

Platelet count and neonatal sepsis: a high prevalence of *Enterobacter* spp.

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ABSTRACT

Introduction: Sepsis is a common complication in the neonatal intensive care unit. It is most common in the smallest and most premature infants in whom the clinical presentation can be subtle and nonspecific. The objectives of the present study were to identify the most common organisms causing sepsis and their associations with thrombocytopenia.

Methods: This is a retrospective case analysis of blood culture positive patients between March 2003 and July 2007 in a single centre. We enrolled 53 eligible neonates whose blood culture yielded positively for any organism. Blood for the culture was obtained from a peripheral vessel. The data was analysed for differences in platelet and neutrophil count in terms of the microorganisms causing sepsis using chi-square and Fisher's exact tests, analysis of variance and Kruskal-Wallis, as appropriate.

Results: The most common organism in the blood culture was *Enterobacter* spp. with 21 cases (39.6 percent) and the least common was coagulase-positive *Staphylococcus* spp. The most common organisms in infants with normal weight and early onset sepsis were coagulase-positive *Staphylococcus* spp. (50 percent and 36.7 percent, respectively), while in other neonates with low birth weight, very low birth weight and late onset sepsis, the most common organism was *Enterobacter* spp. (40.9 percent, 71.4 percent and 47.8 percent, respectively). The patients with *Enterobacter* spp. sepsis had a higher incidence of thrombocytopenia. The mortality rate was 15.1 percent (8/53 cases), which was significantly higher among those with the *Enterobacter* spp. sepsis (five cases, p-value is 0.033).

Conclusion: Our study shows the changes in the pattern of late onset neonatal infections in the neonatal intensive care unit. *Enterobacter* spp.

is the most common organism causing neonatal sepsis accompanying thrombocytopenia.

Keywords: *Enterobacter* spp., neonatal infection, neonatal sepsis, thrombocytopenia

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INTRODUCTION

Sepsis is a common complication in the neonatal intensive care unit (NICU). It is most common in the smallest and most premature infants, in whom the clinical presentation can be subtle and nonspecific.⁽¹⁾ The incidence of neonatal sepsis is 1–5 per 1,000 live births, and its mortality rate is 5%–20%.⁽²⁾ Disseminated intravascular coagulation and thrombocytopenia are well-known complications of sepsis.⁽³⁾ In the paediatric surgery literature, Ververidis et al have shown that thrombocytopenia is a common finding in necrotising enterocolitis. An earlier study by Scheifele et al demonstrated evidence of a relationship between Gram-negative infections and thrombocytopenia.⁽⁴⁾

Enterobacter spp., a normal member of the gastrointestinal tract flora, has showed up as a significant nosocomial pathogen in the NICU.^(4,6) Recent reports on invasive *Enterobacter* spp. infections in neonates have focused especially on the molecular epidemiology of outbreaks that occurred in the NICU.^(7,8) However, we have very scant information about the current state of this infection among neonates and the most suitable measures to interrupt the transmission of epidemic strains.⁽⁹⁾ The objective of the present study was to identify the most common organisms causing sepsis and their relations to thrombocytopenia. During our study, we found that there was a high prevalence of *Enterobacter* spp. in our NICU, therefore we focused on this organism in parts of this survey.

METHODS

This a retrospective study in which we enrolled all patients whose blood culture yielded any microorganism between March 2003 and July 2006 at the NICU of Najmiyeh and Baqiyatolah Hospitals in Tehran, Iran. 53 patients were included in the survey. Blood for culture was obtained from a peripheral vessel. The patients were classified by

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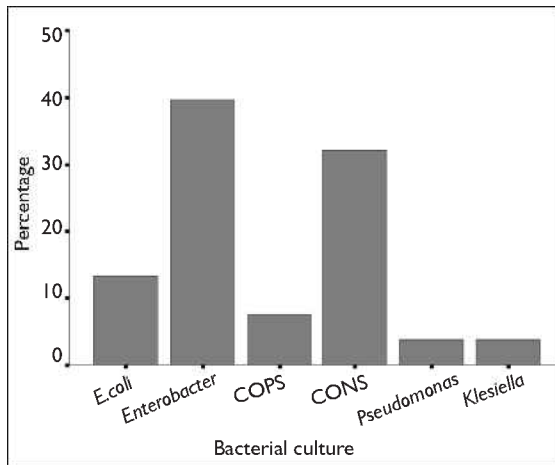


Fig. 1 Bar chart shows the frequency of bacterial isolates in neonates with sepsis. CONS: coagulase-negative *Staphylococcus* spp.; COPS: coagulase-positive *Staphylococcus* spp.

