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# Late-onset neonatal sepsis in Arab states in the Gulf region: two-year prospective study

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SUMMARY

*Objectives:* This study aimed to investigate the incidence of late-onset sepsis (LOS) in neonatal intensive care units (NICUs) in Arab states in the Gulf region and to describe the main causative organisms and their antibiotic resistance.

*Methods:* This observational prospective cohort study was conducted over a 2-year period in five NICUs in Kuwait, Saudi Arabia, and the United Arab Emirates. LOS was defined as the growth of a single potentially pathogenic organism from blood or cerebrospinal fluid in infants >3 days of age with clinical and laboratory findings consistent with infection.

*Results:* Seven hundred and eighty-five cases of LOS occurred among 67 474 live births. The overall incidence of LOS was 11.63 (95% confidence interval (CI) 10.84–12.47) per 1000 live births, or 56.14 (95% CI 52.38–60.08) per 1000 admissions. Coagulase-negative staphylococci and *Klebsiella spp* were the most common organisms, causing 272 (34.65%) and 179 (22.80%) of LOS cases, respectively. No evidence of a seasonal variation in the incidence of *Klebsiella spp* or in the incidence of all Gram-negative organisms was found. More than half of the *Klebsiella spp* were resistant to third-generation cephalosporins.

*Conclusion:* LOS poses a major burden in this area, which could be due to the increasing care of premature babies. Gram-negative organisms, particularly *Klebsiella spp*, are having an increasing role in LOS in this region, with high levels of resistance to third-generation cephalosporins. NICUs in the area should create a platform through which to share experience in reducing neonatal sepsis and contribute to a common antibiotic stewardship program.



## Introduction

A significant decrease in under-5 mortality has been achieved worldwide in recent years. However, neonatal mortality has decreased at a much lower rate and currently represents 44% of all under-5 mortality.[1] Neonatal sepsis is one of the main direct causes of neonatal mortality and is responsible for approximately 36% of the four million neonatal deaths that occur annually,[2] leading to 670 000 deaths in Asia, Sub-Saharan Africa, and Latin America alone.[3] Neonatal sepsis is set to increase globally because of the increase in premature infants,[4,5] who are particularly prone to neonatal sepsis due to their impaired innate immune function and the need for invasive procedures to sustain their life-support.

Unlike early-onset sepsis, which occurs within 72 h of birth and is caused mainly by organisms from the maternal vaginal flora, late-onset sepsis (LOS) is a hospital-acquired infection and is a frequent complication of extreme prematurity. Coagulase-negative staphylococci (CoNS) have consistently been reported as the main causative organisms,[6–8] but the role of Gram-negative organisms is increasing and drug resistance is rising steadily.

The Arab states in the Gulf region have a distinct nature as high-income countries compared to neighboring countries, including those in the World Health Organization (WHO) Eastern Mediterranean Region. It is postulated that the adoption of sophisticated

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tertiary care (involving the use of invasive devices to sustain life-support care) without strict measures against infections has had a significant impact on the incidence of neonatal sepsis and the pattern of causative organisms in the Arab states in the Gulf region.[6] The investigation of organisms causing neonatal sepsis and the monitoring of their antimicrobial sensitivity can be used to guide appropriate empirical treatment and help develop cost-effective interventions to prevent neonatal deaths. While this essential information is collected and updated regularly in developed countries, data from the Arab states in the Gulf region remain scarce. This study aimed to investigate the incidence of culture-proven LOS in Arab states in the Gulf region over a 2-year period and describe the causative organisms of LOS and their antimicrobial resistance.

## Methods

This observational prospective cohort study was conducted in five neonatal intensive care units (NICUs) in the following hospitals: Al Sabah Maternity Hospital in Kuwait, Dubai Hospital and Tawam Hospital in the United Arab Emirates, and King Abdulaziz Hospital and the Maternity and Children's Hospital in Saudi Arabia. Data were collected prospectively over a 2-year period (June 2013 to May 2015) using a standardized data collection form. In order to standardize data collection across all units, detailed guidelines for collecting and reporting data were prepared and used throughout the study. The study was approved by the ethics committee at the Health Science Centre, Kuwait University; individual study sites obtained approval from their respective authorities when deemed necessary.

