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Neonatal Late-Onset Sepsis in a NICU: Analysis of Causative Organisms and Antimicrobial Susceptibility Ali Asghar Children Hospital from (2004/5-2007/5), Tehran, Iran

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Abstract: Bacterial sepsis is one of the most common causes of significant mortality and morbidity in neonates. The researchers analyzed bacterial isolates and their antibiotic susceptibilities for cases of septicemia in a Neonatal Intensive Care Unit (NICU) of a teaching hospital in Tehran, Iran. During a 36 months period, the incidence of bacteremia and the causing organisms and mortality of sepsis as well as antibiotic susceptibility were investigated. Neonatal Late-Onset Sepsis (LOS) was defined as clinical signs suggestive of infection with a positive Blood Culture (B/C) after 72 h of birth. About 909 neonates were admitted to the NICU. A total of 9.13% of neonates (83/909) had at least one positive B/C after 72 h of birth. The vast majority (56.6%) of sepsis were caused by Gram-negative organism. Gram-positive pathogens accounted for 41% infections. The most common cause of late-onset sepsis was *Klebsiela p.* (31%) and followed by *Staph aureus* (18.1%). In this study, the researchers have observed that the old empiric therapy with cephalothine plus Amikacin for suspected late-onset sepsis seems ineffective. Now, however may be the best choice regimen is the combination vancomycin plus amikacin and the vancomycin plus imipenem for the severe ill patients.

Key words: Late-onset sepsis, antibiogram, neonate, bacteremia, nosocomial, Iran

INTRODUCTION

Sepsis is considered to comprise a spectrum of disorders that result from infection by bacteria, viruses and fungi ora parasites or the toxic products of these microorganisms. Bacteremia, viremia, fungemia and parasitemia refer to bloodstream invasion that may be associated with fever but no other signs or symptoms of circulatory compromise or end-organ malperfusion or dysfunction (Stoll, 2004; Palazzi *et al*., 2006). Neonatal sepsis may be categorized as early or late onset.

About 85% of newborns with early-onset infection present within 24 h, 5% at 24-48 h and a smaller percentage of patients present between 48 h and 6 days of life (Palazzi *et al*., 2006; Edwards, 2006). Late-onset sepsis syndrome occurs from 3rd- 90th days of life and is acquired from the caregiving environment.

Organisms that have been implicated in causing late-onset sepsis syndrome include *Coagulase-Negative Staphylococci* (CONS), *Staphylococcus aureus*, *E. coli*, *Klebsiella*, *Pseudomonas*, *Enterobacter candida*, *Group-B Streptococcus* (GBS), Serratia, Acinetobacter and anaerobes. The infant's skin, respiratory tract, conjunctivae, gastrointestinal tract and umbilicus may become colonized from the environment, leading to the possibility of late-onset sepsis from invasive microorganisms (Palazzi *et al*., 2006). Surveillance of late-onset neonatal sepsis is required to monitor the quality of Neonatal Intensive Care Unit (NICU) related care (Cloherty *et al*., 2004).

Despite major advances in NICU, sepsis continues to be an important cause of morbidity/mortality among neonates. A gradual change in the spectrum and organisms responsible for neonatal sepsis has been recognized. Constant surveillance is important to guide empirical antibiotic therapy. The pathogens associated with neonatal sepsis are known to vary geographically. Antibiotic regimens for treatment or prevention of these infections have been associated with variable (Stoll, 2004; Palazzi *et al*., 2006; Edwards, 2006; Cloherty *et al*., 2004; Gomella and Cunnigham, 2004). In order to understand, the epidemiology of late-onset sepsis in the NICU of Ali-Asghar Hospital, a teaching center, the researchers retrospectively collected data on bacteremia to analyze its microbiology and determine the antibiotic susceptibilities of the causative organisms.

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MATERIALS AND METHODS

Ali-Asghar Hospital NICU is a level III referral nursery in Iran University of Medical Sciences, Tehran, Iran. This NICU is one of the greatest tertiary-teaching level (III) in Iran. It has 6 units with >40 neonatal beds capacity and one neonatal surgery unit (6 beds).

Study population: From 2004/5 -2007/5 all neonates with age >72 H admitted to the NICU of Ali-Asghar Hospital were included in this study. This study is based on results of blood culture in neonatal late-onset sepsis. Empirical antibiotic regimen for suspected LOS was changed on the basis of organism antimicrobial susceptibility. Neonatal LOS was defined as clinical signs suggestive of infection with a positive Blood Culture (B/C) after 72 h of birth. That similar with definition of LOS at the Ohio State University Medical Center (Cordero *et al*., 1999) and NICU of (VGH-Taipei) in Taiwan (Lee *et al*., 2004).

