J Pediatr Res 2019;6(3):180-5
DOI: 10.4274/jpr.galenos.2018.01488

Original Article

Risk Factors of Bloodstream Infections Caused by Carbapenem-resistant Gram-negative Pathogens in Pediatric Critical Care Settings

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ABSTRACT

Aim: Infections and sepsis are the leading causes of death in non-cardiac intensive care units (ICUs) and account for 40 percent of all ICU expenditures. Data regarding bloodstream infections (BSIs) due to a carbapenem-resistant gram negative (CRGN) microorganisms in pediatric ICUs still remain limited.

Materials and Methods: This study was conducted retrospectively in patients who were admitted to two pediatric critical care units between January 2011 and December 2017. Patients were assigned to two groups. Patients with BSI caused by a CRGN microorganism and infections were assigned to the BSI group and those other than BSI were assigned to the non-BSI group.

Results: This study included 89 critically ill children with a mean age of 52.1 (±65.1) months. The requirements for invasive procedures including tracheostomy, Foley catheter and central venous catheter were not statistically different among the groups, p values were 0.159, 0.291 and 0.803, respectively. The majority of the patients admitted to pediatric intensive care unit were due to sepsis/septic shock in the BSI group (n=18, 58%) and in the non-BSI group, this figure was 37.9% (n=24). Prior third/fourth generation cephalosporin exposure was significantly more common in the BSI group (51.6% vs 15.5%, p<0.001), carbapenem exposure was not significantly different among the groups (35.5% vs 56.9%, p=0.054). Neutropenia (<500/mm^3) and thrombocytopenia (150x103/mm^3) were significantly more common in the BSI group (p=0.011 and p=0.010) and the C-reactive protein level was significantly higher (p=0.018). Crude and attributable mortality did not show any significance between the groups, p values were 0.578 and 0.955, respectively.

Conclusion: CRGN infections are still a major cause of morbidity, mortality and healthcare associated infections. In this study, we evaluated patients with BSI due to a CRGN microorganism and compared them with other infection types. The risk factors and outcomes were similar except for prior cephalosporin exposure. As a conclusion, we have to enhance infection control programs and prevent patients from redundant antibiotic exposure.

Keywords: Carbapenem-resistant gram-negative microorganism, bloodstream infection, pediatric critical care unit

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Received: *05.10.2018* **Accepted:** *11.10.2018*

Introduction

Antibiotic resistance across Gram-negative bacteria has progressively disseminated to countries worldwide, presenting a serious public health concern. Although intensive care units (ICUs) account for fewer than 10 percent of total beds in most hospitals, the majority of all healthcare associated infections occur in ICU departments of hospitals (1,2). Infections and sepsis are the leading causes of death in non-cardiac ICUs and account for 40 percent of all ICU expenditures (3). A recent review which evaluated carbapenem-resistant *Enterobacteriaceae* (CRE) infections reported that the majority of children (53%) acquired carbapenem-resistant gram negative (CRGN) infections during their ICU stay (4). Vincent et al. (3) concluded that infections are common in patients in contemporary ICUs, and a longer duration hospital stay correlated with the risk of infection. Infections due to CRE in adult populations have been associated with poor clinical outcomes, including mortality rates as high as 40-65% while mortality can reach up to 90% in children (4,5). Data regarding bloodstream infections (BSIs) due to a CRGN pathogen in pediatric ICUs still remain limited (6,7). Therefore, we evaluated the clinical and laboratory features of BSIs caused by a CRGN pathogen and compared them with other types of infections including urinary tract infections (UTI), ventilator-associated pneumonia (VAP) and meningitis.

Materials and Methods

This study was conducted retrospectively in patients who were admitted to two pediatric critical care units between January 2011 and January 2017. The demographic characteristics, medical history, comorbidity, pathogens isolated and antimicrobial susceptibility of isolated pathogens, treatment administered, administration of other nephrotoxic agents, duration of pediatric intensive care unit (PICU) stay before the isolation of resistant microorganisms, presence of medical devices, such as ventriculo-peritoneal devices, central catheters, urinary catheters, and endotracheal or tracheostomy tubes were recorded retrospectively from the medical records.

Ethics

This study was granted permission by the Ethical Board of İzmir Katip Çelebi University (approval number: 58/March 24,2016). Informed parental consent was not obtained due to retrospective design of this study.

