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Bacterial Etiology and Antibiotic Resistance Patterns in Neonatal Sepsis in the West of Iran

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Abstract

Background: Antimicrobial resistance is an important public health issue worldwide, which is prevalent in developing countries such as Iran. The present study aimed to assess the bacterial sepsis and patterns of antimicrobial susceptibility in neonatal sepsis.

Methods: This cross-sectional study was conducted on 430 neonates with the clinical suspicion of septicemia, who were admitted to the neonatal intensive care unit (NICU) of Beasat Teaching and Referral Hospital in Sanandaj, Kurdistan, and west of Iran from May 2018 to April 2019. Data analysis was performed using the WHONET software version 5.6, and the research units were described based on frequencies and proportions.

Results: From a total of 430 neonates, 41 blood cultures were positive. Early onset sepsis (EOS) and late onset sepsis (LOS) were detected in 17(41.5%) and 24 (58.5%) cases, respectively. *Coagulase-negative Staphylococci (CONS)* and *Acinetobacter spp*. were identified in 18/41 (43.9%) and 7/41(17%) isolates as the most predominant species. *CONS* and *Acinetobacter spp*. had the highest resistance against ampicillin (13; 72.2% and 5; 71.4% respectively). In addition, Gram-negative and Gram-positive bacteria both showed resistance to third-generation cephalosporins, while multidrug resistance was observed in 22 isolates (53.7%). On the other hand, the isolates of Gram-positive bacteria exhibited more efficient susceptibility patterns against third-generation antibiotics, such as clindamycin, vancomycin, and ciprofloxacin.

Conclusion: According to the results, neonatal sepsis was primarily caused by *CONS* and *Acinetobacter spp*. as they showed high resistance to first- and second-generation antibiotics at the NICU. Therefore, it is recommended that proper policies be adopted to restrict antibiotic use without prescription in the community.

Key Words: Antibiotic Resistance, Intensive Care Unit, Multidrug Resistance, Neonatal sepsis.

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1- INTRODUCTION

Neonatal sepsis is a leading cause of mortality and morbidity in neonates in developing countries (1). Furthermore, the high risk of bacterial sepsis is a major threat to the life of neonates as the prevalence rate has been reported to be 1-10 per 1,000 live births across the world. According to statistics, sepsis is a significantly more severe health issue in developing countries compared to developed countries as in the former, the mortality rate of the disease has been estimated to be 50% or higher in untreated cases (2). Early onset sepsis (EOS) is an infection that occurs within the first six days of life. And in Late onset sepsis (LOS), the clinical features of sepsis appear between 7 and 28 days of age (3-4).

EOS is considered to be a severe multi-organ disease, which is associated with pulmonary failure, meningitis, shock, acute tubular necrosis, and disseminated intravascular coagulation (5). On the other hand, LOS mainly occurs in healthy newborns after discharge from the neonatal intensive care unit (NICU). Gram-positive and Gram-negative bacteria are considered to be the leading causes of neonatal sepsis, while some cases have been attributed to fungi such as Candida species as well. The bacteria that cause neonatal sepsis have significant geographical diversity, with the spectrum constantly changing regardless of location (4, 6). Blood cultures are considered to be the 'gold standard' for the diagnosis of blood infections, which are mandatory in every case suspected of sepsis prior to the prescription of antibiotic treatment (7). Antibiotic resistance is a major health concern across the globe, and there have been growing reports regarding the spread of multidrug-resistant bacteria that cause neonatal sepsis in developing countries, especially in NICUs. Since neonatal sepsis has no specific clinical signs and symptoms, its timely diagnosis is challenging, and a key consequence of this issue is the increased use of empiric antibiotics, which may contribute to the selection and spread of antimicrobial-resistant bacterial strains. In the proper care routine for neonatal sepsis, the regular monitoring of the responsible bacterial pathogens and their susceptibility patterns are essential in every hospital setting. Recognition of the main causes of neonatal sepsis and their antimicrobial sensitivity patterns could enhance the effectiveness of therapy, while significantly decreasing antibiotic resistance (3, 6). The present study aimed to determine the etiology of neonatal sepsis and evaluate the antimicrobial susceptibility patterns in the NICU of Beasat teaching and referral hospital in Sanandaj, Kurdistan, located in the West of Iran.

