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Clinical Studies

Bloodstream infections in children caused by carbapenem-resistant versus carbapenem-susceptible gram-negative microorganisms: Risk factors and outcome

Yasemin Ozsurekci [a,*], Kubra Aykac [a], Ali Bulent Cengiz [a], Sevgen Tanır Basaranoglu [a], Banu Sancak [b], Sevilay Karahan [c], Ates Kara [a], Mehmet Ceyhan [a]

[a] Department of Pediatric Infectious Diseases, Hacettepe University Faculty of Medicine, Ankara, Turkey
[b] Department of Microbiology, Hacettepe University Faculty of Medicine, Ankara, Turkey
[c] Department of Biostatistics, Hacettepe University Faculty of Medicine, Ankara, Turkey

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ABSTRACT

Carbapenems are often considered the last resort agents reserved for treatment of infections due to highly antimicrobial resistant organisms such as *A. baumannii* and *P. aeruginosa.* However, carbapenem-resistant Gram-negative (CRGN) pathogens have become much more prevalent in the last decade. The objective of this study was to determine risk factors for and outcome of bacteremia caused by Gram-negative microorganisms in a pediatric tertiary-care hospital. Among 97 patients with hospital-acquired Gram-negative bacteremia, 66 patients with carbapenem-susceptible Gram-negative pathogens (CSGN) were compared with the remaining 31 with CRGN isolates. The overall clinical response and microbiological response rates were 83.3% and 43.9% in CSGN group, and 54.8% and 32.3% in CRGN group, respectively ($P = 0.002$ and $P = 0.004$, respectively). The treatment failure and relapse rates were 18.2% and 6.1% in CSGN group, and 38.7% and 6.5% in CRGN group, respectively ($P = 0.03$ in each). The infection-related mortality rates were 10.8% in the CSGN group and 32.3% in the CRGN group ($P = 0.01$). The total length of stay in hospital before infection was longer in patients with CRGN bacteremia than that of the CSGN bacteremia ($P = 0.002$). The extended spectrum antibiotic usage prior to infection was significantly different between the groups ($P = 0.008$). Infections due to CRGN are generally associated with poorer patient outcomes. Longer hospital stay and extended spectrum antibiotic usage prior to infection are the most important risk factors for CRGN bacteremia in our cohort.

1. Introduction

Infections caused by multi-drug resistant gram-negative bacteria constitute a serious public health problem on account of the scarcity of the treatment options of these infections. In addition, there are no established guidelines for their management due to the rarity of robust clinical data (Boucher et al., 2009; Kosmidis et al., 2012; Rice, 2008; Spellberg et al., 2008). Prevalence of carbapenem-resistant gram-negative bacterial pathogens (CRGNs) has dramatically increased during the last decades, due to the acquisition of new resistance mechanisms, largely attributed to the widespread use of those antimicrobials (Kosmidis et al., 2012; Lee and Doi, 2014). Carbapenem resistance often coexisted with resistance to all beta-lactam agents apart from resistance to other non-beta-lactam agents including aminoglycosides and quinolones. Numerous studies evaluating outcome of the infections caused by highly resistant gram-negative bacterial pathogens have reported that these infections are important causes of morbidity and mortality ranged between 40 and 50% (Anderson et al., 2006; Patel et al., 2008; Roberts et al., 2009).

Since extensively resistant gram-negative organisms continue their rapid spread, antimicrobial resistance is now a global threat (Huttner et al., 2013). Even if awareness is increasing in many parts of the world, the lack of basic infection control measures and isolation and cohorting measures bring about delays in preventing and diagnosis (Lee et al., 2011; Pittet et al., 2009). Furthermore, high costs and low yield of a new antimicrobial discovery prompted the pharmaceutical companies to abandon the production process (Huttner et al., 2013). We need new data to understand the nature of those infections and to determine our local epidemiologic profile. Therefore, we planned a study aimed to identify the possible risk factors for and outcome of bacteremia caused by CRGN versus carbapenem-sensitive gram-negative bacterial pathogens (CSGN).

2. Materials and methods

2.1. Study group

This retrospective cohort study was performed at Hacettepe University Department of Pediatric Infectious Diseases in Turkey.

* Corresponding author. Tel.: +90-312-3114963; fax: +90-312-3108241.
E-mail address: yas.oguz99@yahoo.com (Y. Ozsurekci).

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This study was conducted between January 2014 and February 2015 in patients who were aged between 1 month and 18 years, and with a diagnosis of hospital-acquired bloodstream infection (BSI) were enrolled in the study. All the patients who were included in this study were infected with a strain of *Pseudomonas*, *Acinetobacter*, *Klebsiella*, *Enterobacter*, or other gram-negative microorganisms. The children who admitted with bacteremia as primary diagnosis were excluded from the study. The patients were categorized into two groups according to resistance patterns of microorganisms: carbapenem resistant gram-negative infections (CRGN group) or carbapenem sensitive gram-negative infections (CSGN group). Data on children with CRGN and CSGN microorganism infections were obtained from infection control surveillance records and the microbiology laboratory database. All the patients had been treated in the inpatient wards with a diagnosis of BSI caused by gram-negative microorganisms. The investigation was reviewed and approved by the ethical committee of the Zekai Tahir Burak Maternity Teaching Hospital, Ministry of Health, Ankara, Turkey (no.5/2016).

