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Epidemiologic Indicators of Neonatal Sepsis in Teaching Hospitals of Ilam, Western Iran during (2012-2017)

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Abstract

Background

Neonatal sepsis is a type of neonatal infection and specifically refers to the presence in a newborn baby of a bacterial blood stream infection (BSI) in the setting of fever. This study aimed to evaluate the prevalence, pathogen distribution, antibiotic resistance pattern and the most common clinical features in infants with suspected sepsis admitted to teaching hospitals of Ilam, Iran.

Materials and Methods

This retrospective study was conducted in two teaching hospitals of Ilam city, Iran, during 2012-2017. After calculating sample size, simple random sampling was started in a total of 166 infants; of these, 22 infants were excluded from the study. The data collection method for each record was reviewed by two researchers and finally, the accuracy of the data extracted was examined by the third researcher. Required data were extracted based on the prepared checklist.

Results

The prevalence of neonatal sepsis was estimated to be 10.4%. The most common pathogens were *Escherichia coli* (46.7%), and *Staphylococcus epidermidis* (20%). Prematurity (46.7%) and low birth weight (35.4%) were the most common risk factors for sepsis. The most common clinical features in neonatal sepsis were lethargy (53.3%), jaundice (46.7%), and respiratory distress (40%), respectively. Neonatal sepsis was not significantly correlated with mother's age, gestational age, infant's age, infant's weight, gender, and normal vaginal delivery ($p>0.05$).

Conclusion

The results of the study showed that prevalence of neonatal sepsis was 10.4% and the most common pathogen was *Escherichia coli.* Lethargy, jaundice and respiratory distress, were the most common clinical features in neonatal sepsis.

Key Words: Antibiotic resistance, Iran, Neonatal Sepsis, Prevalence.

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1- INTRODUCTION

Neonatal sepsis is a bacterial infection that initially affects blood flow in infants during the first four weeks of life (1). Neonatal sepsis is divided into two types of early-onset and late-onset: the early-onset type is in infants younger than 7 days of age, most of them caused by pre- and postpartum factors and the late-onset type is in infants older than 7 days, most of them caused by environmental and hospital factors (2, 3). Despite recent advances in healthcare, of all children who died under-five years, 51.8% died of infectious causes, and 44% died in the neonatal period (4, 5), and most of these deaths occur in low-income countries (7.6%) that infection, prematurity, and asphyxia are the main causes of deaths. Approximately, 1.6 million of these mortalities were attributed to infectious causes, including sepsis, meningitis, and pneumonia (8).

The various prevalence of neonatal sepsis in different countries depend on the level of health and healthcare system, and the prevalence of this disease in developing countries is much higher than developed countries (9-10). Many factors increase the chance of developing neonatal sepsis, including premature rupture of membranes (PROM), complicated childbirth, uterine inertia, fever and pyelonephritis in the mother (11-12). Delay in the treatment of neonatal sepsis leads to a high level of mortality, hence the disease requires rapid diagnosis and treatment (13-14). It takes at least 72 hours to complete the blood culture and to reach a definitive answer. Therefore, for the treatment of these patients, empiric antibiotics are commonly used until the initial results of the laboratory are prepared (15-16). Clinical features of sepsis are mostly non-specific, but the most important clinical features of this disease include failure to feed, icterus, lethargy, tachycardia, narcosis, cyanosis, respiratory distress, fever and seizure (17-19). Antibiotic resistance patterns and bacterial agents involved in neonatal sepsis can be diverse in different countries, cities, and even hospitals (3, 20-21). Studies have shown that in developing countries, *Group B streptococcu*s and *Escherichia coli* (*E.coli)* played the more important role in neonatal sepsis (22). In a study in Iran, infections caused by *Klebsiella* were identified as the most common pathogens of neonatal sepsis (23). Knowing the most common bacterial agents and their antibiotic patterns in each region and city may play a significant role in selecting the appropriate antibiotic for empiric treatment (24). Therefore, this study was conducted to determine the prevalence of sepsis, pathogen distribution, drug resistance pattern and clinical features in infants with suspected sepsis admitted to the teaching hospitals affiliated to the Ilam University of Medical Sciences, Ilam (Western Iran).