2- Materials and Methods

2-1. Study Setting

This cross -sectional study was conducted at the NICU of Be'sat Teaching and Referral Hospital, in Sanandaj city, Kurdistan province, Iran during May 2018-April 2019. The NICU of this hospital admits approximately 1,900 neonates per year. During the study period, 1,822 neonates were admitted to the NICU, and the subjects were selected using the WHO (world health organization) neonatal sepsis screening tool, which was adapted to the National Neonatal Intensive Care Unit Manual (7).

2-2. Patients

Based on the time of sepsis diagnosis, the selected neonates were divided into two groups of EOS (Early onset sepsis), and LOS (Late onset sepsis). The inclusion criterion was the confirmed diagnosis of microbiological bacteremia and/or clinical sepsis. The study included consecutive cases of clinical septicemia episodes in children aged 1–30 days in the NICU.

2-3. Bacterial Isolates and Identification

Forty one blood cultures were collected from the neonates with the clinical diagnosis of sepsis. To this end, aseptic precautions were taken to obtain the blood samples by trained laboratory technicians. Following that, one milliliter of blood was drawn from a new venipuncture site and placed in bottles containing 5 milliliters of the blood culture media. At the next stage, the blood cultures were incubated aerobically (BACTEC- 9050, Co; BD USA) (6), and subcultures were prepared on various enriched, selective media, such as blood agar, chocolate agar, and MacConkey agar. The culture plates were assessed in terms of bacterial growth after incubation for 24-48 hours. Standard techniques were employed to identify the isolated bacteria; some of the main approaches in this regard included morphological and colony feature assessment, Gram staining, and evaluation of biochemical reaction properties, such as oxidase, catalase, indole, triple sugar iron agar, lysine iron agar, motility, ornithine, citrate, and urease. After seven days, no growth was observed, and the blood cultures were declared negative (7).

2-4. Antibacterial Susceptibility

The Kirby-Bauer diffusion method was applied for antibacterial sensitivity testing in accordance to the Clinical Laboratory Standard Institute (CLSI) (8). Furthermore, Mueller-Hinton agar was used with incubation for 24 hours at the temperature of 37°C. Multidrug-resistant (MDR) bacteria were determined based on resistance to three or more antimicrobial classifications (9) using several antibiotic discs, including ampicillin (10 µg), cloxacillin (5µg), Cefotaxime (30 µg), gentamicin (10 µg), amikacin (30 µg), ciprofloxacin (5 µg), vancomycin (30 µg), clindamycin (2 µg), imipenem (10 µg), erythromycin (15 µg), Tetracycline (30µg), Ceftazidime (30 µg), and Trimethoprim-sulfamethoxazol (1.25/23.75) (9).

2-5. Operational Definition

In the present study, early onset sepsis (EONS): Sepsis diagnosed in the first six days of life and late onset sepsis (LONS): Sepsis diagnosed between ages of 7 to 28 days of life (3-4). First-line antibiotics included ampicillin and gentamycin (8, 10), second-line antibiotics were third-generation cephalosporin and third-line antibiotics included clindamycin, vancomycin, and ciprofloxacin (7, 10).

2-6. Ethical consideration

This research was approved by the ethical committee of Kurdistan University of Medical sciences with the number of IR.MUK.REC.1397/5033.

2-7. Data Analyses

The analysis of the obtained data was carried out using the WHONET software version 5.6 (WHO, Geneva, Switzerland), and the research units were described based on frequencies and proportions. In all the statistical analyses, P-values less than 0.05 were considered significant.

3- RESULTS

In total, 430 neonates were admitted to the NICU of the selected hospital with the clinical diagnosis of sepsis. Among these subjects, 41 cases (9.5%) had been diagnosed based on their clinical symptoms and results of microbiological laboratory tests. According to the results, the prevalence of sepsis was higher in the male neonates (n=25; 61%) compared to the females (n=16; 39%). In addition, EOS was diagnosed in 17 neonates (41.5%), and LOS was diagnosed in 24 neonates (58.5%) (**Table 1**).

