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Major Article

The prospective evaluation of risk factors and clinical influence of carbapenem resistance in children with gram-negative bacteria infection

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Key Words:
Carbapenem-resistant
Carbapenem-susceptible gram-negative infection
Outcome

Background: Carbapenem-resistant gram-negative (CRGN) infections have been increasing in recent years and associated with significant morbidity, mortality, and health care costs. The aim of this study was to evaluate the epidemiologic and clinical risk characteristics, risk factors, and outcome of CRGN infections and to compare with carbapenem-sensitive gram-negative (CSGN) infections in children.

Methods: Newly diagnosed CRGN infections in hospitalized children younger than age 18 years were prospectively recorded and all patients infected with a CSGN pathogen in the same unit within 48 hours of diagnosis were included in a control group between April 1, 2014, and December 31, 2014.

Results: Twenty-seven patients with CRGN infections and 28 patients with CSGN infections were enrolled in this study. Ventilator-associated pneumonia was the most common type of infection in both groups. Prior exposure to carbapenems (relative risk [RR], 11.368; 95% confidence interval [CI], 1.311-98.589), prolonged hospitalization (RR, 5.100; 95% CI, 1.601-16.242) were found to be independent risk factors for acquiring CRGN infections. Septic shock was significantly more frequent in the CRGN group (RR, 9.450; 95% CI, 1.075-83.065). The in-hospital mortality was higher in the CRGN group (RR, 7.647; 95% CI, 1.488-39.290).

Conclusions: Prior carbapenem exposure and prolonged hospitalization are the most important risk factors for acquiring CRGN infections in our hospital. This study demonstrated, similar to previous reports, that carbapenem resistance increases morbidity, mortality, and health care costs.

Antibiotic resistance among gram-negative bacteria has gradually spread around the world, representing a serious public health concern. Carbapenems, β-lactam antibiotics with the broadest spectrum to gram-negative organisms, have been used as a last resort for resistant gram-negative infections; however, the recent increase in carbapenem-resistant pathogens has led to carbapenem failures and may contribute to increased mortality. Carbapenem-resistant gram-negative (CRGN) pathogens are a major cause of health care-related infections and are associated with high morbidity and mortality. They also cause significant direct and indirect costs resulting from prolonged hospitalizations due to antibiotic treatment failures.[1-4] Despite heightened awareness in many parts of the world, delays in prevention and diagnosis can occur due to a lack of basic infection control measures and isolation in developing countries. Previous studies evaluating the outcomes of CRGN bacterial infections have reported that these infections are important causes of mortality, and the mortality rate of CRGN infections ranged between 15.9% and 57.4%.[5-8]

Case-control studies have been used frequently in retrospective studies to determine the risk factors for antibiotic-resistant organisms. However, the selection of patients infected with a susceptible organism as a control group may lead to a bias of relative risk (RR) due to differences in exposure frequency in the source population. Therefore, patients in the present study were enrolled in the control group if admitted to the same ward within 48 hours. Understanding the characteristics that differentiate patients at risk of infection due to CRGN microorganisms will assist clinicians in making decisions regarding early treatment, which directly influences

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the outcomes of infection. Therefore, we aimed to specifically identify the risk factors for acquiring CRGN bacterial infections and to evaluate the outcome influence of carbapenem resistance in patients with gram-negative microorganism infection.

MATERIALS AND METHODS

This study was conducted at a large reference hospital in the Izmir/Ege Region of Turkey between April and December 2014. Patients aged between 0 and 18 years, and with a diagnosis of hospital-acquired CRGN and carbapenems-suseptible gram-negative (CSGN) infection, were enrolled in the study. Patients from whom strains were isolated within the first 48 hours of admission were excluded. All patients having CRGN or CSGN infection at least 48 hours after admission, hospitalized in our general pediatric ward, pediatric intensive care unit, neonatal intensive care unit, hematology ward, and oncology ward, were eligible for this study. The control group included a patient if CSGN infection was acquired in the same ward with a case group, because the differences in exposure frequency in the source population could led a bias of RR.

