ORIGINAL REPORT

# Changing Trend of Empirical Antibiotic Regimen: Experience of Two Studies at Different Periods in a Neonatal Intensive Care Unit in Tehran, Iran

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**Abstract-** Bacterial sepsis is one of the most common causes of mortality and morbidity in neonates. It has been recognized a gradual change in spectrum of organisms responsible for neonatal sepsis. In this study we have evaluated changing trend of incidence and antibiotic susceptibility in neonatal late – onset sepsis (LOS) in 2-periods. This study is based on results of blood culture in neonatal late-onset sepsis, in 2--periods study throughout 12 – years. Neonatal LOS was defined as clinical signs suggestive of infection with a positive blood culture (B/C) after 72 hrs of birth. During first *study (period: 1990-1992)*, the most common bacteremia in LOS was staphylococcus aureus (staph aureus) (34%). Overall gram- negative bacteria (GNB) were the predominant organism (66%). It was shown that 60% of GNB were resisted to gentamicin and 3% to amikacin, while in case of gram-positive bacteria (GPB); about 95% were resisted to ampicillin and 28% to cephalothin. *In the second study (period: 2004-2007),* the vast majority (56.6%) of septic cases were caused by GNB. The most common cause of late– onset sepsis was klebsiela p. (31%). The GPB were resistant to cephalothin (90%). There has been a dramatic increase resistance to cephalothin and aminoglycosides and 3rd –generation cephalosporins. The combination of cephalothin plus amikacin in suspected LOS was no longer the effective therapeutic regimen in our neonatal intensive care unit (NICU). Now, it seems the best choice for empiric antibiotic regimen in suspected LOS is the combination vancomycin plus amikacin. Constant surveillance is important to guide empirical antibiotic therapy and changes in trends.



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**Key words:** Infant, newborn; anti-bacterial agents; therapy; intensive care units, neonatal

## Introduction

Sepsis is considered to comprise a spectrum of disorders that result from infection by bacteria, viruses, fungi, or 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 of circulatory compromise or end-organ malperfusion and dysfunction (1, 2). Neonatal sepsis may be categorized as early or late onset. Eighty-five percent of newborns with early-onset infection present within 24 hours, 5% present at 24-48 hours, and a smaller percentage of patients present between 48 hours to 6 days of life (2, 3). Late-onset sepsis syndrome occurs at 7-90 days of life and is acquired from the care giving environment. Organisms that have been implicated in causing late-onset sepsis syndrome include coagulase negative *staphylococci* (CONS), staphylococcus aureus, *Escherichia coli* (*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 (2). Surveillance of late-onset neonatal sepsis is required to monitor the quality of neonatal intensive care unit (NICU) related care (4). Despite major advances in NICU, as gradual change in the spectrum and organisms responsible for neonatal sepsis, it continues to be an important cause of morbidity/mortality among neonates. Therefore,

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constant surveillance is important to guide empirical antibiotic therapy. There is limited information available on the incidence and microbiological spectrum and antibiotic susceptibilities for cases of late onset sepsis in our NICU at a teaching hospital during a long period (more than ten years). In this study we evaluated changing trend of incidence and antibiotic susceptibility in neonatal late onset sepsis in both periods.

## Patients and Methods

Ali-Asghar Hospital, Tehran/Iran NICU is a level III referral nursery affiliated to Iran University of Medical Sciences. This study is based on results of blood culture in neonatal late-onset sepsis, in 2-period study throughout 12 – years. First study period was monitored from 1990 to 1992 and last one from 2004 to 2007. We retrospectively collected data on positive B/C to analyze the microbiology and determine the incidence and antibiotic susceptibilities of the causative organism.

Empirical antibiotic regimens for suspected LOS were changed on the basis of organism antimicrobial susceptibility. Neonatal LOS was defined as clinical signs suggestive of infection with a positive (B/C) after 72 hrs of birth. That is similar to the definition of LOS at The Ohio State University Medical Center (5). Statistical analysis was carried out using SPSS (version 11.5),and data presented as figures.

## Results

***Study during first period (1990-1992)***

About 1139 neonates were admitted at the NICU of this center during this period. Among them 124 cases had positive blood culture of LOS. Blood culture results show that the most common bacteremia in LOS was *Staphilococcus aureus* (34%), and followed by other bacteremia such as *Eenterobacter, Klebsiela pneumoniae.* Overall Gram- negative bacteria were the predominant organisms (66%) and 80% of bactermia were caused by *Staphilococcus aureus*, *Enterobacter* and *Klebsiela pneumoniae*. Assessment of resistance to antibiotics shows that 60% of GNB were resistant to gentamicin and 3% to amikacin, while in case of GPB; about 95% were resistant to ampicillin and 28% to cephalothin (Figure 1).

There is not enough information about the antibiogram for cefotaxim (a 3rd generation cephalosporins) and this is because at that moment cefotaxim was not the current antibiotic. Therefore, treatment protocol from 1992 to 2007 was to use the empirical antibiotic for suspected LOS with combination of cephalothin and amikacin.

***Study during second period (2004-2007)***

About 909 neonates were admitted in NICU and among them 83 cases had positive B/C after 72hrs of birth. The most common bacteremia was caused by [*Klebsiela pneumoniae* (31%), *Staphilococcus aureus* 18.1% CONS 15.7%, *Enterobacter* 10.8%]. Gram-positive bacteria were resistant to cephalothin (90%), cloxacilin (75%), cefotaxim (77%) but all of GPB were susceptible to vancomycin (100%) and imipenem. The most sensitive antimicrobial agents against GNB were imipenem (95%), amikacin (43%), gentamicin (35.5%). More than 90% cefotaxim were resistant to GNB (Figure 2).

