Clinical symptoms, laboratory, and microbial patterns of suspected neonatal sepsis cases in a children’s referral hospital in northwestern Iran

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Abstract
Sepsis is the systemic response to infection manifested as hyperthermia or hypothermia, tachycardia, tachypnea, and shock. This condition represents a major life-threatening factor in all age groups, particularly in neonatal period. The present study aimed to examine the results of blood, cerebrospinal fluid (CSF), and urine culture tests in suspected neonatal sepsis cases in northwestern Iran.

This descriptive-analytical study was conducted on suspected neonatal sepsis cases hospitalized in Tabriz Children’s Hospital. All subjects underwent complete blood count with white blood differential, C-reactive protein, blood culture and, if deemed necessary, CSF and urine culture tests and analyses. Laboratory findings in positive culture cases were scored based on the hematological scoring system (HSS) for the diagnosis of neonatal sepsis. The data were then collected, entered into SPSS v18 and analyzed.

Among 838 suspected neonatal sepsis cases, 102 (12.17%) neonates with positive cultures were examined; 59.8% of whom were male with a mean age of 9.9 days, gestational age of 36.91 weeks, and mean weight of 2.966 kg. 76.47% of neonates with positive culture were term, 69.6% had normal birth weights, 68.6% were diagnoses with late-onset sepsis, 65.6% had positive blood culture, 36.2% had positive urine culture with no positive CSF culture case. Poor feeding (39.21%) and lethargy (35.29%) were the most common clinical symptoms and previous history of hospital stay (40.19%) and surgery (21.56%) the most common risk factors for neonatal sepsis development. Results revealed that 50 (49.01%) neonates achieved HSS scores equal or greater than 2 (HSS ≥2), and that the mean HSS score in deceased positive blood culture neonates was significantly higher than that of survived ones (2.21 vs 1.37). In this study, coagulase-negative staphylococcus and Staphylococcus aureus represented the most common bacteria isolated from blood with 37.31% and 12.43%, respectively. Fungi (38.5%) and Klebsiella (28.20%) were the most common microorganism urine isolates.

The results suggested that only a small percentage of suspected neonatal sepsis cases had positive blood and/or urine cultures (12.17%) and that coagulase-negative staphylococcus (CoNS) and S. aureus were highly prevalent in positive blood cultures, whereas fungi and Klebsiella were the most common microorganisms found in positive urine cultures.

Abbreviations: CBC = complete blood count, CoNS = coagulase-negative staphylococcus, CRP = C-reactive protein, CSF = cerebrospinal fluid, S. aureus = Staphylococcus aureus.

Keywords: blood culture, neonates, sepsis, urine culture

1. Introduction
Sepsis is the systemic response to infection manifested as hyperthermia or hypothermia, tachycardia, tachypnea, and shock.[1] This condition represents a major life-threatening factor in all age groups, particularly in neonatal period.[2] The incidence of sepsis among preterm (premature) neonates is 6 times greater than that of full-term infants (approximately 1:1500 in full-term and 1:250 in preterm infants) which can be attributed to more immature immune systems of preterm infants and their prolonged periods of hospitalization which increase the risk of nosocomially contracted infections.[1] According to official statistics of Iran, neonatal infectious diseases were responsible for 4.1% of the overall neonatal mortality rate in 2001.[3]

Neonatal sepsis requires antibiotic therapy, in a way that initial supportive measures and empirical antibiotic therapy are recommended to be immediately taken and provided in suspected neonatal sepsis cases after sampling for laboratory evaluations.[4] However, a single antibiotic regimen cannot be recommended for all medical centers, with antibiotic selection being dependent on the endemic bacteria in specific centers and antibiotic susceptibility.[5,7] The incidence of sepsis and its pathogens varies across places and time periods. It can even differ in various hospitals located in a specific area.[7] Therefore, the microbial incidence of neonatal sepsis should be determined for individual medical centers and primary antibiotic regimens be prescribed accordingly. No research has been previously conducted on this subject in northwestern Iran.
Investigating previous studies on neonatal sepsis in developing countries, Vergnano et al.\[8\] concluded that conducive pathogens to neonatal sepsis in developing countries (most often Gram-negative organisms and \textit{S aureus}) differ from those seen in developed countries.