The variables potentially associated with the infections included: age; sex; medical history; use of medical devices (central catheters, urinary catheters, and endotracheal or tracheostomy tubes, etc.); laboratory findings; type and antimicrobial susceptibility of the isolated microorganisms; length of hospital stay; dose, duration, and side effects of antimicrobial therapy; intensive care unit (ICU) admission; polymicrobial bacteremia; antimicrobial exposure (only those used for at least 48 hours during the previous 14 days were analyzed): beta-lactam antibiotics including penicillin derivatives, cephalosporins, monobactams, and carbapenems, fluoroquinolones, aminoglycosides, anaerobicidal agents and glycopeptides; and exposure to more than one of the antibiotics studied. The data were collected via patients' charts, computerized administrative, pharmacy, and laboratory databases at the Hacettepe University.

2.2. Definitions

The diagnosis of infection was made by clinical and laboratory findings of individual patients, imaging results, and the isolation of microorganisms from blood. A laboratory-confirmed bloodstream infection (BSI) was defined according to followings: a) the patient has a recognized pathogen identified from one or more blood specimens by a culture or non-culture based microbiological testing method which is performed for purposes of clinical diagnosis or treatment [e.g., not Active Surveillance Culture/Testing (ASC/AST)], and b) organism (s) identified in blood which is not related to an infection at another site (Centers for Disease Control and Prevention (CDC), 2016, Hugonnet et al., 2004).

A definitive diagnosis of catheter-related bloodstream infection (CRBSI) requires that the same organism is isolated from at least 1 peripheral blood culture and from a culture of the catheter tip, or that two concurrent positive blood cultures obtained from the catheter hub and peripheral vein meeting the CRBSI criteria (Mermel et al., 2009; Theodorou et al., 2012).

Updated definition of Carbapenem-Resistant Enterobacteriaceae (CRE) was used to identify CRE according to followings: x) resistant to any carbapenem antimicrobials including doripenem, meropenem, imipenem, and ertapenem, and y) documented to produce carbapenemase (Centers for Disease Control and Prevention (CDC), 2015).

Treatment of CRGN/CSGN microorganism infections was considered convenient in the event that at least one effective drug was used in the therapeutic regimen within 48 hours of the development of signs of infection. The outcome of infection was assessed on day 6 and at the end of the therapy. The treatment outcomes of the patients were classified as follows: (i) a clinical response on day 6 and at the end of the therapy that is resolution of fever (temperature <38 °C), leukocytosis (WBC <10,000), and local signs and symptoms of infection; (ii) microbiological response with eradication of the organism that caused the infection, which was proven by repeated negative cultures at the end of the therapy; (iii) treatment failure, defined as a lack of resolution or worsening of the signs and symptoms of infection; and (iv) relapse, defined as recurrence of the infection with the same microorganism at any site of the body within a month after the discontinuation of the therapy (Hachem et al., 2007). Patients who died during the treatment were included in the assessment as infection-related if the death had been caused by the infection (Ozsurekci et al., 2016).

2.3. Microbiological methods

Gram-negative bacteria were identified by matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS), and antimicrobial susceptibility testing was performed with the VITEK 2 (BioMérieux, Marcy-l'Étoile, France) system. Susceptibilities of microorganisms to amikacin, ceftriaxone, ceftazidime, cefepime, piperacilin-tazobactam, cefoperazone-sulbactam, imipenem, meropenem, colistin, and tetracycline were determined according to Clinical and Laboratory Standards Institute (Clinical and Laboratory Standards Institute (CLSI), 2014).

2.4. Statistical analysis

All statistical analyses were performed using SPSS version 19.0 (SPSS, Inc., Chicago, IL, USA). Descriptive statistics were used to summarize the participants' baseline characteristics, including means, standard deviations (SDs), medians, and interquartile ranges for continuous variables and frequency distributions for categorical variables. P values were calculated using the Chi square or Fisher's exact tests for categorical variables and the Student *t* or Mann–Whitney *U* tests for continuous variables according to the normality assumption. Kolmogorov–Smirnov test was used to test the normality of quantitative variables. Logistic regression was used to determine the adjusted effect of the resistance pattern on each of the outcomes, including the clinical response, microbiological response, relapse, and infection-related mortality. Variables for which the *P* value was <0.20 in bivariate analysis were included in a full multiple logistic model according the magnitude of their effect. Survival curves were prepared using Kaplan–Meier estimation and compared using the log-rank test. In all the analyses, all tests were two-tailed and $P < 0.05$ was considered significant.

3. Results

Ninety-seven pediatric patients infected with CSGN or CRGN microorganism infections were identified during the study period, 66 of whom had been identified as CSGN and 31 of whom had been identified as CRGN. Most of the patients in the CSGN group were males (62.1%). The median age of the CSGN group was 25 months (interquartile range [IQR], 5–82) and the CRGN group was 20 months (IQR, 5–122). No statistically significant differences were found between the groups in terms of gender ($P = 0.82$) and age ($P = 0.99$) (Table 1).

The types of underlying diseases were not different between the CSGN and CRGN groups ($P = 0.16$). In both groups, the most frequently isolated gram-negative bacteria were Klebsiella spp. and *E. coli*. The other isolated gram-negative pathogens were *Acinetobacter* spp., *Pseudomonas* spp., and *Enterobacter* spp. The median treatment duration of the CSGN group (15.0 days; IQR, 11.0–21.0) was not different as compared with the CRGN group (15.0 days; IQR, 5.0–25.0) ($P = 0.75$). The median treatment duration from the time of hospitalization to infection in the CRGN group (35.0 days; IQR, 12.0–58.0) was significantly longer than in the CSGN group (11.0 days; IQR, 2.0–24.0; $P = 0.002$). The median treatment duration from the time of infection to hospital discharge in the CSGN group was 23.0 days (IQR, 13.0–42.0) and in the CRGN group was 19.0 days (IQR, 3.0–52.0) ($P = 0.76$) (Table 1).

Blood stream infections were considered catheter-related in 13 (41.9%) patients with CRGN infection and in 20 (30.3%) patients with