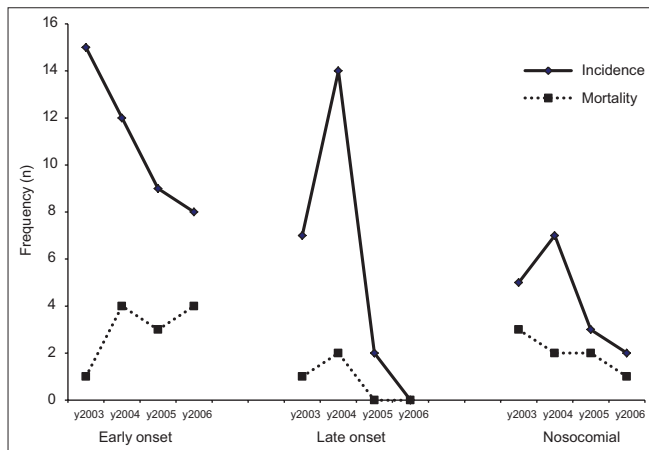

Figure 3: The trend for the incidence and mortality rate of different types of sepsis over the years between 2003 and 2006

to sepsis was observed in 89.3% (75 out of 84 patients) of the patients, and this was comparable in three other groups (EOS; 90.9%, LOS; 87.0%, nosocomial sepsis; 88.2%, *P*=0.873). Morbidity following neonatal sepsis was higher in children delivered via a Cesarean section (OR=6.280, *P*=0.025) [Table 4].

DISCUSSION

Our study has documented the variables of neonatal sepsis among Iranian hospitalized neonates and infants, in two referral medical centers. The common pathogens causing the condition, the incidence of the different types of sepsis (early-onset, late-onset and nosocomial), and the determinants of mortality and morbidity due to NS were

Table 2: Bacterial pathogens related to early onset and late onset neonatal sepsisas seen in the study

Bacterial pathogens	EOS group (*n*=44)	LOS group (*n*=23)	Nosocomial group (*n*=17)	*P* value
Enterobacter	15 (34.1)	11 (47.8)	7 (41.2)	0.769
CONS	11 (25.0)	6 (26.1)	3 (17.6)	0.865
Klebsiella	6 (13.6)	1 (4.3)	6 (35.3)	0.081
Escherichia coli	4 (9.1)	3 (13.0)	0	0.370
PONS	4 (9.1)	2 (8.7)	0	0.929
Pseudomonas	4 (9.1)	0	1 (5.9)	0.174

EOS - Early onset neonatal sepsis; LOS - Early onset neonatal sepsis

Table 3: Variables in terms of mortality due to neonatal sepsis by multivariable logistic regression analysis as seen in the study

Item	Multivariate *P* value	Odds ratio	95% confidence interval
Male gender	0.025	5.630	1.249-25.384
Low birth weight	0.012	4.261	1.379-13.166
Pre-term status	0.927	0.953	0.336-2.703
EOS	0.394	0.523	0.118-2.320
Pre-maturity	0.064	5.010	0.912-27.525
Cesarean section	0.192	0.363	0.079-1.664

EOS - Early onset neonatal sepsis. Hosmer-Lemeshow goodness-of-fit: χ^2=10.233, *P* value=0.176

Table 4: Variables in terms of morbidity due to neonatal sepsis by multivariable logistic regression analysis as seen in the study

Item	Multivariate *P* value	Odds ratio	95% confidence interval
Male gender	0.921	0.928	0.211-4.073
Low birth weight	0.551	1.511	0.389-5.871
Pre-term status	0.976	0.980	0.262-3.662
EOS	0.881	1.128	0.233-5.462
Pre-maturity	0.595	0.564	0.068-4.661
Cesarean section	0.025	6.280	1.253-31.490