Data collection: Data collection for neonate with positive B/C included: gender, birth weight and gestational age, the pathogenic bacteria of positive B/C and their antibiotic susceptibilities. B/C were performed routinely on all neonate with clinical sepsis.

RESULTS AND DISCUSSION

About 909 neonates were admitted to the NICU. A total of 9.13% of neonates (83/909) had at least one positive B/C after 72 h of birth. About 60% of the infants were male. The proportion late-onset sepsis in neonates with normal-birth weight (45/81) (>2500 g) and low-birth weight (26/81) (<2500 g) and very low-birth weigh (12/81) (<1500 g) was (54.32, 30.86, 14.82%), respectively. Very low-birth weight infants average rate is lower in this study because usually more complicated term cases refereed to the NICU as referral center. GNB was higher in very low birth-weight than other groups.

The vast majority (56.6%) of septic cases were caused by gram-negative organism. *Klebsiela p.* were the most common pathogens (31.3%) of all infections, 55.31% (26/47) of gram-negative infections. Other gram-negative organisms included *Enterobacter*, *Acinetobacter*, *E. coli, Pseudomonase* (Fig. 1). Gram-positive pathogens accounted for 41% infections. *Staphylococcus aureus*, CONS, other *Streptococcus* sp. and *Enterococus* were the most frequent gram-positive pathogens. Fungal organisms were responsible for 2.4% of sepsis. The most common cause of late-onset sepsis was *Klebsiela* sp. (31%) and followed by *Staph aureus* (18.1%).

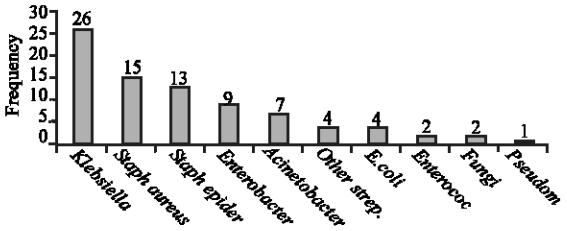

Fig. 1: The incidence of neonatal LOS by frequency of bacteria

Overall 27(32.5%) of the 83 infants with sepsis died. About 15/30 neonates (50%) in the group of neonates surgery were died. The highest mortality rate was due to *Klebsiela pneumonia* in the group of neonates surgery. The most common cause of mortality in this group might be sepsis or complications of surgery.

Antibiotic susceptibilities: The antibiotic susceptibilities of gram-positive cocci shown in Fig. 2. GPC was resistant to most of the antibiotics including cephalothin, Cloxacillin, Ampicillin, Cefotaxime. Strains resistant to vancomycin and imipenem were not found in the gram-positive pathogens. All cultured CONS and *S. aureus* organism were vancomycin-sensitive. *S. aureus* was resistant to cephalothin (87.5%), cefotaxim (70%), cloxacilin (66.67%), ampicillin (50%).

The antibiotic susceptibilities of gram-negative bacilli shown in Fig. 3. GNB was resistant to most of the antibiotics including cefotaxim, ceftazidim, gentamicin and amikacin. GNB had high sensitivity to imipenem (95%) and only one strains of *E. coli* was resistant to imipenem. *Klebsiela* sp. was resistant to cefotaxim (95%), ceftazidim (93.75%), gentamicin (87%) and amikacin (80%). All cultured *Klebsiela* sp. was imipenem-sensitive.

Sepsis is a severe problem for neonates. The most common nosocomial infection among neonates is blood stream infections. It is associated with marked morbidity and mortality and should be a major focus of surveillance and prevention efforts in high-risk nurseries. Positive B/C together with clinical signs of infection makes the diagnosis of blood stream infection more accurate. The reserchers have found the LOS rate of 9.13% in the center.

The overall incidence of bacteremia in NICU have ranged from 1.9-30.4% (Lee *et al*., 2004; Fok *et al*., 1998; Jogn *et al*.,1982). Some other investigators in different centers of NICU in Iran had shown similar results (Samaee, 1998; Movahedion *et al*., 2006). In the NICU the case fatality rate due to sepsis was 32.5%. Among them, >50% mortality was taken place in the group of neonates after surgery. The predominant causative organisms in the

