

Prevalence of Bacterial infection in septic neonates in South of Iran

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ABSTRACT

Background: Neonatal sepsis is a syndrome that occurs in the first month of life with symptoms and signs of infection with or without bacteremia. Septicemia, meningitis, pneumonia, osteomyelitis and urinary tract infections are the most common outcome. The aim of the study was to evaluate the type and antibiotic susceptibility pattern of bacterial infections in neonatal sepsis in two main OB/GYN centers affiliated with Shiraz University of Medical Sciences.

Material and methods: This retrospective study has been performed during 2016 to 2018 on 258 enrolled patients. Risk factors in early onset sepsis, such as maternal risk factors, preterm and low birth weight were collected in a standard questionnaire with the following information: sex, medical history, presence and kind of clinical symptoms of infection, and laboratory data. Isolated organisms were categorized in gram positive and negative bacteria.

Result: From 250 enrolled patients 60.4% were male. Out of 250 studied infants, 113 (45.2%) cases were preterm, and 56 (22.4%) infants were with very low birth weight. *Staphylococcus aureus*, was conducted as the most prevalent infection (62.4%), followed by coagulase-negative staphylococci (21.2%). *Escherichia coli* were detected as the most prevalent gram-negative bacteria with 8.4% prevalence. The most effective antibiotic was vancomycin in gram-positive and meropenem in gram-negative isolates, and the highest resistance to amikacin was observed in both groups of bacteria.

Conclusion: This study provides descriptive information about clinical signs and symptoms, neonatal and maternal risk factors for infant sepsis.

Keywords: Epidemiology; Antibiotic resistance; Newborn infant; Neonatal sepsis

INTRODUCTION

Neonatal sepsis is a systemic infection that occurs in infants at the first month of life with or without bacteremia which causes meningitis, pneumonia, osteomyelitis and urinary tract infections [1]. Sepsis is one of the most important causes of morbidity and mortality of newborns [2]. About 30 to 50 percent of neonatal deaths in developing countries occur due to sepsis even with the widespread use of antibiotics [3]. Neonatal sepsis is divided into early and late-onset. Early-Onset (EOS) is mostly caused by bacterial pathogens transmitted vertically from

mother to infant before or during delivery and consistently occurs in the first days of life. Preterm delivery, premature rupture of membranes, type of delivery, uterine inertia and fever, and maternal infections are the most cause of EOS [4]. Late-Onset Sepsis (LOS) may be caused by vertically or horizontally acquired pathogens and mostly may occurs in term infants after 72 h hospitalization in NICU or at first 7 days of life. In some circumstances LOS may occur up to the age of <90 or 120 days. One of the most important problems in neonatal sepsis detection is definitive diagnosis based on bacterial culture, which is time consuming and complex [5]. Although different

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microorganisms cause neonatal sepsis in different areas, group B *streptococcus*, *Escherichia coli*, *Klebsiella pneumonia* and *Listeria monocytogenes* are the most prevalent bacterial agents [6]. The development of antibiotic resistance is a major challenge in treating neonatal infections. More than half of the microorganisms that cause neonatal infections are resistant to ampicillin and gentamicin as the first-line used antimicrobials [7]. Prescription of prophylactic antibiotics and outside of stewardship guidelines causes changes in the pattern of infections and formation of resistant microorganisms. Based on some studies it has been showed that vaccine and antibiotic prophylaxis have reduced group B *streptococcus* and *E. coli* resistant predominant in united states of America [8]. Over the past two decades due to the discriminatory use of antibiotics and the lack of rationale guidelines for control of multi-drug resistance formation in pathogenic bacteria, a huge expansion happened in prevalent infections such as neonatal sepsis [9,10].

Given the higher risk of bacterial sepsis and the uncertainty of optimal empiric antimicrobial selection for infants with suspected bacterial infection, we conducted a multicenter investigation of infants with sepsis in the referral Obstetrics and Gynecology Centers affiliated with Shiraz University of Medical Sciences (SUMS). Our objective was to describe the identification of pathogenic bacteria, related risk factors, and their antimicrobial susceptibilities in infants.