2- MATERIALS AND METHODS

2-1. Study Design and Ethical Approval

This retrospective cross-sectional study was begun after approval by the Ethics Committee of Ilam University of Medical Sciences.

2-2. Study area and study population

Ilam one of the city of Ilam province is located in west of Iran. This city is closed by mountains, with highly variable annual weather profile. Its population is Kurdish and Muslim. In 2011 census, the population of the Ilam city is approximately 213,579 people (**Figure.1**). Study population was all admitted infants with suspected sepsis in teaching hospitals of Ilam. The sample size was estimated based on Sayehmiri et al. study (10) with the neonatal sepsis prevalence of 14.3% for 94 participants using the following formula = $1/d^2(z^2\ P[1-P])$ with a 95% level of the confidence interval (CI), and 7% as a margin of error. The sampling method of this study was simple random. This study

was performed by investigating all medical records of admitted infants with suspected sepsis in Imam Khomeini and Mostafa Khomeini hospitals, affiliated to Ilam University of Medical Sciences, during a four-year period (March 2012 to December 2017) through the census.

Fig.1: The location of Ilam City, West of Iran.

2-3. Inclusion and exclusion criteria

The inclusion criteria were all admitted infants with suspected sepsis, and the exclusion criteria were a major defect in the file, lack of blood culture, and admission date outside 2012 to 2017.

2-4. Data collection

In order to extract the required information, a checklist was prepared according to the study objectives, including: file number, hospitalization date, age of the infant, gender, weight, hospitalization section, type of delivery, place of birth, gestational age, clinical manifestations, the result of blood culture, urine culture and cerebrospinal fluid, the result of anti-bio gram, maternal age, maternal education, and neonates blood type. The data collection method for each record was reviewed by two researchers (with a minimum undergraduate degree in medicine), and finally, the accuracy of the data extracted was examined by an expert (a pediatric infectious disease specialist).

2-5. Definitions

The definitive diagnosis of sepsis was defined as positive blood culture in suspected cases. Early-onset neonatal sepsis was defined as sepsis in infants younger than 7 days old and late-onset sepsis was defined as sepsis in infants older than 7 days old (2-3).

2-6. Data analysis

Data were analyzed using SPSS software (version 18.0). Central index and dispersion index was used in the descriptive statistics and Chi-square and t-test were used based on Kolmogorov-Smirnov test in analytical statistics. P-value less than 0.05 were statistically significant.

3- RESULTS

3-1. Characteristics of the subjects

After applying the inclusion and exclusion criteria, of 166 infants with suspected sepsis during these years, 22 cases were excluded due to defects in the file and not doing a blood culture. Finally, 144 neonates were entered into the study (47, 22, 29, 5, 34 and 7 cases for years of 2012, 2013, 2014, 2015, 2016 and 2017, respectively). Of 144 infants with suspected sepsis, 70 (54.3%) were boys. The mean age and weight of newborns were 1.46 ± 2.75 days and 2751.21 ± 768.78 gr, respectively. Eighty-three infants (64.3%) were the result of cesarean section. The mean age and gestational age of mothers was 28.64 ± 5.70 years and 35.92 ± 2.90 weeks. Mothers with high school diploma had the highest frequency (34.7%) (50 infants); other demographic features are shown in **Table.1**.

3-2. Prevalence and etiology

The prevalence of neonatal sepsis was estimated to be 10.4%. It prevalence for years of 2012, 2013, 2014, 2015, 2016 and 2017 was estimated to be 4.3%, 0%, 24.1%, 0%, 14.7%, and 14.3%, respectively (**Figure.2**); and relationship of prevalence of neonatal sepsis and tear of the study was significant (p = 0.39). No significant correlation was found between infants' age and neonatal sepsis (p = 0.69). All cases of sepsis were of the early-onset type. The organisms of *E.coli* with 7 cases (46.7%) and after that, *Staphylococcus epidermidis* with 3 cases (20%) were the most frequent pathogens (**Figure.3**).