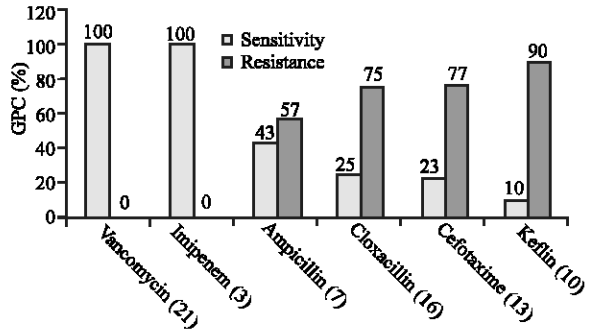

Fig. 2: The antibiotic susceptibilities of gram-negatieve cocci in neonatal LOS

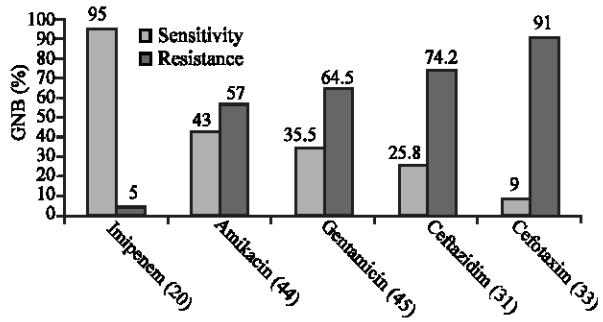

Fig. 3: The antibiotic suscepitbilties of gram-negative bacilli in neonatal LOS

study were gram-negative organism (56.6%). Overall, there was a greater distribution of gram-negative bacilli than gram positive infections. This data consistence with the finding of other NICU centers in Iran (Samaee, 1998; Masheof, 1999). While gram-positive cocci including coagulase-negative staphylococci is the most common isolated organisms in late-onset sepsis in NICU at other countries (Palazzi *et al*., 2006; Lee *et al*., 2004; Kapoor *et al*., 2005; Yalaz *et al*., 2006; Haque *et al*., 1990; Rubin *et al*., 2002). It seems that incidence of CONS infection is increasing as important pathogen in late-onset sepsis in the NICU. It is may be because of different approach of the neonatologists about the definition, interpretation and management of suspected late-onset sepsis, particularly those caused by CONS positive blood culture in neonatal period.

Therefore, it should be cautiously interpreted CONS positive blood culture as possibility of contamination. At the present study, *Klebsiela* sp. was the most common bacteria (31.3%) followed by *Staph aureus* (18.1%) and CONS (10.7%). Overall the data that *Klebsieal* sp. is one of the three common bacteria is consistent with other reports in different center in Iran with previous study in this center at 1992 (Samaee, 1998; Movahedion *et al*., 2006; Masheof, 1999) and with the report from hospital in Dehli, India (Yalaz *et al*., 2006). A study from Ohio shows that the number of bacteremia due to *Klebsiella* sp. and Enterobacter were more prominent and more often than the previous years (Cordero *et al*., 1999). In this study, most of GNB cases were highly resistant to aminoglycosides (gentamicin and amikacin) and 3rd generation cephalosphorins (cefotaxim, ceftazidm) while sensitive to the imipenem. Since 1983, productions of Extended Spectrum Beta-Lactamase (ESBL) have been found in many GNB, such as *Klebsiela* sp., *E. coli*, Enterobacteriacea (Paterson *et al*., 2004). The occurrence of multi-drug resistant in our NICU and recently prominence of *Klebsiela* sp. might result from these mechanism that was against most 3rd generation cephalosporins in the routine usage.

However, further analysis should be done for confirmation. Unfortunately, we observed increase resistant of *Klebsiela* sp. to Amikacin (80%), gentamicin (87%) and cefotaxim (95%) that's is similar with other study in Iran (Masheof, 1999). While cordero in Ohio reported that 100% *Klebsiela* sp. were sensitive to gentamicin and cefotaxim and the combination of (vancomycin and gentamicin) for suspected LOS been successful (100% sensitivity).

In this study, GPB were highly resistance to cephalothin (90%), cloxacillin (75%) and cefotaxim (77%). All of them were susceptible to vancomycin and imipenem. While, Rashidy *et al*. (2003) in Sanandage, Iran reported that GPB resistance to vancomycin was 8.6% (Makhoul *et al*., 2005).

The data have shown that fungemia was the lowest incidence (2.4%) which is unlike high incidence of fungemia in Turkey (18%) and Tel-Aviv University so that in both studies antifungal was added to the routine empirical antibiotic regimen for LOS, especially in VLBW (Haque *et al*., 1990; Makhoul *et al*., 2001, 2005). In the NICU, prophylactics antibiotics were prescribed for suspected late-onset sepsis with Cephalothin plus amikacin as the empiric therapy, according to previous studies (>10 years ago). In this study, the researchers have observed that the old empiric therapy with cephalothine plus amikacin for suspected late-onset sepsis seems ineffective. Now, therefore may be the best choice regimen is the combination of vancomycin plus amikacin and the vancomycin plus imipenem for the severe ill patients.

CONCLUSION

Studies of bacterial etiology have implications for presumptive antibiotic therapy of bacterial infection in

neonates. Now, the significance of antibiotic resistance is recognized to be a global unsolved problem and the emergence of antibiotic-resistant pathogens is particularly alarming in developing countries. The some reason of this problem seems due to the widespread availability of antibiotics and inappropriate use of it at outpatients, uncontrolled antibiotics programs, overuse of antibiotics at inpatients, especially lack of establish protocols to prohibit the unnecessary administration of antibiotics in neonates whose culture are negative.