EOS - Early onset neonatal sepsis; Hosmer-Lemeshow goodness-of-fit: χ^2=10.794, *P* value=0.214

recorded in our study. We observed that more than half of the NS cases were related to early-onset sepsis with the incidence rate of 52.4%, which was slightly higher than that reported in the previous studies. In another study by Aftab *et al.,* 42% of all hospitalized neonates at the NICU with the diagnosis of sepsis presented as EOS.[12]

In the World Health Organization's (WHO) young infants' study, 30% of neonatal sepsis cases were early-onset.[13] Considering the recent WHO reports, the estimates of the incidence of early-onset bacterial sepsis vary widely, and the available data indicates a high burden of the disease among neonates.[13] In a study by Khalili *et al.,* the incidence of suspected EOS was estimated at 85.6%,[14] which is considerably higher than data published from other countries.[3,9] However, the overall incidence of EOS considerably decreased from 1995 to 1999, from 6.8/1000 births to 0.6/1,000 births.[15] In a study on the Korean population, the estimated incidence rate of neonatal sepsis during the first 3 years was 30.5 per 1000 live births for clinical sepsis, and 6.1 per 1000 live births for sepsis with positive culture.

When only EOS was considered, the incidence of the neonatal sepsis was 25.1 per 1000 births.[16] However, EOS infections can be by different bacteria and also the type of infection varies depending upon the infant being full term or preterm. It was shown that the rate of EOS following group B streptococcal infection decreased faster than non-group B streptococcal infection.[15] In fact, preterm infants have EOS due to gram negative organisms more frequently, and full term infants with gram positive.[17] It seems that the incidence of EOS also depends on the resistance of common pathogens to antibiotics, the quality of the interventions used and whether or not reliable information is available about the burden of sepsis and its consequences. In our centers, pregnant women have received antibiotics for Group B Streptococcus (GBS) prophylaxis, and this could justify the higher prevalence of gram negative bacteria and coagulase negative *staphylococci* (CONS) in the EOS cases of the present study.

The predominantly isolated pathogen in all the study groups in our study was *Enterobacter spp.,* and other pathogens such as *Escherichia coli* and coagulase-positive *staphylococci* were less common. Other studies have reported less similar findings. A study by Weston *et al.* reported Group B *Streptococcus* as was the most common pathogen, followed by *Escherichia coli.*[18] Naderi-nasab *et al.* reported gram positive organisms were more frequent than gram negative organisms in nosocomial and acquired infections in NICUs of Mashhad, Iran.[19] Also, in a study on the Pakistani population, *Escherichia coli* was the most common organism followed by *Klebsiella,* and among the

gram positive organisms, *Staphylococcus aureus* was most frequent.[12]

Most of the previous reports have emphasized on the pivotal role of Gram-negative organisms such as *E. Coli, Klebsiella* and *Staphylococcus aureus* as main pathogens causing neonatal sepsis.[11,20-30] *Enterobacter* species can cause fatal conditions such as urinary tract infections, hepatobiliary sepsis, endocarditis, surgical wound infection, bacteremia and neonatal sepsis, and also stem the further development of antibiotic resistance.,[29] Hence preventing the spread of this pathogen especially in developing countries such as Iran could help to reducing the mortality and morbidity. Mortality rate in our study was lower than that reported in similar other studies which could be due to the difference in the type of the affecting pathogens.[19,30]

According to our study findings, the resistance of isolated pathogens responsible for neonatal sepsis against cephalosporins' class of antibiotics was relatively unchanged over the years from 2003 to 2006 in comparison to that against more commonly used antibiotics, such as gentamycin and imipenem, which gradually reduced over the years. Resistance of sepsis-related pathogens against routine antibiotics has been reported widely. Aftab *et al.* found higher resistance to gentamycin and cephalosporins compared to imipenem, with acceptable sensitivity against sepsis-related pathogens.[12] Aurangzeb *et al.* reported considerable resistance to commonly used antibiotics such as ampicillin, amoxicillin, ceftazidime, cefotaxime, and comparatively low resistance to gentamycin, tobramycin, imipenem, amikacin, ofloxacin and ciprofloxacin.[20]