Hosseini et al.\[9\] reported incidence of sepsis in neonates whose have central lines (PICC) about 14% in Alzahra Hospital of Tabriz, and the most common cause of infection was \textit{enterococcus}.

In a study by Afjeiee et al.\[10\] in Mahdieh Hospital of Tehran, the most common neonatal sepsis bacterium was reported to be \textit{Staphylococcus epidermidis} (\textit{S epidermidis}) based on blood culture results. According to the National Neonatal Perinatal Database 2000, the most common bacteria conducive to neonatal sepsis in India were \textit{Klebsiella pneumonia} followed by \textit{S aureus}.\[11\]

Taking the specified points into account, it is incumbent upon all medical centers to identify the pathogenic neonatal sepsis microorganisms among their patients and utilize this information for subsequent therapeutic measures and proper antibiotic prescription, as the incidence of developing various microorganisms is contingent upon the condition of patients and departments, requiring various treatment protocols. Given the lack of previous research in the study region and the significance of neonatal mortality control as an indicator of national development, the present study aimed to examine neonatal sepsis to avoid future complications and medical expenses. Given its increased sensitivity in diagnosing infectious agents, the BACTEC radiometric method was used in this study to evaluate blood, cerebrospinal fluid (CSF), and urine cultures collected from septic neonates in the largest children’s medical education center in northwestern Iran. The present study aimed to examine the results of blood, CSF, and urine culture tests in suspected neonatal sepsis cases in northwestern Iran.

2. Methodology

This descriptive-analytical study was conducted on suspected neonatal sepsis cases hospitalized in Tabriz Children’s Hospital.

The subjects included all neonates under 1 month of age hospitalized in the neonatal intensive care unit (NICU) or Department of Pediatrics of Tabriz Children’s Medical Education Center during May 22, 2015 to May 20, 2016 exhibiting clinical symptoms of sepsis such as poor feeding, lethargy, reduced primitive reflexes, fever, hypothermia, apnea, cyanosis, convulsion, respiratory distress, emesis, and abdominal distension or were considered likely to have developed neonatal sepsis during hospitalization.

All subjects underwent complete blood count (CBC) with white blood differential, C-reactive protein (CRP), blood culture and, if deemed necessary, CBF and urine culture tests and analyses. Cultures were collected using the BACTEC 9120 blood culture system and the PEDS culture medium (broth). Chest or abdominal X-rays were performed in cases of respiratory or digestive symptoms. Early- or late-onset sepsis was diagnosed based on exhibited clinical symptoms during the first 72 hours or 3 to 30 days after birth, respectively. Definitive sepsis was diagnosed based on the clinical symptoms of sepsis, and positive blood or CSF or urine cultures. Cultures were immediately recollected in case of probable septic cultures.

Laboratory findings in positive culture cases were scored based on the HSS for the diagnosis of neonatal sepsis.

Data were coded and entered into SPSS v18. In order to compare quantitative variables, 1-way ANOVA and nonparametric Mann–Whitney test were used. Chi-square test was used to compare qualitative variables. Descriptive statistics were then used to tabulate and diagram data. \( P < 0.05 \) was considered the significance level in all tests.

Medical records were merely compiles in the diagnosis and treatment processes with no intervention. The study was performed after the approval of the Ethics Committee of Tabriz University of Medical Sciences (code: 94/1–5/11).

3. Findings

Eight hundred thirty-eight suspected neonatal sepsis cases were examined, 102 (12.17%) of which had positive cultures. The study was conducted on positive culture subjects. The incidence of definitive sepsis was calculated as 3.87% (102/2633) based on the total population of hospitalized neonates in the Neonatal Ward and NICU during the study period. The median neonatal age was 7 (1–35) days with 61 (59.8%) male neonates.