3-3. Clinical features

Table.2 shows the clinical features in infants with positive and negative blood culture. The most common clinical features in infants with positive blood culture were lethargy (8 infants, 53.3%), jaundice (7 infants, 46.7%), respiratory distress (6 infants, 40%).

3-4. Risk factors

In infants with neonatal sepsis, the most common risk factors were prematurity (46.7%), and low birth weight (35.4%). Neonatal sepsis was not significant relationship with Mother's age (p = 0.10), gestational age (p = 0.17), infant's age (p = 0.69), infant's weight (p = 0.39), gender (p = 0.59) and normal vaginal delivery (NVD) (p = 0.26) (**Table.3**).

3-5. Antibiotic resistance

An antibiotic sensitivity and resistance pattern for other bacteria is shown in **Table.4.** *E. coli* was susceptible and resistible to antibiotics such as ampicillin (2 sensitive case [66.7%] and 1 resistant case [33.3%]), vancomycin (2 sensitive case [50%] and 2 resistant case [50%]), gentamicin (2 sensitive case [66.7%] and 1 resistant case [33.3%]), cefazolin (2 sensitive case [66.7%] and 1 resistant case [33.3%]), ceftizoxime (1 resistant case [100%]), trimethoprim (4 sensitive case [100%]), ciprofloxacin (2 sensitive case [100%]) and ceftriaxone (3 sensitive case [75%] and 1 resistant case [25%]), nitrofurantoin (1 sensitive case [100%]), Imipenem (1 sensitive case [50%] and 1 resistant case [50%]), cefalotin (1 resistant case [100%]), Clindamycin (1 sensitive case [50%] and 1 resistant case [50%]), penicillin (1 sensitive case [50%] and 1 resistant case [50%]), and cefotaxime (3 sensitive case [100%]).

Table-1: Demographic characteristics of neonates and mothers in teaching hospitals of Ilam during 2012-2017

Variables		Non-sepsis		Sepsis		
		Mean ±SD		Mean ±SD		P-value
Mother's age (year)		28.30±5.4		30.78±7.80		0.1
Gestational age (week)		35.78±2.90		36.87±2.20		0.17
infant's age (day)		1.69±3.4		1.33±1		0.69
Birth weight (gr)		2733.8±789.07		2910±473.09		0.39
Variables		Frequency	Percent	Frequency	Percent	P-value
Mother's education	Under the diploma	26	28.3	1	16.6	0.56
	Diploma	45	48.9	5	83.3	
	Associate Degree	6	6.5	0	0	
	Bachelor's degree	13	14.1	0	0	
	Master degree	2	2.2	0	0	
Delivery	NVD	46	35.7	3	20.0	0.26
	CS	83	64.3	12	80.0	
Gender	Boy	70	54.3	7	46.7	0.59
	Girl	59	45.7	8	53.3	

SD: Standard deviation; NVD: Normal vaginal delivery; CS: Cesarean section.