LOS was defined as the growth of a single potentially pathogenic organism (bacterium or fungus) from blood or cerebrospinal fluid (CSF) in infants >3 days of age with clinical and laboratory findings consistent with infection.[9,10] Likely contaminants were excluded by clinical judgment. The isolation of organisms from blood or CSF, as well as their susceptibility or resistance to antibiotics, was recorded using recognized methods of antibiotic susceptibility testing, but was not standardized across the different sites. Data were also collected on the nationality of the mother, type of delivery, gestational age, complications during pregnancy, and use of intrapartum antibiotics. Data related to infants such as birth weight, sex, age at which the positive blood culture was obtained, and whether the baby was born in the hospital (intramural admission) or outside the hospital (extramural admission) were also collected. Finally, data on the number of admissions to the neonatal units and the number of live births in the hospitals were also collected.

Data were entered into a database using EpiData Entry software and then transferred to Stata 12.0 (StataCorp, College Station, Texas 77845 USA) for data analysis. Categorical data were tested using the Chi-square test, or Fisher's exact test, as appropriate. The incidences of LOS were calculated by dividing the number of inborn infants with LOS by the number of live births in the hospitals or the number of admissions to the NICUs. The 95% confidence interval (95% CI) was calculated using the binomial distribution. Logistic regression was used to investigate the risk factors for death from the neonatal infection while adjusting for potential confounders, such as the type of organism, gestational age, and birth weight.

## Results

Seven hundred and eighty-five cases of LOS occurred among 67 474 live births over the study period. Table 1 shows the characteristics of the mothers and their infants who had LOS. More than half of the infants with LOS were born by caesarean section and the majority were premature infants. The median (interquartile range) birth weight of this group of infants was 1240 (850–2120) g, and about two-thirds had a very low birth weight (<1500 g). The overall incidence of LOS was 11.63 (95% CI 10.84–12.47) per 1000 live births, or 56.14 (95% CI 52.38–60.08) per 1000 admissions (Table 2). There was a significant difference in the incidence of LOS between the study sites, whether this was based on the number of admissions or the number of live births ($p < 0.0001$, $p < 0.001$).

Table 3 shows the most common organisms causing LOS at all study sites. CoNS followed by *Klebsiella spp* were the most common organisms, causing 272 (34.65%) and 179 (22.80%) of LOS cases, respectively. *Escherichia coli*,*Acinetobacter spp*, and *Pseudomonas spp* were responsible for 38 (4.84%), 36 (4.59%), and 35 (4.46%) of the LOS cases, respectively. There was no evidence of seasonal variation in the incidence of *Klebsiella spp* or in the incidence of all

**Table 1**
Characteristics of 785 mothers and their neonates with late-onset sepsis in Arab states in the Gulf region over the 2-year study period.

| Characteristics | | *n* (%) |
|---|---|---|
| Nationality | GCC country | 614 (78.22) |
| | Other country | 171 (21.78) |
| Gravidity | Primigravida | 336 (42.80) |
| | Multigravida | 449 (57.20) |
| Type of pregnancy | Singleton pregnancy | 566 (72.29 |
| | Multiple pregnancy | 217 (27.71) |
| Mode of delivery | Normal | 358 (45.61) |
| | Caesarean section | 422 (53.76) |
| | Other | 5 (0.64) |
| Gestational age | Extreme preterm <28 weeks | 263 (33.50) |
| | Very preterm 28 to <32 weeks | 229 (29.17) |
| | Moderate/late preterm 32 to <37 weeks | 155 (19.75) |
| | Full-term | 138 (17.58) |
| Intra-partum antibiotic[a] | Yes | 121 (15.41) |
| Sex[b] | Male | 413 (52.88) |
| Birth weight[c] | g, median (IQR) | 1240 (850–2120) |
| | Very low birth weight <1500 g | 521 (66.7) |
| | Low birth weight <2500 g | 137 (17.5) |
| | Normal birth weight ≥2500 g | 123 (15.8) |

GCC, Gulf Cooperation Council countries; IQR, interquartile range.
[a] Missing for six cases.
[b] Missing for four cases.
[c] Missing for four cases.