Results from the examination of the age of symptom onset revealed that the symptoms of sepsis were manifested in 70 neonates (68.6%) following the first 3 days after birth, meaning that they suffered from late-onset sepsis.

The mean gestational age at birth was 36.91 ± 2.67 weeks, with 78 (76.47%) full-term neonates. The mean birth weight was 2.966 ± 0.814kg, with 71 (69.6%) neonates having normal birth weights.

The study of neonatal clinical symptoms demonstrated poor feeding in 40 (39.21%) and lethargy in 36 (35.29%) neonates. It should be noted that 68 (66.66%) neonates displayed more than one symptom at the time of admission to the emergency department. In addition, risk factors for the development of sepsis were examined among subjects, with 44 (43.1%) neonates lacking such risk factors altogether. Previous history of hospitalization with 41 (48.23%) cases and surgery with 22 (23.88%) cases were the most common risk factors, respectively. The results revealed that 37 (36.27%), 16 (15.68%), and 5 (4%) neonates exhibited 1, 2, and 3 risk factors for sepsis, respectively.

CRP tests were conducted for all neonates, with 38 (36.9%) negative and 44 (43.1%) positive CRP cases. Results from the white blood cell count tests revealed that leucopenia and leucocytosis varied from a minimum of 2200 to a maximum of 27,570 cells/mm³ with a mean of 12,334 ± 5994 cells/mm³. It was also demonstrated that 12 (11.8%) and 7 (6.8%) neonates had leucocytosis and leucopenia higher and lower than 21,000 and 4500 cells/mm³, respectively.

The absolute neutrophil count (ANC) varied between 400 and 19,910 cells/mm³, with a mean of 6219 ± 4429 cells/mm³. It was revealed that 46 (45.1%) neonates had high (greater than 5400 cells/mm³) ANC levels.

The neonatal platelet counts varied from a thrombocytopenic condition of 20,000 to 808,000 cells/mm³, with a mean count of 278,000 ± 138,000 cells/mm³. After classification of neonatal platelet counts to a range of 150,000 to 400,000 cells/mm³, it was revealed that 37 (36.2%) neonates had abnormal (thrombocytopenic) platelet conditions. Results revealed that 50 (49.01%) neonates achieved HSS scores equal or greater than 2 (HSS ≥2).

Results from neonatal blood cultures indicated positive cultures in 67 (65.7%) neonates, with a number of them exhibiting positive blood cultures on more than one occasion. In general, out of 76 positive blood cultures, 38 (50.6%) cases were Gram-positive and 30 (39.47%) were Gram-negative bacteria, with the remaining 8 (10.5%) cases being fungi. Analysis of isolated pathogens from neonatal blood samples revealed that
coagulate-negative staphylococcus (CoNS) and S aureus represented the most common bacteria isolated from blood with 25 (37.31%) and 9 (12.43%) cases, respectively. It should be noted that more than 2 bacteria were isolated from neonatal blood cultures in 6 cases.

Among 102 subjects, 32 (31.37%) neonates underwent CSF culture and analysis, with positive results in merely 5 (15.62%) cases. All CSF cultures were negative. Results from urine cultures showed 39 (38.2%) cases of positive cultures with fungi (n=15, 38.5%) and Klebsiella (n=11, 28.2%) representing the most common microorganismic urine isolates.

The mean length of stay (LOS) was 18.84±17.82 days, with the majority of neonates (n=37, 36.3%) hospitalized for over 15 days. Ultimately, 75 (73.5%) neonates were discharged from the hospital with stable general conditions.

