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Original Article

Comparative study between different types of neonatal sepsis among newborns admitted to the neonatal intensive care unit in Mataria Teaching Hospital, Cairo

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Abstract

Background
Sepsis is the most frequent cause of neonatal deaths globally, varying in incidence between different countries. Sepsis is a burden on families and health care resources.

Objectives
To identify prevalence, type of organism, and outcome of early-onset sepsis (EOS) and late-onset sepsis (LOS).

Patients and methods
A cross-sectional study was conducted at the neonatal ICU of Mataria Teaching Hospital from November 2018 to October 2019. Demographic, clinical, and laboratory data of proved septic neonates were collected. Classification of cases according to the onset of sepsis: EOS (group I), in which sepsis is presented clinically before the third day of life, and LOS (group II), in which sepsis presented clinically after the third day of life. The LOS is subsequently divided into hospital-acquired infection (nosocomial infection) (group IIa) and community-acquired infection group (group IIb).

Results
A total of 51 neonates were diagnosed as having sepsis, with a prevalence of 2.8% of total admitted neonates for EOS and 4.4% for LOS (3.7% for nosocomial and 0.7% for community-acquired infection). Vomiting, poor feeding, and respiratory distress were the commonest presenting symptoms in EOS and LOS. Blood transfusion is needed mostly in EOS. Gram-negative organisms were common in EOS and nosocomial infection, whereas gram-positive organisms were the commonest in community-acquired infection. *Klebsiella* was the commonest responsible organism for neonatal sepsis, which is sensitive to meropenem, imipenem, and ciprofloxacin. The total mortality rate was 25%, with no difference among the three groups.

Conclusion
Late onset sepsis (LOS) has a higher prevalence than early-onset one. *Klebsiella* was the commonest responsible organism for neonatal sepsis in our unit, and the most sensitive antibiotics are imipenem, meropenem, and ciprofloxacin regardless the onset of sepsis. Still neonatal sepsis has a high mortality rate irrespective of the onset of sepsis.

Keywords: Community-acquired infection, early-onset sepsis, hospital-acquired infection, late-onset sepsis

Introduction

Sepsis is an important cause of morbidity and mortality among newborn infants. The global annual cases of neonatal sepsis was 1.3 million cases [1] with 15.6% mortality [2]. Neonatal sepsis can be caused by a variety of organisms, making it difficult to design appropriate antibiotic regimens [3].

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Pathogens that cause neonatal sepsis vary in range and relative relevance depending on other factors such as the timing of infection (e.g. perinatal or postnatal) and whether the infection was acquired in the community or in a hospital [4]. Neonatal sepsis is divided into two categories: early-onset sepsis (EOS), which presents clinically before the third day of life, and late-onset sepsis (LOS), which presents clinically after the third day of life [5]. Another classification considers EOS and LOS if it happened before or after the first week of life [6]. Neonatal sepsis consumed around five hundred billions US$ in sub-Saharan Africa [7]. In spite of the advances in infection control measures and strict protocols used in NICUs especially for preterm neonates, neonatal sepsis prevalence has increased in conjunction with increased antibiotic resistant to both gram-negative and gram-positive organisms, with a higher mortality rate [8].

Aim

The aim was to identify the prevalence, type of organism, antibiotic sensitivity, and outcome of EOS and LOS.

Patients and Methods

A cross-sectional study was conducted at the neonatal ICU of Mataria Teaching Hospital from November 2018 to October 2019. Demographics, maternal history of infection, birth weight and gestational age, length of hospital stay (LHS), and clinical data (fever, hypothermia, mottling skin, respiratory distress, poor feeding, diminished activity, lethargy, and/or seizures) were all obtained from all admission sheets. Complete blood count, C-reactive protein, and blood cultures are examples of laboratory tests that were collected. The cases with proved sepsis by blood culture were classified into three groups: EOS (group I) in which sepsis diagnosed less than third day of life, and LOS (group II) in which sepsis presented after third day of life, which was subsequently divided into nosocomial infection (group IIa) community-acquired infection group (group IIb). Inclusion criteria were all neonates admitted in the period from November 2018 to October 2019. Exclusion criteria were neonates with congenital anomalies, surgical condition, and/or with suspected immune deficiency (positive family history, frequent neonatal deaths, physical dysmorphism, or characteristic clinical examination).