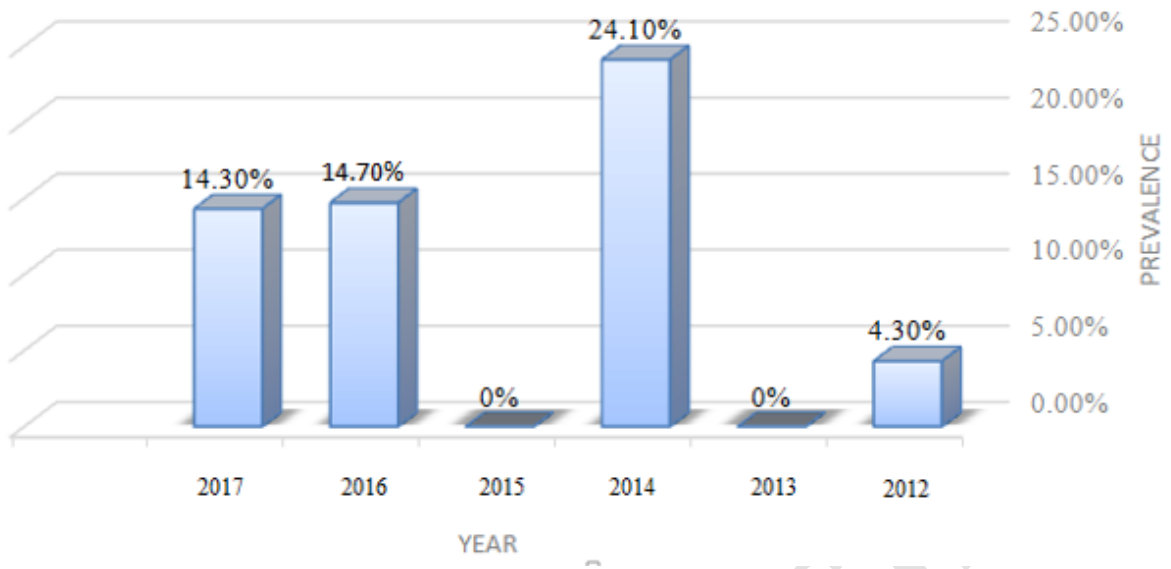

Fig.2: The prevalence of neonatal sepsis based on years of the study.

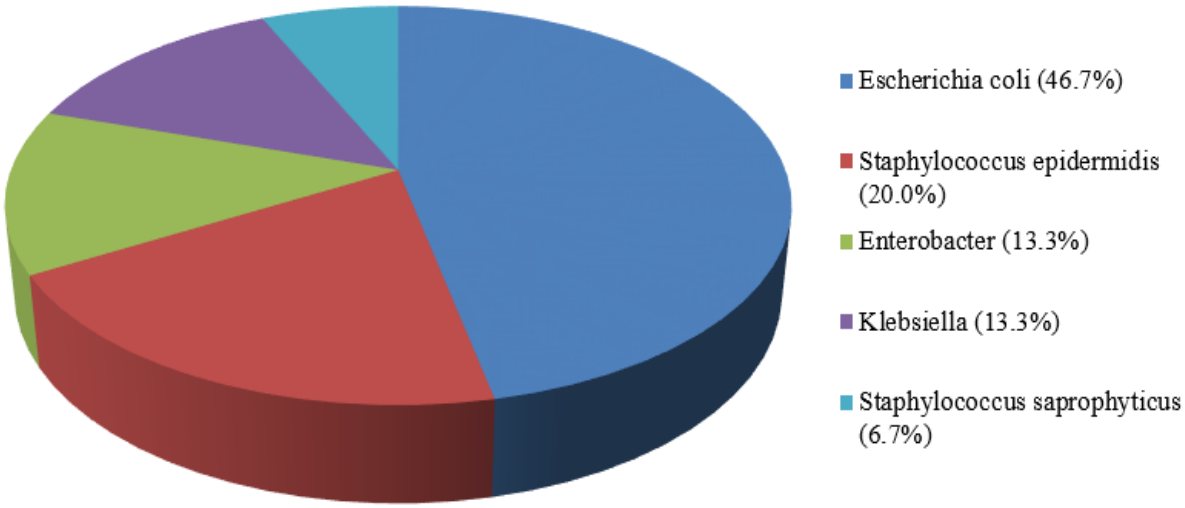

Fig.3: Frequency of isolated bacteria from neonatal blood culture.