The antibiograms of neonatal blood cultures were evaluated individually, collectively, and for Gram-negative microorganisms, respectively. Results revealed that the highest antibiotic susceptibility of CoNS was to imipenem with 71.7%, followed by gentamicin (57.4%), amikacin (51.8%), and cefotaxime (40.7%) (Table 1). The highest susceptibility of S aureus to vancomycin, amikacin, gentamicin, and cefotaxime was 100%, 88.8%, 88.8%, and 53.5%, respectively. The highest susceptibility of Gram-negative microorganisms was to imipenem with 71.7%, followed by gentamicin, amikacin, and cefotaxime (40.7%) (Table 1).

Results from the relationship between isolated microorganisms and final patient outcomes revealed that, infection with K pneumonia, Acinetobacter, and Enterobacter led to 100% mortality (Chi-square=42.28, df=22, exact P-value=.02). Following the classification of neonatal microorganisms, it was demonstrated that the highest statistically significant mortality rate was associated with Gram-negative microorganisms (Chi-square=25.01, df=4, exact P-value<.001).

The results pointed to no significant relationship between isolated bacteria from urine cultures and the final patient outcome, with only one deceased case with positive fungal culture (Chi-square=2.506, df=6, exact P-value=.97).

Examining the relationship between HSS scores the final outcome of positive blood culture patients, it was shown that the mean HSS score was significantly higher in deceased patients than survived ones (Z(Mann–Whitney)=−3.065, P=.002). The mean HSS scores in terms of detected microorganisms were also evaluated, the results of which revealed that the mean HSS scores in Gram-negative microorganisms isolated from blood cultures were higher than the other 2 groups without any statistical significance (F(df1=2,df2=58)=2.81, P=.07).

### 4. Discussion

In the study by Adib et al,[12] 53% of neonates were male with a mean age of 5.73 days, gestational age of 36.8 weeks, and a 59.3% incidence of early-onset sepsis. Moaning, lethargy, and feeding problems were the most common clinical symptoms. In the study by Shamsizadeh et al,[13] 63.2% of neonates were male, with a 29.4% and 70.6% incidence of early- and late-onset sepsis, respectively. In the study by Aftab and Iqbal,[14] in India, 42% of neonates were diagnosed with early-onset sepsis and the rest (58%) with late-onset sepsis. In the study by Borna et al,[15] the mean age of septic neonates was 6.3 days with a mean gestational age of 36.8 weeks. 52.6% of neonates were male. Fever, poor feeding, neonatal icterus, tachypnea, and respiratory distress were common clinical symptoms. In the study by Rafati et al,[16] male neonates constituted 63% of septic patients and the rest were female. Twenty-seven percent of neonates were preterm, 20 neonates suffered from low birth weight (LBW), icterus, cough, convulsion, hypoglycemia, and neonatal respiratory distress syndrome. The literature review suggested that male neonates were more susceptible to septicemia (sepsis) than females, which can be attributed to gender-specific genes involved in the immune system.[17,18] In addition, fever, lethargy, and disruptive feeding behaviors were among the common symptoms reported in the majority of studies. The probability of sepsis should not be rejected if any of the specified symptoms were identified in neonates.

Examining the inflammatory status of septic neonates, it was revealed that the mean white blood cell count was 12,334, the mean ANC was 6219 and the mean platelet count was 278,000 cells/mm³. Positive CRP levels and HSS ≥2 were seen in 43.1% and 49.01% of patients, respectively. In the study by Adib et al,[12] 6.2% of neonates suffered from leukopenia with a mean leukocyte count of 11,407 cells/mm³ and a mean CRP level of 22.1 mg/dL at the time of admission. In the study by Shamsizadeh et al,[13] 68 (11.3%) neonates had positive cultures from among 593 studied cases. In the study by Aftab and Iqbal,[14] 54% of neonates had positive cultures for sepsis. In the study by Iregbu et al,[19] 22% of all suspected neonatal sepsis cases had positive blood cultures. In the study by Borna et al,[15] 61%, 7%, 74%, and 8.7% of suspected neonatal sepsis cases exhibited leukocytosis, increased neutrophil counts, increased CRP levels, and positive blood cultures. In the study by Rafati et al,[16] 20% of neonates had positive cultures for sepsis. In addition, 25%, 41%, and 2.2% positive cultures for sepsis were, respectively, reported by Shyva,[20] Samiae,[21] and Hosseini[22] the last of which was conducted in Zahedan, Iran. Comparison of the study results with those of previous studies revealed that a small percentage of neonates (12.17%) had positive cultures which can probably be attributed to the great sensitivity shown by the medical personnel of Tabriz Children’s Hospital to suspected neonatal sepsis cases.