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REFERENCES

Cloherty, J.P., E.C. Eichenwald and A.R. Strark, 2004. Manual of Neonatal Care. 5th Edn., Lippincot, Philadelphia, pp: 287-311.

Cordero, L., M. Sananes and I.W. Ayers, 1999. Blood stream infections in a Neonatal ICU: 12 years experience with an antibiotic control program. Infect. Control Hospital Epidemiol., 20: 242-246.

Edwards, M.S., 2006. Postnatal Bacterial Infections. In: Neonatal Perinatal Medicine, Fanaroff, A. and R.J. Martin (Eds.). Mosby, Philadelphia, pp: 791-825.

Fok, T.F., C.H. Lee, E.M.C. Wong, D.J. Lyon and W. Wong *et al*., 1998. Risk factors for enterobacter septicemia in a neonatal unit: Case-control study. Clin. Infect. Dis., 27: 1204-1209.

Gomella, T. and D. Cunnigham, 2004. Neonatology. 5th Edn., McGraw Hill, New York, pp: 434-441.

Haque, K.N., A.H. Chagia and M.M. Shaheed, 1990. Half a decade of neonatal sepsis, Riyadh, Saudi Arabia. J. Trop. Pediatr., 36: 20-23.

Jogn, J.F., R.J. Sharbaugh and E.R. Bannister, 1982. Enterobacter cloacae bacteremia, epidemiology and antibiotic resistance. Rev. Infect. Dis., 4: 13-28.

Kapoor, L., V.S. Rondhawa and M. Deb, 2005. Microbiological profile of neonatal septicemia in a pediatric care hospital in Delhi. J. Commun. Dis., 37: 217-232.

Lee, N.C., S.J. Chen and B.T. Hwang, 2004. Neonatal bacteremia in a neonatal intensive care unit: Analysis of causative organisms and antimicrobial susceptibility. J. Chin. Med. Assoc., 67: 15-20.

Makhoul, I.R., I. Kassis, T. Smolkin, A. Tamir and P. Sujov, 2001. Review of 49 neonates with acquired fungal sepsis further characterization. Pediatrics, 107: 61-66.

Makhoul, I.R., P. Sujov, T. Smolkin, A. Lusky and B. Reichman, 2005. Pathogen–specific early Mortality in very Low Brith. Weight infant with Los: A national survery. Clin. Infect. Dis., 40: 218-224.

Masheof, R.U., 1999. Bacteriology of neonatal septicemia and antibiotic susceptibility in hamedan hospital. J. Hamedan Univ. Med. Sci., 2: 136-143.

Movahedion, A.H., R. Moniri and Z. Mosayebi, 2006. Bacterial culture of neonatal sepsis. Iran. J. Publ. Health, 35: 84-89.

Palazzi, D.l., J.O. Klein and C.J. Baker, 2006. Bacterial Sepsis and Meningitis. In: Infectious Disease of the Fetus and Newborn, Remington, J.S. and J.O. Klein (Eds.). Saunders, Philadelphia, pp: 248-283.

Paterson, D.L., A. von Gottberg, S. Mohapatra, J.M. Casellas and H. Goossens *et al*., 2004. Antibiotic therapy for klebsiella pneumonia bacteremia: Implications of production of extended-spectrum-beta-lactamases. Clin. Infect. Dis., 39: 31-37.

Rashidy, Q., S.H. Bahmani and N. Ghotbi, 2003. Assessing the etiology and sensitivity of causative organisms initiating bacterial sepsis in the newborn at Besat hospital in sannandage. J. Kordestan Univ. Med. Sci., 10: 26-32.

Rubin, L.G., P.J. Sanchez, J. Siegel, G. Levine and L. Saiman, 2002. Evaluation and treatment of neonates with suspected Late-onset sepsis: A survey of neonatologists practices. Pediatrics, 110: 42-49.

Samaee, H., 1998. Assessing the etiology and sensitivity of causative organisms initiating bacterial sepsis in the newborn. J. Med. Council Islamic Rep. Iran, 15: 151-154.

Stoll, B.J., 2004. Pathogenesis and Epidemiology of Neonatal Infection. In: Nelson Textbook of Pediatrics, Behrman, R.E. and R.M. Kliejman (Eds.). Saunders, London, pp: 400-623.

Yalaz, M., H. Cetin, M. Akisu, S. Aydemir, A. Tunger and N. Kultursay, 2006. Neonatal nosocomial sepsis in a level-III NICU: Evaluation of the causative agents and antimicrobials usceptibilities. Turk. J. Pediatr., 48: 13-18.