Table-2: Frequency of neonatal clinical features and its relation with sepsis in teaching hospitals of Ilam during 2012-2017

Clinical features		Non-sepsis	Sepsis	P-value
		Frequency (percent)	Frequency (Percent)	
Lethargy	Yes	57 (44.2)	8 (53.3)	0.58
	No	72 (55.8)	7 (46.7)	
	Total	129 (100)	15 (100)	
Respiratory distress	Yes	52 (40.3)	6 (40)	0.90
	No	77 (59.7)	9 (60)	
	Total	129 (100)	15 (100)	
Jaundice	Yes	40 (31)	7 (46.7)	0.25
	No	89 (69)	8 (53.3)	
	Total	129 (100)	15 (100)	
Cyanosis	Yes	22 (17.1)	4 (26.7)	0.47
	No	107 (82.9)	11 (73.3)	
	Total	129 (100)	15 (100)	
Failure to feed	Yes	23 (17.8)	1 (6.7)	0.46
	No	106 (82.2)	14 (93.3)	
	Total	129 (100)	15 (100)	
Weak sacking	Yes	27 (20.9)	2 (13.3)	0.73
	No	102 (79.1)	13 (86.7)	
	Total	129 (100)	15 (100)	
Hypotonia	Yes	20 (15.5)	2 (13.3)	0.90
	No	109 (84.5)	13 (86.7)	
	Total	129 (100)	15 (100)	
Reducing neonatal reflexes	Yes	12 (9.3)	0 (0)	0.61
	No	117 (90.7)	15 (100)	
	Total	129 (100)	15 (100)	
Granting	Yes	6 (4.7)	3 (20.0)	0.053
	No	123 (95.3)	12 (80.0)	
	Total	129 (100)	15 (100)	
Nausea and vomiting	Yes	14 (10.9)	1 (6.7)	0.90
	No	115 (89.1)	14 (93.3)	
	Total	129 (100)	15 (100)	
Fever	Yes	10 (7.8)	2 (13.3)	0.36
	No	119 (92.2)	13 (86.7)	
	Total	129 (100)	15 (100)	
Gastrointestinal bleeding	Yes	5 (3.9)	1 (6.7)	0.49
	No	124 (96.1)	14 (93.3)	
	Total	129 (100)	15 (100)	
Restlessness	Yes	4 (3.1)	0 (0)	0.90
	No	125 (96.9)	15 (100)	
	Total	129 (100)	15 (100)	

Table-3: Risk factors for neonatal sepsis in teaching hospitals of Ilam during 2012-2017

Risk factors		Non-sepsis	Sepsis	P-value	Test
		Frequency (Percent)	Frequency (Percent)		
Gender	Boy	70 (54.3)	7 (46.7)	0.59	Chi-square
	Girl	59 (45.7)	8 (53.3)		
	Total	129 (100)	15 (100)		
Prematurity	Yes	65 (50.4)	7 (46.7)	0.99	Chi-square
	No	44 (47.3)	6 (60)		
	Total	129 (100)	15 (100)		

PROM	Yes	29 (22.5)	2 (21.5)	0.52	Chi-square
	No	100 (77.5)	13 (86.7)		
	Total	129 (100)	15 (100)		
Pyelonephritis in mother	Yes	3 (2.3)	0 (0)	N/A	Chi-square
	No	126 (97.7)	15 (100)		
	Total	129 (100)	15 (100)		
LBW	Yes	47 (36.4)	4 (26.7)	0.57	Chi-square
	No	82 (63.6)	11 (73.3)		
	Total	129 (100)	15 (100)		
NVD	Yes	46 (35.7)	3 (20)	0.26	Chi-square
	No	83 (64.3)	12 (80)		
	Total	129 (100)	15 (100)		
Variables		Mean ±SD	Mean ±SD	P-value	T-test
Mother's age (year)		28.30±5.4	30.78±7.8	0.1	T-test
Gestational age (week)		35.78±2.9	36.87±2.2	0.17	T-test
Infant's age (day)		1.69±3.4	1.33±1	0.69	T-test
Birth weight (gr)		2733.8±789.07	2910±473.09	0.39	T-test

PROM: Premature rupture of membranes; LBW: Low birth weight; Normal vaginal delivery; SD: Standard deviation.