3-1. Patterns of the Isolated Microorganism

In total, Gram-positive bacteria were detected in 25 cases (61%), and Gram-negative bacteria were identified in 16 cases (39%). The neonates that were diagnosed with LOS had higher counts of

Gram-positive bacteria (n=16; 64%) (P=0.001), while 8 (50%) the bacterial isolates of the neonates with EOS were Gram-negative. It is also notable that *CONS* (n=18/25; 72%), and *Acinetobacter* (n=7/16; 43.8%) were the most frequent organisms in both EOS and LOS (**Table 2**).

Table-1: Demographic characteristics of the sample

	Neonates with EOS Number (%)	Neonates with LOS Number (%)	Total Number (%)
Blood culture results proven sepsis	17(41.5)	24(58.5)	41
Male	10(40)	15(60)	25 (61)
Female	7(43.8)	9(56.2)	16(39)

EOS: early onset sepsis, LOS: Late onset sepsis

Table-2: Distribution of isolated bacteria based on EOS and LOS upon sepsis diagnosis at NICU

Bacteria Isolated	EOS N (%)	LOS N (%)	P-value
CONS	5 (27.8)	13 (72.2)	0.001
S. aureus	2 (50)	2 (50)	
Streptococcus spp.	2 (33.3)	1 (66.7)	
E. coli	2 (40)	3 (60)	
Citrobacter spp.	2 (75)	1 (25)	
Acinetobacter spp.	3 (42.9)	4 (57.1)	
Enterobacter spp.	1(100)	0	

CoNS: Coagulase-Negative Staphylococcus; S. aureus: Staphylococcus aureus; Streptococcus spp: Streptococcus subspecies; E.coli: Escherichia coli; NICU: Neonate Intensive Care Unit.

3-2. Resistance Patterns of the Isolated Bacteria

3-2-1. Gram-Positive Bacteria

In the present study, the bacterial strains showed significant resistance to the first-line (ampicillin and gentamicin), and second-line antibiotics (third generation cephalosporin) that were used at the NICU. The resistance rates of *CONS*, *S. aureus*, and *Streptococcus* spp. against ampicillin was observed in 13 (72.2%), 2 (50%), and 1 (33.3%) organisms, respectively, while resistance to gentamicin was observed in 9 (50%), 2 (50 %), and 1(33.6%) microorganisms, respectively. Furthermore, *CONS* exhibited high resistance against tetracycline (n=14; 77.8%), and trimethoprim/ sulfamethoxazole (n=11; 61.1%). On the other hand, the lowest resistance was observed in the isolated Gram-positive bacteria against vancomycin, clindamycin, and ciprofloxacin (**Table 3**).

3-2-2. Gram-Negative Bacteria

According to the findings, the Gram-negative bacteria showed significant resistance to common empiric antibiotics used at the NICU (**Table 4**). *Acinetobacter* species and *E. coli* were extremely resistant to ampicillin (n=5; 71.4% and n=3; 60%, respectively). Similarly, these bacteria exhibited high resistance against gentamicin (n=4; 57.1% and n=3; 60%, respectively). On the other hand, imipenem, ciprofloxacin, and amikacin

were observed to be more effective against the identified Gram-negative bacteria.

Table-3: Antimicrobial resistance patterns against Gram-positive Bacteria at NICU

Antibiotics	CONS N (%)	S. aureus N (%)	*Streptococcus* spp. N (%)
Imipenem	5(27.8)	1(25)	2(66.7)
Ampicillin	13 (72.2)	2 (50)	1 (33.3)
Gentamicin	9(50)	2 (50)	2 (66.7)
Erythromycin	8 (44.4))	1 (75)	2 (66.7)
Cloxacillin	9(50)	2 (50)	1 (33.3)
Ciprofloxacin	6 (33.3)	1 (33.3)	1 (33.3)
Tetracycline	14 (77.8)	1 (33.3)	1 (33.3)
Ceftazidime	10 (55.5)	2 (50)	1 (33.3)
Trimethoprim/sulfamethoxazole	11 (61.1)	2 (50)	1 (33.3)
Vancomycin	4(22.2)	1 (33.3)	0
Clindamycin	5(27.8)	1 (33.3)	0