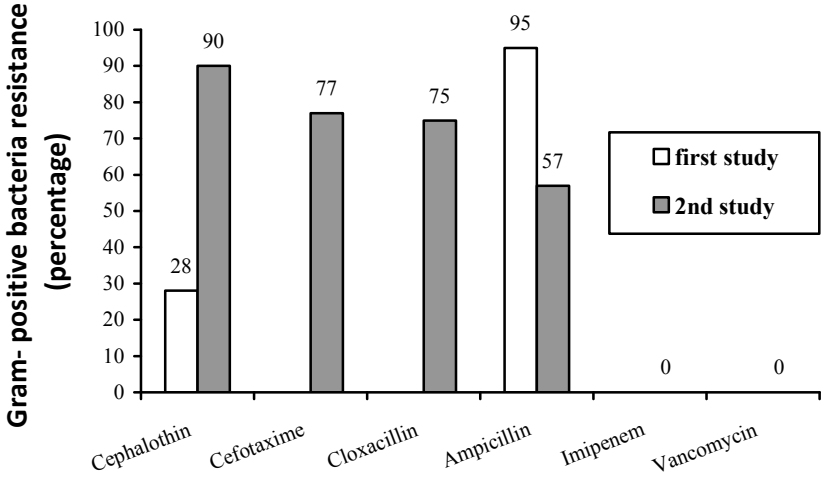


**Figure 1.** Prevalence of antibiotic resistance of gram- positive bacteria in first and second- studies.

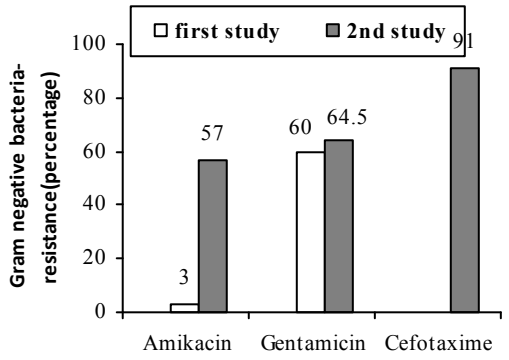


**Figure 2.** Prevalence of antibiotic resistance of gram-negative bacilli in first and second- studies.

## Discussion

Sepsis is a severe problem for neonates. It always results in mortality or prolonged hospitalization, and the control over nosocomial infections has been a formidable challenge for a long period of time. According to numerous recent studies, Nosocomial CONS-bacteremia is a new and growing problem in the NICU (6- 9). This clinical perception is not supported by our 2-period studies throughout 12-years review of the result of blood culture from neonatal LOS in the NICU at Ali-Asghar Hospital, Tehran/Iran. We have noted that there is no significant change in the rates of B/C growing of these organisms over this extended period. This data is similar to Sidebottom et al study in Boston Hospital. He reported no significant increase in incidence of CONS bactermia overtime by analysis of linear-trend (6). However, CONS bacteremia is the most common bacteria in NICU at developed countries (6, 10). Unlike two studies from United States (5) and Korea (11), the incidence of CONS dramatically increased in our study in the period 1986-1997. Analysis of linear trend organism in the present study and other studies in Iran has showed that incidence of GNB in neonatal LOS was dominant over time (12, 13). This finding is in contrast with the experience of other centers during the last decade studies (5, 6, 11, 14). Like other investigators, all of GPB in this study were susceptible to vancomycin (100%). Detailed analysis of data from 1990 to 1992 and 2004 to 2007 revealed that the incidence of klebsiela p. is increasing now. The most common pathogen in LOS at our NICU is *Klebsiela pneumoniae* while, in last decade it was *Staphilococcus aureus* which coincides with other studies (13).

One of the most important findings in this study was the significant change in initial empirical antibiotic regimen susceptibility. The combination cephalothin and amikacin have been the preferred empirical antibiotic regimen for suspected LOS in our NICU for many years until second period study (e.g. 2004-2007). Meanwhile, due to the extensive use of this current antibiotic and also routine use of 3rd generation cephalosporines, without an antibiotic control program, leads to antimicrobial resistance among GNB and GPB especially, and rapid resistance of cefotaxim to *Klebsiela pneumoniae* (91%). Antibiotic susceptibility patterns for LOS (vancomycin and gentamicin) and EOS (ampicilin and gentamicin) remained essentially unchanged over time in other studies (11, 15). Anti fungal was added to the routine empirical antibiotic regimen for suspected LOS, especially in very low birth weight (VLBW) in some studies (15-18), while in our studies the incidence of fungal infection was very low.

In summary, there has been a significant increase resistance to cephalothin, aminoglycosides and 3rd generation cephalosporins among other authors and our studies. In our NICU, concomitant administration of cephalothin and amikacin to suspected LOS has revealed antimicrobial resistance, and it seems it is no longer a significant effective therapeutic regimen.

Moreover, it emerges that the best choice for empiric antibiotic regimen in suspected LOS could be the combination of vancomycin and amikacin. Although, vancomycin combined with imipenem seems more effective for sever ill patients.

In conclusion, different NICUs have different epidemiology nosocomial infections. Therefore, it will be important to continue surveillance of neonatal sepsis in order to follow loosely changes in trends, to obtain information for empiric antibiotic therapy.

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