Marzban *et al.* demonstrated a prominent increase in the resistance of bacteria to aminoglycosides, cephalothin and 3rd generation cephalosporins in a NICU unit in Tehran, Iran.[31] Recently, a high incidence of resistance to aminoglycosides was noted amongst most gram negative organisms, whereas imipenem was effective in most of the ases.[30] Therefore, the therapeutic role of some antibiotics such as quinolones, may gain considerable importance in the near future, mainly due to the emergence of resistant bacterial strains in the NICUs. Reduction of the susceptibility of the bacteria to imipenem can be attributed to its over-prescription in our population that emphasizes on prescribing antibiotics such as third-generation cephalosporins for these patients.

In our study, death due to neonatal sepsis was significantly higher in the male gender and in low birth weight infants. Except for urosepsis, which may be more common in females, no gender tendency for a particular type of sepsis has been found in any other studies.[32,33] Also, an inverse relationship has been proven between the risk for EOS and birth weight.[34,35] The majority of the neonatal deaths in the

NICUs are due to neonatal sepsis, complicated with preterm and/or low birth weight conditions.[36]

Also, we observed that the infants delivered via cesarean section had higher chances of developing EOS in comparison to infants delivered via vaginal delivery. Cesarean sections, especially before 39 weeks of pregnancy, can be associated with several adverse neonatal events, such as, respiratory complications and hypoglycemia due to prematurity. This leads to higher NICU admissions and higher chances of developing newborn sepsis.[37] Also, some data has suggested an association between cesarean deliveries and increased risk of neonatal mortality; however, Durie *et al.* demonstrated that cesarean delivery can enhance the chances of other newborn morbidity but not sepsis.[38,39] However, there are evidences supporting higher correlation between neonatal mortality and planned elective cesarean, versus planned vaginal delivery. Further research is needed to confirm these relationships with the current evidence being insufficient.

To summarize, our study has demonstrated a high rate of EOS among hospitalized neonates in the NICU, especially in preterm neonates, and in those with respiratory distress syndrome. However, we need to bear in mind that thses findings cannot be generalized to all the medical centers in the country. Like other studies in the developing countries, the most common isolated pathogen in early onset, late onset, and nosocomial neonatal sepsis in our population was *Enterobacter spp.*, which was responsible for 31.4%, 47.8% and 41.2% of the episodes of these sepsis types, respectively. Sensitivity to imipenem and gentamycin gradually reduced during the four years period, whereas the sensitivity against most of the cephalosporins was statistically unchanged. Total mortality and morbidity rates due to neonatal sepsis were estimated at 27.4% and 89.3%, respectively. Mortality following sepsis was found more in boys and those with low birth weight, and higher sepsis related co-morbidity could have potentially occurred following cesarean delivery. Appropriate identification of the sepsis source, prompt antibiotic prescription, and aggressive management can effectively prevent adverse events following neonatal sepsis. Determination of the neonatal sepsis incidence, its' bacterial pathogens, and the patterns and rates of antibiotic resistance among all the neonate and infant populations are necessary. Our study had few limitations, as the study was a retrospectives historical cohort by nature, and also the sample size was small. Hence we cannot generalize the results of our study to other hospitals of Iran.

ACKNOWLEDGMENTS

REFERENCES

1. Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: Definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med 2005;6:2-8.

2. Marik PE. Definition of sepsis: Not quite time to dump SIRS? Crit Care Med 2002;30:706-8.

3. Seale AC, Mwaniki M, Newton CR, Berkley JA. Maternal and early onset neonatal bacterial sepsis: Burden and strategies for prevention in sub-Saharan Africa. Lancet Infect Dis 2009;9:428-38.

4. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med 2003;348:1546-54.