Sample size

The estimated required sample size of 48 neonates was calculated assuming the proportion of LOS in the population is 0.40 [4], alpha = 0.05, power = 0.80 with confidence interval 95%. The sample size was calculated using STAT 10.

Statistical analysis

After collection of data and coding, the data were entered into IBM computer. Mean, standard deviation (SD), and range (minimum and maximum) were used for description of quantitative data and frequency tables were used for qualitative data. χ^2 test was used to compare qualitative data, and *P* value at a level of 0.05 significance was used. The statistical package for the social sciences program (version 20.0; SPSS Inc., Chicago, ILLinois, USA), was used to conduct the statistical analysis.

Ethical consideration

This study was approved by the Committee of Ethics of GOTHI, and informed consent was taken from the parents.

Results

The study included 51 neonates. Neonates with EOS were 20, with a prevalence was 2.8% of totally admitted cases, and neonates with LOS were 31, with a prevalence of 4.4% (3.7% for nosocomial and 0.7% for community-acquired infection). Comparison between the studied groups revealed no statistically significant difference regarding sex, maternal infection, gestational age ($P > 0.05$), and birth weight (Table 1). Preterm babies were 35% in group I, 53.8% in group IIa, and 60% in group IIb. Signs of sepsis are present in all of the studied groups with different frequencies. In EOS, hyperthermia was found in only one (5%) neonate, whereas 30% of the included neonates had hypothermia. In nosocomial infection, five (19.2%) neonates had hyperthermia, whereas six (23.1%) had hypothermia. Seizures, diarrhea, and abdominal distention were predominant with community-acquired infection. The majority of community acquired infection does not require blood transfusion (80%), whereas 40% of EOS and 38.5% of nosocomial sepsis had history of blood transfusion (Table 2).

There is no significant difference between the studied groups regarding hemoglobin, white blood cell, platelet counts, and C-reactive protein.

In our study, *Klebsiella* was the commonest organism responsible for EOS and LOS, and both *Klebsiella* and *Staphylococcus aureus* were the commonest organisms detected in community-acquired infection (Tables 3 and 4).

Ciprofloxacin was the most sensitive antibiotic followed by amikacin and gentamicin. *Klebsiella* was equally sensitive

Table 1: Comparison between studied groups regarding history of maternal infection, sex, body weight, and gestational age

	Group I (20, 39%)	Group II (*n*=31) [*n* (%)]		*P*
		Group IIa (26, 51%)	Group IIIb (5, 10%)	
Maternal Infection (*n*=36)	13 (65)	20 (76.9)	3 (60)	>0.05
Sex				>0.05
Female (*n*=14)	7 (35)	6 (23.1)	1 (20)	
Male (*n*=37)	13 (65)	20 (76.9)	4 (80)	
	Mean±SD	Mean±SD	Mean±SD	*P*
GA (weeks)	35±3	35±4	34±4	>0.05
BW (kg)	2.17±0.73	2.38±1.03	2.26±75	>0.05

BW, birth weight; GA, gestational age.

to meropenem, imipenem, and ciprofloxacin in most of the cases (Table 5).

Table 6 shows a statistically significant difference between the studied groups regarding the type of causative organism, with *P* value of 0.02, as most of EOS and nosocomial infections were caused by gram-negative organisms, and most of community-acquired infections were caused by gram positive organisms.

There was no statistically significant difference comparing early and late neonatal sepsis cases and nosocomial infection with respect to mortality, with *P* value more than 0.05 (Table 7). The mortality ratio between male to female was 3: 1, being prominent in males (Table 8).