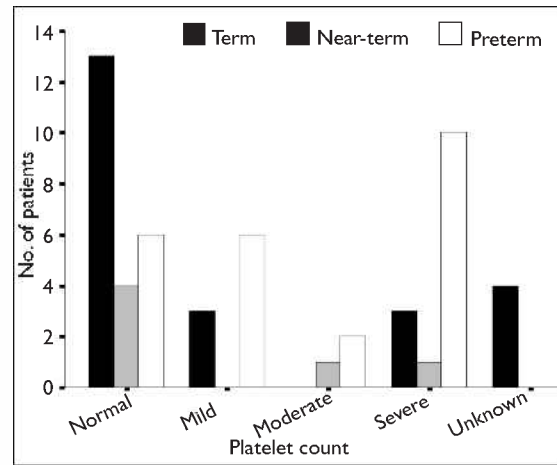


Fig. 2 Bar chart shows the significant correlation between gestational age and severity of thrombocytopenia in neonates with sepsis.

their age; either the blood culture was positive at early onset (birth to 5 days of age) or at late onset (≥ 6 days after birth) sepsis. Thrombocytopenia was divided into three categories: mild ($100,000\text{--}150,000/\text{mm}^3$); moderate ($50,000\text{--}100,000/\text{mm}^3$); and severe ($\leq 50,000/\text{mm}^3$). Neutropenia was divided into three categories: mild ($1,000\text{--}1,500/\text{mm}^3$); moderate ($500\text{--}1,000/\text{mm}^3$) and severe ($\leq 500/\text{mm}^3$).

The neonates were also categorised into three groups by their weight: normal ($\geq 2,500$ g); low birth weight (LBW) ($1,500\text{--}2,500$ g); and very low birth weight (VLBW) ($\leq 1,500$ g). Finally, they were classified into three groups by their gestational age at birth: term (> 37 weeks); near-term (35–37 weeks); and preterm (< 35 weeks). Due to the small sample size, we divided patients into two groups: Group A, early sepsis; and Group B, late and nosocomial sepsis. Statistical analysis was performed using the Statistical Package for Social Sciences version 13.0 (SPSS Inc, Chicago, IL, USA). Analysis of the data for differences in platelet and neutrophil counts in terms of the microorganisms causing sepsis was done by χ^2 and Fisher's exact tests, analysis of variance and Kruskal-Wallis, as appropriate. The data was expressed at mean \pm standard deviation (SD) or number (percent). Statistical significance was considered at a p-value < 0.05 .

RESULTS

During the period of study, the number of births was 12,350. 114 (9.2%) neonates were hospitalised with clinical sepsis. 53 (4.3%) patients had positive blood culture, 27 (50.9%) were female and 26 (49.1%) were male. 23 (43.4%), 6 (11.3%) and 24 (45.3%) patients were term, near-term and preterm, respectively. Ten patients

were VLBW, 19 were LBW and 24 were of normal weight. 30 (56.6%) and 23 (43.4%) patients had early onset sepsis and late onset sepsis, respectively. The most common isolate from blood culture was *Enterobacter* spp., with 21 (39.6%) patients, and the least common was coagulase-positive *Staphylococcus* spp., with 4 (7.5%) patients (Fig. 1). The most common organism in early sepsis was coagulase-negative *Staphylococcus* spp. (CONS) (36.7%) and in late sepsis, *Enterobacter* spp. (47.8%) (Table I). The most common organisms in infants with a normal weight and early onset sepsis were coagulase-positive and negative *Staphylococcus* spp. (50% and 36.7%, respectively), while in other neonates with LBW, VLBW and late onset sepsis, it was *Enterobacter* spp. (40.9%, 71.4% and 47.8%, respectively) ($p > 0.05$).

The neutrophil count was within the normal range in 44 (83%) patients, while 1 (1.9%) had mild and 3 (5.7%) had severe neutropenia with *Enterobacter* spp. sepsis. The platelet count was normal in 23 (43.4%) patients. Of the 14 (26.4%) patients with severe thrombocytopenia, nine (64.3%) had *Enterobacter* spp. sepsis. The other three (5.7%) infants had moderate thrombocytopenia accompanying *Enterobacter* spp. sepsis ($p = 0.012$) (Table II). The pattern of neonatal sepsis during the study showed a decrease in the incidence of sepsis during the late period of our study (Table III). A normal platelet count was found in 13 (56.5%) term, in 4 (16.6%) of near-term and in 6 (25%) preterm infants. The frequency of severe thrombocytopenia in term, near-term and preterm infants was 13%, 16.7% and 41.7%, respectively ($p = 0.028$) (Fig. 2). In all patients, the mean \pm SD duration of admission was 17.43 ± 10.91 (1–52) days. On average, patients with *Klebsiella* spp. and *Enterobacter* spp. sepsis had the

Table I. Frequency of bacterial isolates in neonates with early and late sepsis.