Table-4: Antimicrobial resistance patterns against Gram-negative Bacteria at NICU

Antibiotics	*Acinetobacter* spp N (%)	Citrobacter N (%)	E. coli N (%)	Enterobacter spp N (%)
Imipenem	2 (28.6)	1(33.3)	1(20)	0
Ampicillin	5 (71.4)	2 (66.7)	3 (60)	1(50)
trimethoprim/sulfamethoxazole	4 (57.1)	1(33.3)	3 (60)	1(50)
Gentamicin	4 (57.1)	2 (66.7)	3 (60)	1(50)
Cefotaxime	5 (71.4)	3(100)	4(80)	0
Ceftazidime	4 (57.1)	2 (66.7)	2(40)	1(50)
Amikacin	2 (28.6)	2 (66.7)	2(40)	1(50)
Ciprofloxacin	3 (42.9)	1 (33.3)	2(40)	0
Erythromycin	4 (57.1)	1(33.3)	2(40)	1(50)

3-2-3. Multidrug-resistant (MDR) Bacterial Isolates

According to the obtained results, most of the isolated bacterial strains (22 isolates; 53.7%) from the blood cultures were MDR (Multi drug resistant), mainly against first-line antibiotics.

4- DISCUSSION

The current study aimed to assess the bacterial sepsis and patterns of antimicrobial susceptibility in neonatal sepsis. Neonatal sepsis is a leading cause of morbidity and mortality, requiring immediate empirical antimicrobial therapy. Therefore, the selection of effective antibiotics to target the most common pathogens in this disease is essential (11).

According to the results of the present study, the prevalence rate of neonatal sepsis that was confirmed based on the blood cultures was higher in the neonates with LOS (24; 58.5%) compared to those with EOS (17; 41.5%). The findings reported in Egypt and South Africa in this regard are consistent with the current research (12- 13), while our findings are inconsistent with the studies conducted in Nepal (14), Tanzania (15), and Iran (16). This could be attributed to the variations in the data obtained from the blood culture examination due to the routine prescription

of antibiotics during obstetric care, which might have influenced the blood culture yield of the neonates considering the significant trans placental transfer of these antibiotics to the fetus. According to the current research, the prevalence rate of neonatal sepsis was 9.5%, which is lower than the rates reported from Egypt (32.9%) (17), Tanzania (39%) (18), and Cameroon (37%) (19); and higher than those reported from Australia (0.5 per 1, 1000) (20) and Oman (3.5%) (21). The prevalence of sepsis in other studies conducted in Iran was 7.6% (22), 10.4 %(23), and 11 % (24). The reason of the difference in the prevalence of sepsis in various parts of the world may be the factors such as differential specificity and sensitivity of the culture methods in different laboratories, socioeconomic status, race, climatic conditions, and quality of health care, and preventive strategies (25).