MATERIALS AND METHODS

This retrospective study was designed to examine newborns with symptoms of sepsis in the referral Obstetrics and Gynecology Centers affiliated with SUMS between April 2018 to March 2020. In this study, total of 258 neonates with bacteremia were selected with following clinical features in the first three days: Fever, cold extremities, refusal to feed, vomiting, abdominal distension, bleeding, respiratory distress, grunting, apnea, cyanosis, jaundice, pallor, lethargy, excessive cry, convulsion, rash, diarrhea. Laboratory criteria: 1) Blood culture positive, 2) Micro Erythrocyte Sedimentation Rate (ESR) (>10 mm in 1st hour), 3) Total leucocyte counts (<5000 or >20000/mm³), 4) Elevated C-reactive protein (>6 mg/l), 5) Band cell count more than 20%, 6) Band cell/absolute neutrophil counts ratio (>0.2%). Content and the methods of the study was approved by the ethics committee of SUMS 99741

All risk factors, including maternal risk factors for infection, were considered. For each infant with confirmed sepsis, a standard questionnaire was designed. Demographic information, medical history, the presence of a clinical infection on medical examination, and laboratory information were collected. Clinical features included pathogenic bacteria were considered for this study with the opinion of microbiologists. To identify eligible neonates, the medical records of neonates were reviewed with invasive bacterial infections. Infants whose culture was considered contaminated were excluded from the study. For the identified neonates, demographic variables such as age and sex, medical history including premature birth and very low birth weight, clinical signs, culture results, and antibiotic susceptibility results were obtained through a standard designed questionnaire. Maternal risk factors were also considered for

infants included in the study. Antibiotic susceptibility pattern of isolates was defined according to the Clinical and Laboratory Standards (CLSI) antibiotic recommendation. Categorical variables were expressed as frequency and percentages (%), and continuous variables were expressed as mean. Continuous variables were analyzed by employing Student's t-test. Multiple logistic regression analysis was used to determine the most powerful factors, such as demographic data, including age and gender, and underlying diseases. All statistical analyses were conducted using the SPSS 18.0 software.

RESULTS

Neonates' specifications

During 2 years of study, among 258 enrolled patients, 8 (3.1%) cases were excluded due to defects in considered data. Finally, 250 patients were included in the study with EOS definition. Out of 250 samples, 150 (60%) were male and 100 (40%) were female. The minimum and maximum weight of the neonates was between 540 g and 4500 g with an average of 2478.3 g (SD: 908.3). A total of 37 (14.8%) cases were twins and multiple births. From total cases, 80 (31.8%) cases were born by vaginal delivery and the rest were born by cesarean section. From studied neonates, 113 (45.2%) cases were preterm, and 56 (22.4%) cases were with very low birth weight (<1500 g). In the studied cases, 1 minute Apgar score in 58 (23.2%) neonates was less than 7; this is while 5-minute Apgar in only 27 (10.8%) cases was less than 7.

Maternal risk factors for infection

These criteria were evaluated in 228 pregnant mothers as following:

No fever was reported in mothers during delivery. Only 6 (2.6%) mothers had a history of urinary tract infection in third trimester of pregnancy. Twenty-eight (12.3%) mothers had a premature rupture of membranes and 9 (4%) had chorioamnionitis. Among studied pregnant women, 25 (11%) individuals had a history of gestational diabetes. According to the self-declaration of studied pregnant women, no one were multi-partner, no history of HIV or sexual transmitted infections, and no one have in close contact with animals in the last trimester of pregnancy. Only one patient had cervical cerclage.

Laboratory results

Following the specific microbiology tests, gram-positive bacteria were the most prevalent infections. *Staphylococcus aureus* and coagulase-negative staphylococci with 156 (62.4%) and 53 (21.2%) isolates were the most identified gram-positive bacteria in studied samples. *Escherichia coli* with 21 (8.4%) isolates were the most prevalent gram-negative bacteria and the third prevalent infection. Other identified infections are listed in Table 1.

The results of the antibiotic susceptibility test are shown in Table 1. In summary, most of the isolated bacteria were

susceptibility to the antibiotics investigated in this study.

Table 1: Prevalence of invasive pathogen and antibiotic resistance in early-onset sepsis.