Results revealed that 50 (49.01%) neonates achieved HSS scores equal or greater than 2 (HSS ≥2), and that the mean HSS score in deceased positive blood culture neonates was

### Table 1

| Antibiotics | CoNS | S aureus | Klebsiella spp. | Pseudomonas aeruginosa | Acinetobacter | Enterobacter spp. | Enterococcus spp. |
|-------------|------|----------|-----------------|------------------------|---------------|-------------------|------------------|
| Vancomycin  | 100  | 100      | —               | —                      | 33.3          | 33.3              | 100              |
| Gentamicin  | 76   | 88.8     | 44.4            | 100                    | 0.0           | 33.3              | 0.0              |
| Amikacin    | 72   | 88.8     | 44.4            | 100                    | 0.0           | 33.3              | 0.0              |
| Imipenem    | —    | —        | 92.3            | 100                    | 16.6          | 50                | —                |
| Cefotaxime  | 60   | 55.5     | 33.3            | 50                     | 0.0           | 33.3              | 0.0              |

CoNS = coagulate-negative staphylococcus.
significantly higher than that of survived ones (2.21 vs 1.37). Examining the relationship between HSS scores and fatal microorganism isolated from blood cultures, it was demonstrated that the mean HSS scores of neonates infected with fatal microorganisms were significantly higher than those suffering from other infections. In the study by Alijee et al.,[10] all neonates achieved HSS scores less than 3 with the exception of one neonate who achieved a score of 3. In the study by Narasimha and Harendra Kumar,[23] 100% of neonates diagnosed with definitive sepsis achieved HSS scores greater than 5. Among suspected sepsis cases, the HSS scores were 0 to 2, 3 to 4, and greater than 5 for 27%, 30.76%, and 42.3% of patients, respectively, meaning that HSS scores were significantly higher for definitive sepsis patients. In the study by Makkar et al.,[24] 16.67% and 83.33% of patients diagnosed with sepsis achieved HSS scores of 3 to 4 and higher than 5, respectively. In another study by Khair et al.,[25] the probability of sepsis development for HSS ≤ 2, 3 < HSS < 4, and HSS ≥ 5 was reported as almost improbable, probable, and highly probable, respectively. In other words, HSS ≥ 4 has a sensitivity of 100% and specificity of 60% for sepsis development. In the study by Saleem et al,[26] 51.8% and 48.2% of septic neonates had positive and negative HSS scores, respectively (n = 170). The HSS can enhance the precision of CBC and consequently be used as a screening test for sepsis diagnosis. CoNS and S aureus represented the most common bacteria isolated from blood with 37.31% and 12.43%, respectively. Fungi (38.5%) and Klebsiella (28.20%) were the most common microorganism urine isolates. In general, out of 76 positive blood cultures, 38 (50%) cases were Gram-positive and 30 (39.47%) were Gram-negative bacteria, with the remaining 8 (10.53%) cases being fungi. The most common pathogenic microorganism of neonatal sepsis in developed countries were reported as S aureus and Streptococcus pneumoniae followed by Escherichia coli (E. coli) and Klebsiella,[8] whereas negative-gram microorganisms were the predominant pathogens of neonatal sepsis in developing countries. In India, for instance, Klebsiella and Pseudomonas were reported as the most common pathogenic microorganisms of neonatal sepsis, whereas E. coli and Klebsiella were the most common pathogens in Bangladesh, Pakistan, and Saudi Arabia.[27-29] Numerous studies have been conducted on pathogenic microorganisms of neonatal sepsis in Iran. In a study in Tehran, Klebsiella constitutes 17% in one study conducted in Kashan, the most prevalent microorganisms conducive to neonatal sepsis were Klebsiella and S aureus, respectively.[31] In yet another study in Hamadan, the most common bacterial agents were reported as Pseudomonas, Klebsiella, S aureus, E coli, and S epidermidis, respectively.[32] The results of the present study correspond to a vast number of studies conducted in developing countries and Iran, with S aureus with the sole exception in that it represented 1% of the relatively common organisms in the majority of studies, whereas it constituted about 11.8% of the total neonatal sepsis blood cultures in this study. This is in line with a number of studies conducted in Asia, including India.[29]