Type of microorganism	No. (%) of early sepsis	No. (%) of late sepsis	p-value
<i>Escherichia coli</i>	4 (13.3)	3 (13.3)	0.9
<i>Enterobacter</i> spp.	10 (33.3)	11 (47.8)	0.2
Coagulase-positive <i>Staphylococcus</i> spp.	2 (6.7)	2 (8.7)	0.9
Coagulase-negative <i>Staphylococcus</i> spp.	11 (36.7)	6 (26.1)	0.08
<i>Klebsiella</i> spp.	1 (3.3)	1 (4.3)	0.8
<i>Pseudomonas</i> spp.	2 (6.7)	–	–
Total	30	23	

Table II. Frequency of microorganisms causing mild to severe thrombocytopenia in neonates.

Type of microorganism	No. of neonates with thrombocytopenia				Total
	Normal	Mild	Moderate	Severe	
<i>Escherichia coli</i>	4	1	–	2	7
<i>Enterobacter</i> spp.	3	6	3	9	21
Coagulase-positive <i>Staphylococcus</i> spp.	3	1	–	–	4
Coagulase-negative <i>Staphylococcus</i> spp.	15	1	–	1	17
<i>Klebsiella</i> spp.	–	–	–	2	2
<i>Pseudomonas</i> spp.	2	–	–	–	2
Total	27	9	3	14	53

longest admission (mean 28 and 21.57 days, respectively; $p > 0.05$). The mortality rate was 15.1% (8 out of 53 cases), which was significantly higher in infants with *Enterobacter* spp. sepsis (five cases, $p = 0.033$).

DISCUSSION

Thrombocytopenia was found in 56.6% of our neonatal population, which is in concordance with previous studies (10%–60%). Among patients with *Enterobacter* spp. sepsis, 85.7% had thrombocytopenia (42.9% with severe thrombocytopenia), which was significantly higher than another similar study that reported 42% of their *Enterobacter* spp. sepsis patients as having thrombocytopenia.⁽¹⁰⁾ There was a significant difference between gestational age and severity of thrombocytopenia according to the other studies. In our study, CONS was the most common organism causing early onset sepsis, whereas in other studies, Group B *Streptococcus* spp. and Gram-negative organisms were the predominant pathogens.^(2,3,7,11)

During the last few decades, there have been many reports of outbreaks caused by *Enterobacter* spp. in the neonatal setting, especially by multiple drug-resistant strains.^(4,6,10) However, retrospective studies on the trend of *Enterobacter* spp. infections in neonates over a prolonged period of time are very scarce. Our study shows the changes in the pattern of late onset neonatal infections in an NICU and suggests that *Enterobacter* spp. is now the most prevalent pathogen in neonates.

Table III. Pattern of neonatal sepsis during the study.

Study time period	No. of early sepsis	No. of late sepsis	Total
First year	15	11	26
Second year	10	9	19
Third year	5	3	8
Total	30	23	53

A study in Spain carried out over a 22-year period showed that *Klebsiella pneumoniae* was the most common cause of nosocomial infections from 1977 to 1984; however, *Staphylococcus epidermidis* replaced *Klebsiella pneumoniae* as the predominant pathogen from 1985 to 1991. As seen in that survey, *Enterobacter* spp. clearly re-emerged in their study in the 1990s and became the most frequent cause of late onset infection in the period 1992–1998.⁽¹²⁾ *Enterobacter* spp. is usually a hospital-acquired microorganism. Thus, 57.1% of our *Enterobacter* spp. infections were nosocomial, according to those reported in paediatric patients (57%–67%), but lower than the prevalence reported in adults.^(13–15) There are many factors that favour the development of nosocomial infections in neonates. All our patients had an underlying illness and/or predisposing factors that are known to contribute to the colonisation of neonates by *Enterobacter* spp. A substantial number of patients were premature infants (66.7%) who developed complications, especially respiratory distress and gastrointestinal disease, had invasive medical

interventions to support their survival and received broad spectrum antibiotics. The overall case fatality rate was 15.1%, which is concordant with other studies (13%–15%). Also, the fatality rate for *Enterobacter* spp. was 23%, which is similar to those previously reported (21%–24%), but higher than a study that reported a fatality rate of 6.6% for *Enterobacter* spp.^(9,13)

Hospitalised neonates develop gastrointestinal tract colonisation with *Klebsiella*, *Enterobacter* and *Citrobacter* spp. at a higher rate compared with infants at home in whom *Escherichia coli* is the predominant bowel flora. However, there are also studies suggesting that the emergence of resistant organisms and the use of corresponding antibiotics may be coincidental.^(6,16) In conclusion, due to the small sample size of this study, we divided our patients into two groups—early sepsis, and late and nosocomial sepsis—but there were no statistically significant differences between the two groups for organisms caused by neonatal sepsis. Thus, our findings suggest that *Enterobacter* spp. is the most common pathogen causing neonatal sepsis in NICUs, and it seems that the pattern of late onset sepsis has been changed in NICUs. As thrombocytopenia has been shown to be associated with *Enterobacter* spp. sepsis, notification of that organism is important in NICUs. More studies are required to achieve a better understanding of interactions among platelets and infectious organisms in neonates.

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