Table 2: Distribution of the clinical presentation and the need of blood transfusion between the studied groups

	Group I (20, 39%)	Group II (*n*=31) [*n* (%)]	
		Group IIa (26, 51%)	Group IIb (5, 10%)
Hyperthermia	1 (5)	5 (19.2)	1 (20)
Hypothermia	6 (30)	6 (23.1)	1 (20)
Mottling	10 (50)	17 (68)	3 (60)
Respiratory distress	17 (85)	24 (92.3)	4 (80)
Poor feeding	15 (75)	19 (73.1)	4 (80)
Vomiting	20 (100)	26 (100)	5 (100)
Seizures	1 (5)	2 (7.7)	0
Diarrhea	1 (5)	2 (7.7)	2 (40)
Abdominal distension	4 (20)	7 (29.2)	2 (40)
Central line catheter	2 (10)	3 (11.5)	1 (20)
Blood transfusion			
Once	7 (35)	4 (15.4)	0
>Once	1 (5)	6 (23.1)	1 (20)

Table 3: Complete blood count and C-reactive protein in the studied groups

	Group I (mean±SD)	Group II		*P*
		Group IIa (mean±SD)	Group IIIb (mean±SD)	
Hemoglobin	11.7±6.5	10.6±5.4	13.4±2.6	>0.05
WBCs	13.5±7.3	15.1±8.8	8.0±6.8	
Platelet	151.3±355.6	128.4±139.8	22±12.4	
CRP	28.4±29.7	40.1±35.9	96±45.6	

CRP, C-reactive protein; WBC, white blood cell.

Table 4: Causative organisms in the studied groups

Organism	Group I (20, 39%)	Group II (*n*=31) [*n* (%)]	
		Group IIa (26, 51%)	Group IIb (5, 10%)
Klebsiella (*n*=27)	8 (40)	17 (65.4)	2 (40)
Proteus (*n*=3)	2 (10)	1 (3.8)	0
Pseudomonas (*n*=2)	0	2 (7.7)	0
E. coli (*n*=1)	1 (5)	0	0
Unclassified Gram –ve (*n*=4)	1 (5)	3 (11.5)	0
Streptococcus (*n*=4)	4 (20)	0	0
Staphylococcus (*n*=4)	1 (5)	1 (3.8)	2 (40)
MRSA (*n*=3)	2 (10)	1 (3.8)	0
CONS (*n*=3)	1 (5)	1 (3.8)	1 (20)
Total (*n*=51)	20 (100)	26 (100)	5 (100)

CONS, coagulase-negative staphylococci; MRSA, methicillin-resistant *Staphylococcus aureus*.

Discussion

The prevalence of neonatal sepsis has increased in spite of strict infection control measures; however, with the advancement of neonatal care and modern equipment, a higher survival rate is seen in premature infants who have a higher risk of infection [9]. Severe neonatal sepsis represents one-fourth of all causes of neonatal mortality, as reported by Liu *et al.* [10]. There is a wide heterogeneity regarding the prevalence and the incidence of neonatal sepsis worldwide [11].

In our study, the prevalence of proved neonatal sepsis was 7.2% of all admitted cases, and it was slightly higher in LOS (4.4%) than in EOS (2.8%), which is lower than the study of Mustefa *et al*. [12] who found that the prevalence of sepsis was 78.3%; this may be due to lower gestational age and higher maternal infection in their study.

In terms of sex, there was no statistically significant difference between the groups tested, with *P* value more than 0.0. This goes in line with the study by Bulkowstein *et al.* [6], which also found no statistically significant difference regarding sex between cases of early-onset and late-onset neonatal sepsis, with *P* value of 0.161.

In our study, the prevalence of hypothermia was more than that of hyperthermia in both early-onset and late-onset neonatal sepsis. This goes in line with the study of Ahmad *et al.* [13], which revealed that hyperthermia was less common among neonatal sepsis cases (13.1%), whereas 13.4% had mild hypothermia and 15.5% had moderate hypothermia. This is similar to the study by Shirin *et al.* [8]who reported that hyperthermia was the commonest finding among LOS (25%), and hypothermia was predominant with EOS (39.8%). The occurrence of hypothermia in neonates can be explained by a variety of factors, including age, weight, gestational age, feeding, place of birth, early bathing, Apgar score, ambient temperature, and maternal temperature [14]. In the current study, the majority of community-acquired infection cases have not required blood transfusion (80%), whereas 40% of EOS and 38,5% of nosocomial infection have blood transfusion. Similarly, Manandhar *et al.* [15], reported a higher association between neonatal sepsis and blood transfusion, with *P* value more than 0.005.