Table 4: Risk factors for neonatal sepsis in teaching hospitals of Ilam

Risk factors		Non-sepsis		Sepsis		P-value	Test
		Frequency	Percent	Frequency	Percent		
Gender	Boy	70	54.3	7	46.7	0.59	Chi-square
	Girl	59	45.7	8	53.3		
	Total	129	100	15	100		
Prematurity	Yes	65	50.4	7	46.7	0.99	Chi-square
	No	44	47.3	6	60.0		
	Total	129	100	15	100		
Premature rupture of membranes	Yes	29	22.5	2	21.5	0.52	Chi-square
	No	100	77.5	13	86.7		
	Total	129	100	15	100		
Pyelonephritis in mother	Yes	3	2.3	0	0	N/A	Chi-square
	No	126	97.7	15	100		
	Total	129	100	15	100		
LBW	Yes	47	36.4	4	26.7	0.57	Chi-square
	No	82	63.6	11	73.3		
	Total	129	100	15	100		
NVD	Yes	46	35.7	3	20.0	0.26	Chi-square
	No	83	64.3	12	80.0		
	Total	129	100	15	100		
Variables		Mean ±SD		Mean ±SD		P-value	T-test
Mother's age (year)		28.30±5.4		30.78±7.80		0.1	T-test
Gestational age (week)		35.78±2.90		36.87±2.20		0.17	T-test
Infant's age (day)		1.69±3.4		1.33±1		0.69	T-test
Birth weight (gr)		2733.8±789.07		2910±473.09		0.39	T-test

LBW: Low birth weight; Normal vaginal delivery; SD: Standard deviation.

4- DISCUSSION

In this study, the prevalence of sepsis among infants with suspected sepsis was 10.4%, and the most common pathogen involved in the etiology of neonatal sepsis was *E. coli*. The most common clinical features of neonatal sepsis included lethargy, respiratory distress, and jaundice. Prematurity and low birth weight was the most common risk factors for sepsis. In addition, in gram-negative bacteria, a high percentage of resistance to third-generation cephalosporins (cefotaxime, ceftizoxime, cefoperazone, ceftriaxone, ceftazidime, and moxalactam) was obtained and for gram-positive bacteria, they were resistant to vancomycin in all cases. In different studies in different parts of Iran, the prevalence of neonatal sepsis is reported to be 4% to 50% (10, 23-27). By comparing the results of the studies, it can be observed that the prevalence of this disease varies in different regions of Iran. This could be caused by differences in the level of health, economic conditions and other factors associated with the disease in different regions. In a meta-analysis in Iran (10), the total prevalence of neonatal sepsis was 14.3%, and it was 11% in Western Iran. In other studies from developing countries such as Nepal, Tanzania, Ethiopia, Pakistan, and Egypt were 28.3%, 38.9%, 44.7%, 59.8%, and 40.7%, respectively (3, 28-31).

In the present study, the most common risk factor for neonatal sepsis was prematurity and low birth weight. However, there was no significant difference between the positive and negative culture groups, which was probably due to small sample size. History of maternal urinary tract infection or sexually transmitted infection, intra-partum fever, place of delivery; health center delivery, Premature rupture of membranes (PROM), meconium-stained amniotic fluid, foul-smelling amniotic fluid, prematurity, low birth weight, not crying immediately at birth, low APGAR score at birth are as strong risk factors for neonatal sepsis (32-35). In most studies, prematurity and low birth weight is major risk factors for sepsis (7, 21, 36, 37). The reason for this can be attributed to the undeveloped immune system so that the conditions for the activity of microorganisms and the occurrence of sepsis are provided. On the other hand, premature infants are admitted to the Neonatal Intensive Care Unit (NICU), and stay longer than the term infants. Hence, the likelihood of getting infections in the hospital increases. In the present study, the most common clinical features in infants with sepsis were lethargy distress and jaundice. The spectrum of clinical features has been reported in other Iranian studies; in the studies of FesharakiNia and Miri (38), Matinizadeh et al. (39), and Borna et al. (40), failure to feed was reported as the most common clinical features.