Microbiologic Testing

Presumptive identification of Gram-negative pathogens was identified by Vitek-Mass Spectrometry (MS) (bioMérieux, France). Vitek-MS using Matrix assisted laser desorption ionization time of flight MS technology, which is a new technology for species identification based on the protein composition of microbial cells, was used. The isolate was tested for antibiotic sensitivity on Muller Hinton agar by the Kirby Bauer disc diffusion technique using standard methods. Susceptibilities to amikacin, ceftriaxone, ceftazidime, piperacillin-tazobactam, cefoperazone-sulbactam, imipenem, meropenem, colistin and tigecycline were determined according to the Clinical and Laboratory Standards Institutes guidelines. The isolate was tested for antibiotic sensitivity on Muller Hinton agar by Kirby Bauer disc diffusion technique using standard methods. For susceptibilitytests, *E. col*i ATCC 25922, *P. aeruginosa* ATCC 27853, and *E.coli* NCTC 13846 were used as quality control strains (8).

Definitions

We reviewed the medical records of the enrolled patients and collected their case information. A standard form was used to collect the epidemiologic data including age, sex, underlying diseases (pulmonary disease, malignancy, cardiovascular disease, hematologic/solid organ transplantation, metabolic disease, genetic syndrome, prematurity, renal disease, liver disease), medication or intervention (presence of tracheal cannula, central venous catheter, presence of a Foley catheter, mechanical ventilation, immunosuppressive therapy and steroid, treatment by antibiotics). The diagnosis of infection was based on clinical features and the isolation of bacteria from a normally sterile site. Those patients with CRGN BSI were defined as the BSI group and those patients with other infection types such as VAP, UTI and meningitis were included in the non-BSI group. Standard definitions for nosocomial infections and VAP were used according to the Center for Disease Control and Prevention definitions (9) and diagnosis of sepsis was made according to the International Pediatric Sepsis Consensus (10).

Crude mortality was defined if the patient died within 1 month of the infection and attributable mortality was defined if the patient died directly related to the breakthrough infection.

Statistical Analysis

Statistical analyses were performed using SPSS for Windows (version 22.0; SPSS, Inc., Chicago, IL, USA). Numerical data were expressed as medians (interquartile range). Mann-Whitney U and Wilcoxon tests were used for inter-variable analysis. Categorical variables were evaluated

with the chi-square test or the two-tailed Fisher exact test and presented as percentages in acquiring CRGN infections. Comparisons were referred to as statistically significant if the p values were <0.05.

Ethics

This study was granted permission by the Ethical Board of İzmir Katip Çelebi University (approval number: 58/March 24,2016).

Results

This study included 89 critically ill children with a mean age of 52.1 (±65.1) months between January 2011 and December 2017. The most common type of infection was VAP (59 cases, 66.2%), followed by BSI (31 cases, 39.6%), UTI (10 cases, 11.2%), meningitis (3 cases, 3.3%). Both bloodstream infection and VAP occurred in 7 (7.8%) patients, BSI and UTI occurred in 3 (3.3%) patients and VAP and UTI occurred in 3

Table I. Risk factors and outcomes of Carbapenem-resistant gram-negative bloodstream infections (BSIs) and comparison with non-BSI group