We identified more Gram-positive bacteria in the blood cultures compared to Gram-negative bacteria. Similar findings have been reported from Uganda (26), Tanzania (15), India (6) and Iran (22). Among bacteria isolated *CONS* was most frequently isolated; this is in line with the studies conducted in Ethiopia (27) and Iran (22), while inconsistent with the findings in Egypt and other developing countries (28- 29). However, other reports from Iran showed *CONS* as the leading cause of sepsis in 2014 (22) and 2008 (24). These results support the fact that the microorganisms causing sepsis are diverse in every region and may even remain unchanged under the same circumstances (30). Previous findings in a diversity of developing countries have confirmed the rising incidence of the infections caused by Gram-negative bacteria, especially in NICUs (15, 29, 31). According to the findings of the current research, *Acinetobacter* spp. and *Escherichia coli* were the Gram-negative bacteria that were most frequently isolated from the blood cultures; therefore, they were recognized as the major causes of neonatal sepsis. Other studies in this regard have reported *Klebsiella*, *Pseudomonas*, and *E.coli* in Latin America (32) and the Middle East (33) and *P. aeruginosa* and *CONS* in Iran (34) as the most commonly isolated bacterial organisms associated with neonatal sepsis. These differences in the etiology of bacterial sepsis in various regions can be due to different social, health and economic conditions. In previous studies in some parts of the world, consistent with our finding, prevalence of neonatal sepsis in males was higher than in females. (35-36). Guidelines on neonatal sepsis management in most healthcare centers (6) recommend the use of ampicillin and gentamicin as the first-line empiric therapy in NICUs. In the present study, most of the identified bacteria were extremely resistant. According to the findings reported in India and Egypt (4, 6), isolated bacteria had high resistance against ampicillin (85%, 95%) and gentamicin (57.3%, 72%). Our findings indicated that the Gram-positive bacteria had high resistance against the third-generation cephalosporins, which is consistent with the studies conducted in Tanzania, Nigeria, and other developing countries (15, 37-38). Moreover, our findings indicated that *CONS* had significant resistance against tetracycline (77.8%) and trimethoprim/sulfamethoxazole (61.1%), which is in agreement with the results obtained by Gheibi et al. in Iran (24). In addition, this work indicated other drugs as imipenem and erythromycin rising resistance among streptococci species. There is an increasing incidence of multi-drug resistant in Gram - positive organisms. On the other hand, our findings demonstrated that the isolated Gram-positive bacteria had the least resistance against vancomycin, clindamycin, and ciprofloxacin, which is in line with the reports of other similar findings (15, 39).

This could be attributed to the fact that antibiotics are used as third-line treatment options, less utilized at NICU. On the other hand, ciprofloxacin may not be a proper alternative for the treatment of pediatric patients due to its side-effects. According to the results of the present study, the *S. aureus* isolate (1; 33%) was resistant against vancomycin, which is inconsistent with the findings reported in Egypt and Vietnam (4, 40). This could be attributed to the rising trend of using this third-line antibiotic, as most first-line and second-line antimicrobial agents may fail in such procedures. This finding is in agreement with the previous studies in this regard (38, 40- 41). It is notable that vancomycin remains an essential first-line antimicrobial agent for the treatment of severe infections, such as methicillin-resistant *S. aureus* infection (42). Moreover, our findings were indicative of the better susceptibility of the isolated Gram-negative bacteria against amikacin and ciprofloxacin, which is in line with the previous findings in this regard (38, 40). According to the results of the present study, the Gram- negative bacteria had the highest susceptibility to imipenem, which is in congruence with the other studies (28, 43). Carbapenems (imipenem and meropenem) are reserved antibiotic agents for severe bacterial infections, which have wide applications in the treatment of spectrum β-lactamase-producing Gram-negative bacteria. These agents could be potentially used for the treatment of sepsis in the future (44). *Acinetobacter* spp. and *E. coli* were the predominant Gram-negative bacterial isolates in the current research, which were resistant to a large number of the assessed antimicrobial drugs, such as; ampicillin, third-generation cephalosporins, gentamicin, and trimethoprim/sulfamethoxazole. This is in line with the findings reported in Mexico, Morocco, and Vietnam (40, 45, 46). According to the findings of the current research, MDR Gram-positive and Gram-negative bacteria isolates were prevalent, which is consistent with the previous studies (15, 47-48). The high rate of AMR (antimicrobial resistance) could demonstrate the overuse of the mentioned agents in the empiric treatment of various neonatal health issues, which may not even be infectious in the origin.

5. CONCLUSION

According to the results, Gram-negative bacilli and Gram-positive Cocci were both highly resistant to multiple broad-spectrum antimicrobials. In addition, *CONS*, *Acinetobacter*, and *E. coli* were observed to be the major causes of neonatal sepsis, which were also extremely resistant to the first-line and second-line empiric antimicrobials that are commonly used at the NICU. On the other hand, third-line antibiotics were observed to be effective against the isolated bacteria. The development of AMR (Antimicrobial resistance) has been mainly caused by the overuse of antibiotics, and constant monitoring is required in order to upgrade the national guidelines on antimicrobial therapy.

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7- CONFLICTS OF INTEREST

None.

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