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Original Research Article

Risk Factors in Carbapenem Resistant *Enterobacteriaceae* Infections

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Abstract

Carbapenem resistance, which was rarely observed up until the recent years, is becoming increasingly more common among the *Enterobacteriaceae* family around the world. It is thought that specifying the risk factors for carbapenem-resistant *Enterobacteriaceae* (CRE) infections may be helpful to initiate the appropriate empirical therapy at an early phase and to take the infection control measures. The aim of this study is to observe the risk factors and their relationship with mortality in patients infected with CRE. The control group was randomly selected from amongst the patients who were admitted to the same ward with the patient group during the period when CRE growth was observed, but were tested negative for CRE growth. Two control subjects were enrolled for each patient. Seventy patients where CRE growth was observed were included in the study. Among these patients, 55 were infected with *K.pneumoniae*, 7 with *E.coli*, 6 with *Enterobacter cloacae*, 1 with *Enterobacter asburiae* and one patient was infected with *Enterobacter aerogenes*. Immunosuppression, endotracheal intubation, mechanical ventilation, urinary neumonia des n, total parenteral nutrition (TPN), central venous catheter (CVC), tracheostomy, urinary catheter days before CRE, endotracheal intubation days, ventilator-days, CVC days, TPN days, days of nasogastric intubation, days of abdominal drain were found to be statistically significant. Also, the number of days spent in intensive care before CRE developed, the Acute Physiology And Chronic Health Evaluation II (APACHE II) score; and days of piperacillin/tazobactam, carbapenem, Colistin, and neumonia des use were found to be significant. In order to reduce the infections that happen due to CRE, the surveillance results should be continuously monitored and the recommendations of the infection control committee should be taken under consideration. The indication of invasive procedures should procedures be well-defined and unnecessary invasive procedures should be avoided. In patients who will receive therapy, treatment should be initiated according to the rational antibiotic use principle.

Keywords: Carbapenem-Resistant *Enterobacteriaceae*, Mortality, Risk Factors

INTRODUCTION

Microorganisms in the *Enterobacteriaceae* family consist of a large number of medically important gram-negative (GN) bacteria that form the gastrointestinal flora. These microorganisms are among the most common pathogens that cause infections in humans, such as, cystitis, pyelonephritis, septicemia, pneumonia, device-related infections, peritonitis and meningitis. Furthermore, pathogens in the *Enterobacteriaceae* family are the source of community and hospital-acquired infections (Nordmann et al., 2011). Carbapenem antibiotics became an important treatment in the severe infections caused by gram-negative bacteria, due to the resistance developed towards the antibiotics in the beta-lactamase group and subsequent production of extended-spectrum beta-

lactamase (ESBL) (Jacoby and Munoz-Price, 2005). Carbapenem resistance was first observed in *Acinetobacter spp., Pseudomonas aeruginosa*, then in GN enteric bacteria, due to the more frequent use of carbapenem group antibiotics (Peleg and Hooper, 2010; MacKenzie et al., 1997; Hong et al., 2005). Carbapenem resistance, which was extremely rare up until recent years, increased globally in the *Enterobacteriaceae* family, particularly in *Klebsiella neumonia*. The prevalence of carbapenem-resistant *Escherichia coli* became a significant problem in recent years (Kim et al., 2007; Min-Hyok et al., 2008). In the world, it made in several studies, emphasized the significance of active surveillance studies in controlling the Carbapenem Resistant *Enterobacteriaceae* (CRE) outbreaks and the importance of infection control measures, particularly the contact isolation (Samra et al., 2007). CRE isolates spread in hospital settings, probably due to patient transfer. Therefore, CRE species should be identified and limited through similar efforts in controlling vancomycin-resistant *enterococci*. Strict surveillance and effective infection control measures should be implemented at national level to prevent the spread of these pathogens (Us et al., 2010). Center for Disease Control and Prevention (CDC) published the recommendations for the control of carbapenem-resistant *Enterobacteriaceae* in hospitals in 2009, in order to prevent these infections (Guidance for control of infections with carbapenem-resistant or carbapenemase-producing Enterobacteriaceae in acute care facilities, 2009). It is considered that determination of risk factors in CRE could facilitate the early and appropriate implementation of the empirical treatment and infection control measures (Patel et al., 2008). The aim of the present study was to determine the risk factors in patients infected with CRE and their relationship with mortality.

Material and Method

The present study was carried out between January 2014 and December 2015 in the internal diseases departments, Surgical departments and Intensive Care Units of the Medical Faculty Hospital at Dicle University.

Inclusion criteria in the patients group

- Patients who are 18 years old or older
- Diagnosis during hospitalization and gender was not taken into consideration.
- Patients, who were diagnosed positive for CRE growth through any microbiological culture and whose treatments were initiated due to infectious disease and microbiology specialist opinions, suggesting that the diagnosis was the cause of the disease.

Inclusion criteria in the control group

- Patients who are 18 years old or older
- Diagnosis during hospitalization and gender was not taken into consideration.
- Staying at the hospital on the same date and in the same ward with the patients, who exhibited CRE growth and was included in the patient group.

Two control patients were randomly selected for each case in the present study. A standard data form was prepared to record the patient information and the information was retrospectively scanned from the electronic file system.

