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Risk factors and clinical outcomes for carbapenem-resistant Gram-negative late-onset sepsis in a neonatal intensive care unit

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SUMMARY

Background: Carbapenem-resistant (CR), Gram-negative (GN), late-onset sepsis (LOS) is a serious threat in the neonatal intensive care unit (NICU).
Aim: To assess the prevalence of CR-GN-LOS in NICU patients and to identify the risk factors and outcomes associated with its acquisition.
Methods: Neonates with carbapenem-susceptible (CS)-GN-LOS were compared with those with CR-GN-LOS in a two-year observational study.
Findings: A total of 158 patients had GN-LOS; 100 infants had CS-GN-LOS and 58 infants had CR-GN-LOS. The incidence rate of CR-GN-LOS was 6.5 cases per 1000 patient-days. The most frequent bacterial strain in both groups was *Klebsiella pneumoniae*. The duration of total parenteral nutrition (TPN) ($P = 0.006$) and prior carbapenem use ($P = 0.01$) were independent risk factors for CR-GN-LOS acquisition. CR-GN-LOS was associated with higher mortality than CS-GN-LOS ($P = 0.04$). Birth weight, small for gestational age, time to start enteral feeding, exclusive formula feeding, previous surgery, previous antifungal use, central venous device before onset, duration of central venous device, and infectious complications were identified as dependent risk factors for overall mortality. However, only male gender ($P = 0.04$) and infectious complications ($P < 0.001$) were independent risk factors associated with mortality. Infectious complication rates, duration of mechanical ventilation, and length of hospital stay were significantly higher in infants with CR compared to CS-GN-LOS.
Conclusion: The duration of TPN and carbapenem use were the independent predictors for CR-GN-LOS acquisition. CR-GN-LOS is associated with higher mortality, infectious complication rates, longer mechanical ventilation, and longer hospital stay. Male gender and infectious complications were the independent risk factors for mortality in neonates with GN-LOS.

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Introduction

Neonatal sepsis is an important challenge for clinicians, accounting for ~22% of global annual neonatal deaths [1]. In addition, neonates with severe infections are more liable to have long-term neurodevelopmental impairments [2].

The incidence of nosocomial infections caused by Gram-negative (GN) bacteria has been mounting over recent decades [3]. GN late-onset sepsis (LOS) is often associated with a higher mortality rates than is LOS with Gram-positive (GP) bacteria [4,5]. The emergence of carbapenem-resistant (CR) strains of GN bacteria in neonatal intensive care units (NICUs) has been reported by several surveys [6–8]. Limited antibiotic treatment options, and inappropriate empiric therapy predispose infants with CR-GN-LOS to a more complicated NICU course and poor outcome [9,10]. Most previously published studies have been concerned mainly with molecular characteristics and probable routes of spread of CR strains among NICU patients [9,11], and the clinical data on these infections has been mostly limited to small case series or outbreak reports [8,12–14].

Recognition of the risk factors for acquisition of CR-GN-LOS in NICUs could help neonatologists and infection control teams to implement appropriate infection control measures to decrease these infections. We conducted this prospective observational study to determine the prevalence of CR-GN-LOS in our NICU and to evaluate the risk factors for, and the outcomes of, neonates with CR-GN-LOS.

Methods

Setting and patients

A prospective, observational case–control study was conducted on neonates who developed GN-LOS in the NICU of Mansoura University Children's Hospital from August 2014 to October 2016. This NICU is a level III tertiary unit with 25 incubators in five equal-sized rooms, admitting ~450 neonates per/year; there are no single rooms for isolation. The NICU is staffed by nine physicians (three consultants and five residents); the morning shift is covered by seven nurses, and the afternoon and evening shifts by five nurses. There is an active infection control programme on the NICU. Hand hygiene audit performance (based on a standard of Betadine® for an initial scrub, and alcohol-based antiseptic solution subsequently) was 60–70% among physicians, and 70–80% among nursing and other staff.

Included subjects were inborn and outborn neonates with an episode of blood culture-positive GN-LOS either susceptible or resistant to carbapenems. Excluded subjects were neonates with Gram-positive LOS, major congenital malformations, chromosomal anomalies, inborn errors of metabolism, renal failure, and congenital infection.

Infants were divided into two groups according to whether their infecting organisms were carbapenem-susceptible or resistant. All patient information regarding baseline characteristics, clinical outcomes, and culture results were collected prospectively from the medical records.

The study was approved by the Institutional Review Board of Mansoura Faculty of Medicine.

Patients' care pathway

The unit empiric antibiotic treatment policy for suspected LOS was ampicillin and aminoglycoside (first-line) or vancomycin and cefatoxime (second-line).

Infants were monitored for arterial blood pressure, heart rate, respiratory rate, and skin temperature. Hypotension was defined as mean arterial blood pressure below the 5th percentile of the gestational- and postnatal-age-dependent blood pressure norms. Arterial blood gases were checked at 12 h intervals in case of shock. Shock was diagnosed when the patient's blood pressure remained less than the lower limit of gestational age with no response to volume expander and/or required positive inotropic agents. The response to initial antibiotic was assessed clinically and by complete blood count and C-reactive protein (CRP) after the first 48 h of therapy and then weekly.

Predictors and outcomes

The following risk factors for acquisition of CR-GN-LOS were assessed: birth weight, gestational age, inborn or outborn, time to start enteral feeding, type of feeding, previous antibiotics therapy and their types, previous use of total parenteral nutrition (TPN), presence and duration of use of central line devices, previous corticosteroid therapy, previous surgery, mechanical ventilation and its duration, and underlying chronic conditions.

The following outcomes were assessed: overall mortality before hospital discharge, total length of hospital stay, total duration of mechanical ventilation, and infectious complications.

Identification and susceptibility testing

Bacteria were identified using standard procedures. Antibiotic susceptibility testing was performed by disc diffusion on Mueller–Hinton agar (Becton Dickinson, Le Point de Chaix, France) using CLSI 2013 M100-S23 breakpoint values. Isolates were considered as CR if they were found resistant or intermediate to one or more of ertapenem, imipenem, or meropenem. Carbapenemase production was confirmed in all CR strains using Carba NP test [15].

Statistical analysis

Data were analysed using IBM SPSS software package version 20.0. χ^2-Test or Fisher's exact test was used for comparison of categorical variables. The Mann–Whitney *U*-test was used for comparison of abnormally distributed quantitative variables. Binary logistic regression was used to detect predictors and risk factors using the Forward Wald technique for multivariate analysis. Performance of the regression models was assessed using the Hosmer–Lemeshow test.

Results

During the study period there were 900 admissions, equating to 9000 patient-days. A total of 230 neonates had LOS [incidence rate: 25.6; 95% confidence interval (CI):