In the study of Mosayebi et al. (41) neonatal hyporeflexia and anorexia, in an Arab study (42) Neonatal Hyporeflexia and failure to feed, and Rafati et al. study (13), jaundice and cough were reported as the most common clinical features. In other countries studies such as Jain et al. study (32) respiratory distress syndrome, in Lim et al. study (43) apnea and/or bradycardia and/or cyanosis, increased respiratory effort and poor activity, and Shitaye et al. study (34) hypothermia, respiratory distress and failure to feed were reported as the most common clinical features. These differences confirm that we cannot identify specific clinical features for sepsis in infants. In the present study, gram-negative bacteria were the cause of infant sepsis in 73.3% of cases, and the most common gram-negative organism was *E. coli*. In studies in developing countries, gram-negative bacteria have been identified as the most common bacterial agents for sepsis (44). In other countries studies, *E. coli* have been reported as the most common bacterial

agents for sepsis (45-47). But in some studies, such as Wu et al. (4) (*group B streptococci*) and Shitaye et al. study (34) (*Klebsiella*) was the most common organisms for sepsis, but *E. coli* was also common. In Iran, the bacterial agents involved in neonatal sepsis have been reported in different regions (48-52), and the most common involved microorganisms include a range of gram-positive and gram-negative (*Escherichia coli, Klebsiella, Enterobacteriaceae*) (26, 27, 39, 51). Differences in the etiology of bacterial sepsis in different regions can be due to different economic, social and health conditions in these regions. Therefore, considering that gram-negative bacteria in this study were the most common causes of neonatal sepsis, they should be considered for proper empiric treatment in Iran.

In this study, gram-negative bacteria had the highest resistance to ceftriaxone (57.1%), vancomycin (50%). In addition, gram-positive bacteria had the highest susceptible to trimethoprim (87.5%). In the study of Rashidi et al., the two antibiotics of ciprofloxacin and cefotaxime were reported as the most susceptible antibiotics for the treatment of gram-negative bacteria (51). In the study of Gyawali et al. (52), the most effective antibiotic for gram-positive was vancomycin and ofloxacin was the most effective for gram-negative bacteria. In a study by Behjati et al. (53), the most sensitive antibiotics for gram-negative bacteria were amikacin and cotrimoxazole; while amikacin and cefalotin were the most sensitive for gram-positive bacteria (48). In the study of Dezfoolimaneshm et al. (27), the most sensitive antibiotics were ciprofloxacin, imipenem, and cotrimoxazole for gram-negative bacteria, and ciprofloxacin, imipenem, ceftriaxone for gram-positive bacteria. Comparing the results shows that the pattern of antibiotic resistance varies in different regions and changes over time.

4-1. Strengths and Limitation of Study

One of the limitations of this study was the small sample size. One of the strengths of the current study was examined the various aspects of the epidemiology of neonatal sepsis that could be helpful to physicians.

5- CONCLUSION

This study provides useful information on the prevalence, bacterial etiology, antibiotic resistance patterns and the most common clinical features in infants with suspected sepsis to the physicians and health policymakers. The results of the study showed that prevalence of neonatal sepsis was 10.4% and the most common pathogen was *E. coli*. Lethargy, jaundice and respiratory distress, were the most common clinical features in neonatal sepsis. In this study, the most common etiology for neonatal sepsis was prematurity and low birth weight. Therefore, increasing the pre-natal health care can prevent the birth of such infants. Considering the fact that most of the bacterial agents in the present study were gram-negative, for the initial treatment of neonatal sepsis, anti-bio gram should be tested using effective antibiotics in this region, until antibiotic testing is completed.

6- CONFLICT OF INTEREST: None.

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