Results revealed that the highest antibiotic susceptibility of CoNS was to vancomycin with 100%, followed by gentamicin (76%). The susceptibility of S aureus to vancomycin, amikacin, and gentamicin was 100%, 88.8%, and 88.8%, respectively. The highest susceptibility of Gram-negative microorganisms was to imipenem with 71.7%, followed by gentamicin (57.4%), amikacin (51.8%), and cefotaxime (40.7%). In other words, about 50% of Gram-negative microorganisms were resistant to cefotaxime, amikacin, and gentamicin.

In the study of Gharebaghy and Ma’amuri,[33] the antibiotic resistance of Klebsiella to cefotaxime, gentamicin, amikacin, ampicillin, and co-trimoxazole was 20%, 77%, 88%, 88%, and 18%, respectively. The antibiotic resistance of CoNS to cefotaxime, gentamicin, amikacin, and cefalotin was 25%, 50%, 30%, and 60%, respectively. In the study by Bashar and Gharebaghy,[34] the antibiotic resistance of Klebsiella (when found in blood cultures) to ampicillin, cefalotin, gentamicin, co-trimoxazole, and amikacin was reported as 100%, 90%, 80%, 70%, and 3%, respectively. Moreover, the resistance of E coli to gentamicin and amikacin was 38% and 0%, respectively. The resistance of Pseudomonas to cefalotin, gentamicin, and co-trimoxazole was 100%, 67%, and 100%, respectively. Enterobacter developed 50% resistance to cefalotin, gentamicin, and co-trimoxazole. In a study conducted by Mathur et al,[35] 95% to 97% of Gram-negative and 75% of Gram-positive microorganisms were resistance to ampicillin. In addition, Gram-negative and Gram-positive microorganisms were shown to be highly resistant to third-generation cephalosporins, particularly cefotaxime and fluoroquinolones (ciprofloxacin). Gupta et al.[36] demonstrated the high susceptibility of Gram-negative bacilli to third-generation cephalosporins, cefotaxime in particular. Third-generation cephalosporins are mainly prescribed for Gram-negative sepsis which, despite being only recently introduced to pharmaceutical markets, have been met with bacterial resistance. This is in line with the present study where a great percentage (59.3%) of Gram-negative organisms showed resistant to this drug category. Therefore, caution should be exercised in administering this drug for the treatment of serious infections. Medication selection for neonatal sepsis before culture and antibiogram results should made to cover Gram-positive bacteria such as CoNS and Gram-negative bacteria such as Klebsiella and E coli. Vancomycin and imipenem are currently administered to cover Gram-positive and Gram-negative bacteria in treating neonatal sepsis. However, extensive administration of such drugs entails the risk of resistance. The increased of antibiotic resistance to third-generation cephalosporins and aminoglycosides can be indicative of their extensive administration in departments of pediatrics. One of the most important limitations of this study is its retrospective.

5. Conclusion
It was demonstrated that the highest mortality was associated with Gram-negative microorganisms, with K pneumonia, Acinetobacter, and Enterobacter leading to 100% mortality. In addition, the extensive antibiotic resistance to third-generation cephalosporins and aminoglycosides suggests the necessity for correct planning in antibiotic consumption.

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