Microbiologic methods

Gram-negative pathogens were identified by Vitek MS (bioMérieux, Marcy l Étoile, France) that is using Matrix-assisted laser desorption ionization time of flight mass spectrometry technology, which is a new technology for species identification based on the protein composition of microbial cells. The most prominent advantages are the quick turnaround time and its low cost to access a quality database of reference spectra. The isolates were tested for antibiotic sensitivity on an automated Vitek 2 (bioMérieux) system. Vitek 2 cards were chosen according to Vitek MS results and were inoculated following the manufacturer's instructions. Only 1 strain from each patient was included in the study. Enterobactericeae strains—*Pseudomonas* spp and *Acinetobacter* spp—were detected as carbapenem resistant using the Vitek 2 automated system. Bacterial suspensions were stored in freezing tubes, including beads, at –40°C. Sensitivities to imipenem and meropenem were confirmed by the antimicrobial gradient test in collected isolates. Carbapenem resistance was defined by a minimum inhibitory concentration of ≥16 mg/L for meropenem and imipenem.[9] The susceptibilities of amikacin, ceftriaxone, ceftazidime, piperacillin-tazobactam, cefoperazone-sulbactam, imipenem, meropenem, colistin, and tygecycline were determined according to European Committee on Antimicrobial Suseptibility Testing guidelines.[9] Patients were defined as having CRGN if they were diagnosed with an infection with a microorganism that showed resistance to meropenem or imipenem.

Definition

A standard form was used to collect epidemiologic data, including age, sex, stay in the ward before CRGN isolation, underlying diseases (eg, pulmonary disease, malignancy, cardiovascular disease, hematologic/solid organ transplantation, metabolic disease, genetic syndrome, prematurity, renal disease, and liver disease), and medication or intervention before CRGN isolation (presence of tracheal cannula, central venous catheter, presence of a Foley catheter, mechanical ventilation, immunosuppressive therapy and steroids, and receipt of antibiotics). A patient was defined as a case/control if infected with a CRGN/CSGN bacterial isolate from a relevant biological sample (eg, blood, cerebrospinal fluid, and transtracheal aspirate) and had clinical signs and/or symptoms that occurred more than 48 hours after hospital admission. The culture specimens of biological samples were ordered by the attending physician in the presence of symptoms and signs. Pneumonia was defined as a positive quantitative respiratory culture (>10^4 CFU/mL for bronchoalveolar lavage, and >10^5 CFU/mL for tracheal aspirate or sputum) and a new or progressive and persistent radiographic infiltrate, along with at least 2 of the following: fever (>38°C), leukopenia (<4,000 white blood cells/mm^3) or leukocytosis (>12,000 white blood cells/mm^3), new onset of purulent sputum or a change in sputum character, and worsening gas exchange.[10]

Sepsis and septic shock were defined according to the Centers for Disease Control and Prevention criteria.[10] Urinary tract infections were excluded. Clinical outcomes of the patients were classified as follows: 30-day mortality (within 30 days after the first positive culture), in-hospital mortality, presentation with shock, length of hospital stay before infection, and total length of hospital stay, the latter being defined as the period from first positive culture to discharge.

A multidrug-resistant isolate was defined as "acquired nonsusceptibility to at least 1 agent in 3 or more antimicrobial categories" (ie, ampicillin-sulbactams, aminoglycosides, antipseudomonal carbapenems, antipseudomonal fluoroquinolones, antipseudomonal penicillins + β-lactamase inhibitors, extended-spectrum cephalosporins, trimethoprim-sulfamethoxazole, tetracyclines, and polymyxins).[11] An extensively drug-resistant isolate was defined as "nonsusceptibility to at least 1 agent in all but 2 or more antimicrobial categories" (ie, susceptibility to only 1 or 2 categories).[11] Pandrug resistance was defined as nonsusceptibility to all agents in all antimicrobial categories.[11]

Data collection

The following data were collected prospectively by the same physician (NB) and included the following information: age; gender; underlying conditions; date and ward at hospital admission; previous antibiotic exposure; surgery and administration of carbapenems in the past 2 months; immunosuppressive therapy; risk factors, including invasive procedures; treatment choices; outcomes including mortality (30-day and in-hospital mortality); presentation with shock; and length of hospital stay. Laboratory findings, including complete blood count, C-reactive protein, and bacterial cultures were also recorded. Chest radiograph findings were recorded when available.

Statistical analysis

Statistical analyses were performed using SPSS for Windows (version 22.0; IBM-SPSS, Inc, Armonk, NY). Numerical data were expressed as medians (interquartile range). Mann-Whitney *U* and Wilcoxon tests were used for intervariable analysis. Categorical variables were evaluated with the χ^2 test or the 2-tailed Fisher exact test and presented as percentages in acquiring CRGN infections. Comparisons were referred to as statistically significant if the *P* values were < .05. Logistic regression models were used to analyze risk factors for the CRGN group. All variables with a *P* value < .05 in univariate analysis were included in the multivariate analysis. The days from the first positive culture to death in hospital were shown in Kaplan-Meier curves. A log-rank test was used to compare the CRGN and CSGN groups.

Ethics

This study had the permission of the Ethical Board of Ege University (ethical decision No. 14-2.1/ 49), and written consent was obtained from all the enrolled patients.