In the current study, *Klebsiella* was the commonest organism responsible for EOS and LOS, and both *Klebsiella* and *S. aureus* were the commonest organisms detected in community-acquired infection. This goes in line with the study by Tran *et al.* [4], who also found that *Klebsiella* (20%) and

Table 5: Antibiotic sensitivity to different organisms in the studied groups

	Klebsiella *n*=27	Proteus *n*=3	Pseudomonas *n*=2	E. coli *n*=1	Gram negative *n*=4	Streptococci *n*=4	Staphylococci. *n*=4	MRSA *n*=3	CONS *n*=3
Meropenem	52%	33.33%	50%						
Imipenem	56%	33.33%		100%	16.67%				
Ciprofloxacin	52%	33.33%	100%	100%	33.33%	75%	25%	66.7%	66.7%
Piperacillin-tazobactam	28%	33.33%		100%					
Gentamicin	16%			100%	16.67%	50%		33.3%	66.7%
Amikacin	24%	33.33%	50%		33.33%	50%	25%	100%	
Polymyxin E	16%	33.33%			33.33%				
Erythromycin						50%		33.3%	33.3%
Amoxicillin-sulbactam	4%								
Penicillin						75%	25%		33.3%
Azithromycin	4%						25%	66.7%	66.7%
Vancomycin						25%	75%	100%	100%
linezolid						100%	75%	100%	100%
Cefotaxime				100%					
Cefoxitin	12%					50%	50%	33.3%	100%
Ceftazidime	4%			100%					
Metronidazole		33.33%							
Clindamycin						75%	50%	66.7%	100%
Cefepime	24%		100%	100%					
Cefoperazone-sulbactam	4%		50%	100%	16.67%				
Clarithromycin								33.3%	

CONS, coagulase-negative staphylococci.

Table 6: Comparison between types of sepsis regarding type of causative organisms

Organisms	Group I (*n* 31) [*n* (%)] (20, 39%)	Group II (*n* 31) [*n* (%)]		*P*
		Group IIa (26, 51%)	Group IIb (5, 10%)	
Gram negative (*n*=37)	12 (60.0)	23 (88.5)	2 (40.0)	0.02*
Gram positive (*n*=14)	8 (40.0)	3 (11.5)	3 (60.0)	

*Statistically significant difference.

Table 7: Comparison between the studied groups as regards length of hospital stay

	Group I (mean±SD)	Group II		*P*
		Group IIa (mean±SD)	Group IIIb (mean±SD)	
LHS	15.05±8.7	16.35±11.04	15.2±12.8	>0.05

LHS, length of hospital stay.

Acinetobacter (15%) were the commonest detected organisms in EOS and LOS [4], and El-Mashad *et al.* [16], who found that the most common organism was *Klebsiella*. However, in Sabah Maternity Hospital in Kuwait, group B strept. and *E. coli* were the commonest organisms in EOS [17]. The difference in our study can be attributed to the routine use of prophylactic antibiotic to mothers during labor.

With a *P* value of 0.02 in our study, we discovered a statistically significant difference between the studied groups in terms of type of causative organism, with the majority of EOS and LOS caused by gram-negative organisms and the majority of nosocomial infection caused by gram-positive organisms. This is in line with the study by Hammoud *et al.* [18], which looked at 218 neonates diagnosed with neonatal sepsis to assess the clinical presentation and bacteriological profile of neonatal infections and discovered that gram-negative organisms, such as *Klebsiella*, *E. coli*, and *Enterobacter*, were responsible for the majority of cases of neonatal sepsis, accounting for 28.6, 21.4, and 14.3%, respectively. Chiabi *et al.* [19], discovered in another study that gram-negative organisms were the commonest detected organisms among EOS, LOS, and nosocomial infections, but no statistically significant difference was recorded. This is in contrast to the study by Mariani *et al.* [20], who found that gram-positive organisms were higher in EOS (81%) and LOS (87%) than gram negative, and coagulase-negative staphylococci represent 52% in EOS and 71.4% in LOS.