Gram-positive bacteria					
Bacteria	<i>Staphylococcus aureus</i> n (%)	<i>Coagulase negative staphylococcus</i> n (%)	<i>Bacillus spp</i> n (%)	<i>Enterococci spp.</i> N (%)	<i>Streptococci spp.</i> N (%)
Prevalence Antibiotics	156 (62.4)	53 (21.2)	3 (1.2)	2 (0.8)	2 (0.8)
Vancomycin	0	0	0	0	0
Clindamycin	28 (18)	13 (25)	0	0	1(50)
Meropenem	16 (10)	7 (13)	0	0	0
Imipenem	42 (27)	15 (28)	0	0	0
Cefixime	30 (19)	12 (23)	0	0	0
Cefepime	26 (17)	11 (21)	0	0	0
Cloxacillin	29 (19)	8 (15)	0	0	0
Oxacillin	28 (18)	6 (11)	0	0	0
Co-trimoxazole	32 (21)	15 (28)	0	0	0
Ciprofloxacin	35 (22)	12 (23)	0	0	0
Gentamycin	36 (23)	13 (25)	0	0	0
Amikacin	49 (31)	18 (34)	0	0	0
Gram-negative bacteria					
Bacteria	<i>Escherichia coli</i> n (%)	<i>Klebsiella pneumoniae</i> n (%)	<i>Pseudomonas aeruginosa</i> n (%)	<i>Acinetobacter baumannii</i> n (%)	<i>Enterobacter spp</i> n (%)
Prevalence Antibiotics	21 (8.4)	4 (1.6)	3 (1.2)	3 (1.2)	3 (1.2)
Meropenem	4 (19)	0	0	1 (33)	0
Imipenem	8 (32)	1(25)	0	1 (33)	1 (33)
Cefixime	6 (29)	0	1 (33)	1 (33)	0
Co-trimoxazole	5 (24)	0	0	0	0
Ciprofloxacin	8 (38)	0	1 (33)	1 (33)	0
Amikacin	11 (52)	1 (25)	0	1 (33)	0
Gentamycin	8 (38)	0	1 (33)	1 (33)	0
Ceftazidime	8 (38)	0	0	1 (33)	0
Cephalexin	7 (33)	1 (25)	1 (33)	1 (33)	1 (33)
Cefoxitin	11 (52)	1 (25)	0	1 (33)	0

Cefazolin	5 (24)	0	1 (33)	1 (33)	0
Cefepime	6 (29)	0	1 (33)	1 (33)	0
Piperacillin	3 (14)	0	1 (33)	1 (33)	0

DISCUSSION

Based on the study results, premature birth, low Apgar score, and very low birth weight are the most frequently observed risk factors for neonatal sepsis. Among maternal risk factors, prolonged rupture of membrane and gestational diabetes had more frequency.

In other studies, preterm birth and very low weight criteria have identified the most important risk factors in patients with neonatal sepsis [11-13]. According to studies, maternal risk factors also play a significant role in the development of neonatal sepsis, which confirms our findings [11,14-16].

In the recent study most prevalent pathogen was *Staphylococcus aureus* with the following of coagulase negative staphylococci and *Escherichia coli* isolates, respectively. The most effective antibiotics on gram-positive isolated bacteria were vancomycin, meropenem, oxacillin, cefepime, and cloxacillin and the most gram-negative bacteria were sensitive to meropenem and piperacillin. The highest resistance has been shown in all isolated bacteria to amikacin, ceftazidime, ceftazidime. Similar results were obtained in previous years by Shahian between 2004 to 2007 in on [17,18] in some other studies in and are like this study and *Staphylococcus* and *Escherichia coli* were the most common isolated organisms [11,19,20]. The results obtained from studies in Canada (2017) and America (2008-2013) shows the difference in prevalence of different bacteria, but in these countries also a high prevalence of *Escherichia coli* and *Staphylococcus* has been reported [9,21,22]. In the present study, the most effective antibiotic against gram-negative organisms was piperacillin and meropenem and the highest resistance to amikacin was observed in comparison with other tested antibiotics. The results of a systematic study of conducted in Iran showed that the most effective antibiotics against gram-negative organisms are carbapenems, which confirms our results [16]. In another study by in developing countries, carbapenems were the most effective antibiotic, consistent our results [23]. A study conducted by Dalal in 2017 India similar results to our study have been conducted and they reported that the most effective antibiotics against gram-negative isolates are piperacillin and carbapenems [24]. Previous studies in Pakistan and Egypt in 2013 have shown high susceptibility to third-generation cephalosporins [25,26], but in our study a variable degree of sensitivity to this antibiotic was observed, indicating that the administration of this group of antibiotics should be reconsidered.

In other studies in Iran, the highest susceptibility of gram-positive bacteria to vancomycin was reported [11,16,24].

Limitations of this study include the lack of antibiotic susceptibility testing for ampicillin due to the high use of this

antibiotic as prophylaxis, as well as the conduct of antibiotic susceptibility testing for vancomycin by disk diffusion method, which Performing antibiotic susceptibility testing for vancomycin by disk diffusion method, which is mentioned in the CLSI protocols as the MIC method for measuring susceptibility to this antibiotic.

CONCLUSION

The results of this study showed that preterm birth is one of the most important risk factors for neonatal sepsis. The most common gram-positive and gram-negative isolated organism was *Staphylococcus aureus* and *Escherichia coli*, respectively.

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