	BSI (n=31)	**Non-BSI (n=58)**	**p value**
Age, months, mean ± SD	32.8 (±37.04)	66.7 (±72.9)	0.022
Hospital stay prior to BSI (median, ±SD) (day)	17 (9.5-128.1)	10 (11.6-21.8)	0.803
Total hospital stay (median, ±SD) (day)	27 (2.89-168.65)	34 (34.2-56.9)	0.384
Underlying diseases (n, %)	-	-	0.029
- Previously healthy	1 (3.2)	12 (20.7)	
- Chronic neurological/neuromuscular disorder	9 (29)	18 (31)	
- Hematologic/solid malignancy	1 (3.2)	3 (5.2)	
- Chronic liver diseases	1 (3.2)	4 (6.9)	
- Chronic lung disease	2 (6.5)	9 (15.5)	
- Congenital heart disease	4 (12.9)	6 (10.3)	
- Bone marrow/solid organ transplantation	7 (22.6)	2 (3.4)	
- Primary immune deficiency	3 (9.7)	3 (5.2)	
Others	3 (9.7)	1 (1.7)	
Cause of PICU admission (n, %)			
- Sepsis/Septic shock	18 (58.1)	24 (41.4)	0.165
- Respiratory failure	10 (32.3)	22 (37.9)	
- Trauma	1 (3.2)	9 (15.5)	
- Status epilepticus	0	2 (3.4)	
- Cardiopulmonary arrest	2 (6.5)	1 (1.7)	
Tracheostomy (n, %)	10 (32.3)	11 (19)	0.159
Foley catheter (n, %)	24 (77.4)	50 (86.2)	0.291
Central venous catheter (n, %)	29 (93.5)	55 (94.8)	0.803
Thrombocytopenia (<150x10^3/mm^3) (%)	13 (50)	13 (22.4)	0.031
Neutropenia (<500/mm^3) (%)	4 (13.8)	0 (0)	0.011
WBC (mm^3)	13100 (7677-16018)	12600 (12058-16438)	0.207
ANC (mm^3)	7250 (5040-12477)	9140 (8528-12564)	0.105
PLT (x103/mm^3)	212 (140153-298944)	315 (285627-399193)	0.010
CRP (mg/dL)	9.65 (7.47-12.5482)	7.3 (5.43-82051)	0.018
Attributable mortality (n, %)	5 (16.1)	11 (19)	0.740
Crude mortality (n, %)	5 (16.1)	18 (%31)	0.126

BSI: Bloodstream infection, SD: Standard deviation, PICU: Pediatric intensive care unit, WBC: White blood cell, ANC: Absolute neutrophil count, PLT: Platelet, CRP: C-reactive protein

(3.3%) patients. The most common underlying disease was chronic neurological disorder in the BSI group (n=9, 29%) and also in the non-BSI group (n=18, 31%) and this was followed by bone marrow/solid organ transplantation (n=7, 22.5%) while chronic lung diseases was seen in 15.5% (n=9) in the non-BSI group (Table I). The majority of the patients were admitted to PICU due to sepsis/septic shock in the BSI group (n=18, 58%) and in the non-BSI group, this figure was 37.9% (n=24). The requirement of invasive procedures including tracheostomy, Foley catheter and central venous catheter were not statistically different among the groups, p values were 0.159, 0.291 and 0.803, respectively. The mean age of the patients was significantly younger in the BSI group than the non-BSI group (12 months vs 32 months, p=0.022). Total and prior hospital stay did not show any significant difference, p levels were 0.384 and 0.803, respectively. Prior third/fourth generation cephalosporin exposure was significantly more common in the BSI group (51.6% vs 15.5%, p<0.001), carbapenem exposure was not significantly different among the groups (35.5% vs 56.9%, p=0.054). Crude and attributable mortality did not show any significance between the groups, p values were 0.578 and 0.955, respectively. Neutropenia (<500/mm^3) and thrombocytopenia (150x10^3/mm^3) were significantly more common in the BSI group (p=0.011 and p=0.010) and the C-reactive protein level was significantly higher (p=0.018). White blood cell, absolute neutrophil count and hemoglobin level did not show any statistical significance between the groups, p levels were 0.271, 0.121 and 0.822, respectively (Table I), isolated microorganisms have been shown in Table II.

Discussion

In this study, a retrospective case-control study was conducted to evaluate the risk factors for the acquisition of BSI caused by CRGN microorganisms and to compare with infection types other than BSI in those patients admitted to PICUs of two teaching hospitals. We found BSIs occurred in younger patients and thrombocytopenia and neutropenia were significantly more common in the BSI group. The crude and attributable mortality rate did not show statistical significance between the groups. Over recent years, CRGN infections have been attributed as being a significant cause of healthcare associated infections, significant mortality and morbidity. Previous adult studies suggested that elderly patients are more vulnerable to CRE infections. On the other hand, a recent study from the UK evaluating CRE infections demonstrated the majority of patients (6/9; 66.6%) were under 1 year of age (8). Similarly, we found that patients with BSI were younger than those patients with other types of infection.

A recent study evaluated the risk factors and clinical outcomes of patients with CR *Acinetobacter baumannii* bacteremia and found that the independent risk factors were hematological malignancy, previous cefepim exposure and the use of total parenteral nutrition (11,12). Routsi et al. (13) suggested prior exposure to carbapenems were independent risk factors for the acquisition of CR-GN bacilli. Previous administration of carbapenems was the only factor related with the development of CR-GNB if the source of infection was other than VAP. Patients with bacteremia were more likely to have additional devices and a longer hospital stay. In the present study, the carbapenem exposure rate was similar among the groups while prior cephalosporin was 3-fold more common in the BSI group when compared with the non-BSI group (p<0.001).