5. Kuhl DA. Current strategies for managing the patient with sepsis. Am J Health Syst Pharm 2002;59 (Suppl 1):S9-13.

6. Klinger G, Levy I, Sirota L, Boyko V, Reichman B, Lerner-Geva L. Israel Neonatal Network. Epidemiology and risk factors for early onset sepsis among very-low-birthweight infants. Am J Obstet Gynecol 2009;201:38.e1-6.

7. Morales WJ, Dickey SS, Bornick P, Lim DV. Change in antibiotic resistance of group B streptococcus: Impact on intrapartum management. Am J Obstet Gynecol 1999;181:310-4.

8. Khassawneh M, Khader Y, Abuqtaish N. Clinical features of neonatal sepsis caused by resistant Gram-negative bacteria. Pediatr Int 2009;51:332-6.

9. Stoll BJ, Hansen N, Fanaroff AA, Wright LL, Carlo WA, Ehrenkranz RA, *et al.*, Changes in pathogens causing early-onset sepsis in very-low-birth-weight infants. N Engl J Med 2002;347:240- 7.

10. Clark R, Powers R, White R, Bloom B, Sanchez P, Benjamin DK Jr. Nosocomial infection in the NICU: A medical complication or unavoidable problem? J Perinatol 2004;24:382-8.

11. Ghotaslou R, Ghorashi Z, Nahaei MR. Klebsiella pneumoniae in neonatal sepsis: A 3-year-study in the pediatric hospital of Tabriz, Iran. Jpn J Infect Dis 2007;60:126-8.

12. Aftab R, Iqbal I. Bacteriological agents of neonatal sepsis in NICU at Nishtar Hospital Multan. J Coll Physicians Surg Pak 2006;16:216-9.

13. Bacterial etiology of serious infections in young infants in developing countries: Results of a multicenter study. The WHO Young Infants Study Group. Pediatr Infect Dis J 1999;18(10 Suppl):S17-22.

14. Khalili matin zadeh Z., Amirsalari S., Kaveh Manesh Z., Afsharpeyman Sh., Torkaman M. Evaluation of the most common clinical signs and laboratory finidings of neonatal sepsis in in Baqyatallah and Najmie Hospitals from 1380 to 1384. Journal of Military Medicine. 2007; 9 (3) :233-240

15. Laugel V, Kuhn P, Beladdale J, Donato L, Escande B, Astruc D, *et al.* Effects of antenatal antibiotics on the incidence and bacteriological profile of early-onset neonatal sepsis. A retrospective study over five years. Biol Neonate 2003;84:24-30.

16. Shin YJ, Ki M, Foxman B. Epidemiology of neonatal sepsis in South Korea. Pediatr Int 2009;51:225-32.

17. Maayan-Metzger A, Barzilai A, Keller N, Kuint J. Are the "good old" antibiotics still appropriate for early-onset neonatal sepsis? A 10 year survey. Isr Med Assoc J 2009;11:138-42.

18. Weston EJ, Pondo T, Lewis MM, Martell-Cleary P, Morin C, Jewell B, *et al.*, The Burden of Invasive Early-onset Neonatal Sepsis in the United States, 2005-2008. Pediatr Infect Dis J 2011;30:937-41.

19. Naderi-Nasab M, Farhat A, Tajzadeh P, Sourosh S, Amiri M. Study of the bacterial agents in nosocomial and acquired infections based on the blood culture in neonatal intensive care unit of a hospital, north

east of Iran. Saudi Med J 2007;28:723-6.

20. Aurangzeb B, Hameed A. Neonatal sepsis in hospital-born babies: Bacterial isolates and antibiotic susceptibility patterns. J Coll Physicians Surg Pak 2003;13:629-32.

21. Vergnano S, Sharland M, Kazembe P, Mwansambo C, Heath PT. Neonatal sepsis: An international perspective. Arch Dis Child Fetal Neonatal Ed 2005;90:F220-4.