The study by Bulkowstein *et al.* [6] found no statistically significant difference between EOS and LOS regarding the type of organism, with *P* value more than 0.05.

In this study, we found that meropenem, imipenem, and ciprofloxacin were the most sensitive antibiotics to *Klebsiella* followed by amikacin, which is similar to the study by Afsharpaiman *et al.* [21], which may be attributed to the decrease in the rate of usage of both of them. However, vancomycin is the most sensitive antibiotics to gram-positive organisms in our study, which goes with the study by Sorsa *et al.* [22].

The study by Salama *et al.* [23], found that hospital stay (LHS) range was 3–198, with a median of 8 days. In our study, there

Table 8: Comparison between the studied groups regarding mortality

Outcome	Group I (*n*=20)	Group II (*n*=31) [*n* (%)]		*P*
		Group IIa (*n*=26)	Group IIb (*n*=5)	
Died (*n*=13)	7 (35)	5 (19.2)	1 (20)	>0.05
Full term (4)	3 (15)	1 (3.8)	0	
Preterm (9)	4 (20)	4 (15.4)	1 (20)	
Living (*n*=38)	13 (65)	21 (80.8)	4 (80)	
Full term (17)	4 (20)	11 (40.4)	2 (40)	
Preterm (21)	9 (45)	10 (40.4)	2 (40)	

was no significant difference between groups regarding LHS, which is in agreement with Fenny *et al.* [24], who found that bloodstream infection increased LHS to 10 days. This is in contrast to Mahovo and Velaphi [25], who found that hospital-acquired infection is associated with lengthening of hospital stay and thus can explained by the lower birth weight in their study. Sahiledengle *et al.* [26], stated that there was an association between prolonged hospital stay and HAI in neonates less than 37th gestational weeks.

The total mortality of neonatal sepsis is 25%, and there is no statistically significant difference between early-onset and late-onset neonatal sepsis cases regarding mortality, with *P* value more than 0.05. However, Shehab El-Din En El-Sokkary *et al.* [27], found that the mortality was 17.6%, and also, there was no statistically significant difference between early-onset and late-onset neonatal sepsis cases and community-acquired infection regarding mortality, with *P* value more than 0.05. The same was reported by Afsharpaiman *et al.* [21], who revealed no statistically significant difference between EOS, LOS, and community-acquired infection regarding mortality, with *P* value of 0.05.

This is in contrast to Bulkowstein *et al.* [6] and Salama *et al.* [23], who found a statistically significant increase of mortality among early-onset neonatal sepsis cases. The prevalence of EOS and LOS was comparable in our studied and was higher than community-acquired infection, which was the inverse of the meta-analysis of Fleischmann *et al.* [28], who found that the mortality was quadruple in the hospital-acquired LOS, and this may be attributed to most of deliveries were outside the hospital in their study. In our study, neonatal sepsis mortality was prominent in male neonates, which is similar to Agnche *et al.* [29], who found that male sex is a risk of mortality, as it is high in male infants, which alerted the researchers to investigate the role of sex hormones in this process to decrease this gap in sex difference [30].

Conclusion

Late onset sepsis (LOS) has a high prevalence. *Klebsiella* is the commonest responsible organism for neonatal sepsis and mostly sensitive to imipenem, meropenem, and ciprofloxacin in all types of neonatal sepsis. Still, neonatal sepsis has a high mortality irrespective of its onset.

Recommendation

Further studied are needed to define the associated long-term outcomes of neonatal sepsis and correlation with neurodevelopmental outcomes in different groups.

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Conflicts of interest

There are no conflicts of interest.

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