A recent meta-analysis evaluating 9 studies reported that death rates were higher in patients who had bacteremia caused by a CRGN pathogen when compared with a CSGN pathogen. However, they suggested no difference between the groups; bacteremia and other infections (14). We compared patients with BSI caused by a CRGN pathogen and other types of infection due to a CRGN pathogen and did not

Table II. Isolated microorganisms and isolation sites

Isolated microorganisms	Blood (n=31)	Endotracheal lavage (n=59)	Urine (n=10)	Cerebrospinal Fluid (n=3)
Pseudomonas aeruginosa	6	18	2	1
Acinetobacter baumannii	16	35	5	1
Klebsiella pneumoniae	7	3	2	1
Escherichia coli	1	-	1	-
Serratia marcescens	1	-	-	-
Acinetobacter baumannii+ Pseudomonas aeruginosa	-	2	-	-
Acinetobacter baumannii+ Klebsiella pneumoniae	-	1	-	-

find a significant difference. A case control study was used to identify risk factors and compare outcomes (15). Previous studies demonstrated 3-6 times higher mortality among CRE-infected patients when compared with Carbapenem-sensitive *Enterobacteriaceae* infected patients (16-18). We did not find a significant difference among our groups.

Acquired risk factors for CRE infection in children include underlying chronic medical conditions, invasive medical devices, frequent or prolonged hospitalizations, prior antibiotic exposure, age, and travel from endemic regions (16). Among the BSI and non-BSI groups, prior and total hospital stay duration did not show any difference.

Thrombocytopenia is a common finding in patients with bacterial sepsis as a result of marrow suppression, consumption due to Disseminated intravascular coagulation (DIC) and inflammatory response, being either drug-induced or not. A recent study compared methicillin-resistant and methicillin-sensitive *Staphylococcus aureus* infected patients and found no significant difference for thrombocytopenia (19). A recent multicenter observational study demonstrated that thrombocytopenia within the first 24 hours of septic shock onset to be a prognostic marker of survival at day 28 in a large cohort of ICU patients (20). We found that patients in the BSI group were significantly more likely to develop thrombocytopenia in line with previous reports.

There are several advantages of this study. The main advantages are that this is the largest series in pediatric critical care settings, it is the first study that evaluates the impact of having BSI due to a CRGN pathogen and it has a multicenter design. The main limitations of this study were its retrospective design and the lack of any molecular characterization of the microorganisms which can affect the outcomes of these infections. We additionally defined CRGN as an organism demonstrating resistance to at least one carbapenem antibiotic and therefore could not assess the risk factors particularly for carbapenemase-producing CRGN, which may be distinct from those of non-carbapenemase-producing CRGN.

CRGN infections are still a major cause of morbidity, mortality and healthcare associated infections. In this study, we evaluated patients with BSI due to a CRGN microorganism and compared them with other infection types. The risk factors and outcomes were similar except for prior cephalosporin exposure.

Conclusion

We have to enhance infection control programs and prevent patients from redundant antibiotic exposure. Our current knowledge is based on adult studies due to lack of prospective and case-control design studies. Therefore, further larger and prospective design studies are needed.

Ethics

Ethics Committee Approval: This study was granted permission by the Ethical Board of İzmir Katip Çelebi University (approval number: 58/03, 24,2016).

Informed Consent: Informed parental consent was not obtained due to retrospective design of this study.

Peer-review: Externally peer-reviewed

Authorship Contributions

Concept: Z.Ş.B., Design: Z.Ş.B., Supervision: A.B.A., B.K., Resource: F.K., M.D., P.Y., Materials: F.K., M.D., P.Y., Data Collection and/or Processing: F.K., Z.Ş.B., Analysis and/or Interpretation: Z.S.B., F.K., M.D., P.Y., F.Ç., N.Y.Ö., Literature Search: Z.Ş.B., D.Y.Ç., Writing: Z.S.B., Critical Reviews: Z.Ş.B., A.B.A., B.K.

Conflict of Interest: The authors have no conflicts of interest relevant to this article to disclose.

Financial Disclosure: The authors have no financial relationships relevant to this article to disclose.

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