22. Poyart C, Réglier-Poupet H, Tazi A, Billoët A, Dmytruk N, Bidet P, *et al.* Invasive group B streptococcal infections in infants, France. Emerg Infect Dis 2008;14:1647-9.

23. Milledge J, Calis JC, Graham SM, Phiri A, Wilson LK, Soko D, *et al.* Aetiology of neonatal sepsis in Blantyre, Malawi: 1996-2001. Ann Trop Paediatr 2005;25:101-10.

24. Nathoo KJ, Mason PR, Chimbira TH. Neonatal septicaemia in Harare Hospital: Aetiology and risk factors. The Puerperal Sepsis Study Group. Cent Afr J Med 1990;36:150-6.

25. Laving AM, Musoke RN, Wasunna AO, Revathi G. Neonatal bacterial meningitis at the newborn unit of Kenyatta National Hospital. East Afr Med J 2003;80:456-62.

26. Madhi SA, Radebe K, Crewe-Brown H, Frasch CE, Arakere G, Mokhachane M, *et al.* High burden of invasive Streptococcus agalactiae disease in South African infants. Ann Trop Paediatr 2003;23:15-23.

27. English M, Ngama M, Musumba C, Wamola B, Bwika J, Mohammed S, *et al.* Causes and outcome of young infant admissions to a Kenyan district hospital. Arch Dis Child 2003;88:438-43.

28. Hyde TB, Hilger TM, Reingold A, Farley MM, O'Brien KL, Schuchat A. Active Bacterial Core surveillance (ABCs) of the Emerging Infections Program Network. Trends in incidence and antimicrobial resistance of early-onset sepsis: Population-based surveillance in San Francisco and Atlanta. Pediatrics 2002;110:690-5.

29. Shaw CK, Shaw P, Thapalial A. Neonatal sepsis bacterial isolates and antibiotic susceptibility patterns at a NICU in a tertiary care hospital in western Nepal: A retrospective analysis. Kathmandu Univ Med J (KUMJ), 2007;5:153-60.

30. Macharashvili N, Kourbatova E, Butsashvili M, Tsertsvadze T, McNutt LA, Leonard MK. Etiology of neonatal blood stream infections in Tbilisi, Republic of Georgia. Int J Infect Dis 2009;13:499- 505.

31. Marzban A, Samaee H, Mosavinasab N. Changing trend of empirical antibiotic regimen: Experience of two studies at different periods in a neonatal intensive care unit in Tehran, Iran. Acta Med Iran 2010;48:312-5.

32. Jacobi J. Pathophysiology of sepsis. Am J Health Syst Pharm 2002;59 (Suppl 1):S3-8.

33. Burke C. Perinatal sepsis. J Perinat Neonatal Nurs 2009;23:42-51.

34. Gluck L, Wood HF, Fousek MD. Septicemia of the newborn. Pediatr Clin North Am 1966;13:1131-48.

35. Salem SY, Sheiner E, Zmora E, Vardi H, Shoham-Vardi I, Mazor M. Risk factors for early neonatal sepsis. Arch Gynecol Obstet 2006;274:198-202.

36. Rajindrajith S, Mettananda S, Adihetti D, Goonawardana R, Devanarayana NM. Neonatal mortality in Sri Lanka: Timing, causes and distribution. J Matern Fetal Neonatal Med 2009;22:791-6.

37. Tuuli MG, Odibo AO. Neonatal outcomes in relation to timing of repeat cesarean delivery at term. Womens Health (Lond Engl) 2009;5:239-42.

38. Signore C, Klebanoff M. Neonatal morbidity and mortality after elective cesarean delivery. Clin Perinatol 2008;35:361-71, vi.

39. Durie DE, Sciscione AC, Hoffman MK, Mackley AB, Paul DA. Mode of delivery and outcomes in very low-birth-weight infants in the vertex presentation. Am J Perinatol 2011;28:195-200.

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