The data was analyzed using the SPSS 15.0 software. Categorical data were expressed in number (n) and percentages (%). Numerical data were expressed in mean and standard deviation. The normally distributed data in the comparison of the two independent groups were analyzed via student t-test and the data that did not exhibit a normal distribution was analyzed by Mann-Whitney U test. The categorical data was compared through the Pearson Chi-Square and Fisher Exact tests. Data were analyzed at a 95% confidence level. Values of *p* less than 0.05 were considered significant.

RESULTS

Seventy patients diagnosed positive for CRE at the Medical Faculty Hospital of Dicle University between January 2014 and December 2015, were included in the study. There was no significant difference between patient and control groups based on gender and mean age (Table 1). The most prevalent CRE subtype was *K.pneumoniae* and it was followed by *E. coli* (Table 2). CRE in the patient group was most frequently produced in blood culture and least frequently produced in drainage culture (Table 3). The participants of the patient and control groups were examined for underlying diseases and no statistical difference was determined, except immunosuppression ($p < 0.05$). Endotracheal intubation, mechanical ventilation, urinary catheter, use of total parenteral nutrition (TPN), use of central venous catheter (CVC) and tracheostomy presence were found to be statistically significant ($p < 0.05$) due to the comparison of the patient and control groups based on the invasive procedures applied to CRE infected patients (Table 4). Patients with CRE infection were compared with the control group and it was determined that there was a statistically significant difference in the inpatient and ICU stay durations before the CRE development ($p<0.05$). Antibiotic uses in patient and control groups were examined and it was found that the piperacillin/ tazobactam, carbapenem, colistin and glycopeptide use were significant and the results were significantly different (Table 5). Immunosuppression presence was an independent risk factor for CRE growth.

Table 1. Age and Gender Variables

Demographics		Patient Group n: =70	Control Group n:=140,	P value
Gender n(%)	Female	38(? %)	70(? %)	0.558
	Male	32(? %)	70(? %)	
Age (mean± SD)		57.5 ±19.9	59.3 ±18.7	0.520

Table 2. Subtypes of CRE grown in culture (n= 70)

CRE Subtypes	Patient Group n: 70 (%)
1- K.pneumoniae	55 (78.5)
2- E.coli	7 (10)
3- Enterobacter cloacae	6 (8.5)
4- Enterobacter asburiae	1 (1.4)
5- Enterobacter aerogenes	1 (1.4)

Table 3. Classification of the CRE growth in the patient group based on the growing material (n= 70)

Retrieved material	Patient Group n: 70 (%)
1-ETA Endotracheal Aspirate	18 (25.7)
2-Blood	28 (40)
3-Urine	12 (17.1)
4-Wound	9 (12.8)
5-Drainage	3 (4.2)

Table 4. Relationship of CRE Infection with Invasive Interventions

Invasive Procedures	Patient (n) and (%)	Control (n) and (%)	P value
Endotracheal intubation	41 (%58.6)	47(%33.6)	0.001
Mechanical ventilation	42(%60.0)	50(%35.7)	0.001
Urine catheter	63(%90.0)	104(%74.3)	0.008
TPN	25(%35.7)	28(%20.0)	0.013
Nasogastric tube	31(%44.3)	66(%47.1)	0.695
CVC	38(%54.3)	37(%26.4)	< 0.001
Tracheostomy	11(%15.7)	4(%2.9)	0.001

Table 5. The Relationship between the CRE Infection and Antibiotics

Antibiotics Used	Patient Group (n) and (%)	Control Group (n) and (%)	P value
3rd Generation Cephalosporin	23(%32.9)	40(%28.6)	0.523
Ampicillin / Sulbactam	9(%12.9)	27(%19.3)	0.244
Piperacillin / Tazobactam	31(%44.3)	29(%20.7)	< 0.001
Carbapenem	46(%65.7)	32(%22.9)	< 0.001
Glycopeptide	25(%35.7)	8(%5.7)	< 0.001
Colistin	19(%27.1)	9(%6.4)	< 0.001
Metronidazole	8(%11.4)	15(%10.7)	0.876

DISCUSSION

It is essential to determine the prevalence of antibiotic-resistant nosocomial pathogens for effective infection control strategies and appropriate antibiotic combinations against the agent that causes the infection. Antibiotics in the carbapenem group are highly important in severe and life-threatening infections and in the infections caused by

multidrug resistant GN bacteria. The rate of resistance towards the drugs in the carbapenem group, which increase every year, and the enzymes that could be responsible for the resistance exhibit diversities based on country and center.

In recent years, similar to the global trend, CRE became a highly important problem in Turkey as well and CRE cases became prevalent at the Medical Faculty Hospital of Dicle University in 2014. Thirteen CRE cases were detected at the end of 2014 and the figures rapidly increased in 2015 and reached to 70 by end-2015. The literature review indicated that there existed various risk factors for CRE growth. Several studies reported that immunosuppression was considered as a risk factor for CRE (Wang et al., 2016; Brooke et al., 2016).

The present study determined that immune-suppression presence was an independent risk factor for CRE growth. Currently various invasive procedures are applied through the diagnosis and treatment processes due to the progress in technology and medicine science. Furthermore, these procedures are more frequently applied. Several invasive procedures applied to patients could constitute a risk factor for CRE growth. A literature review on the relationship between the CRE infections and invasive procedures indicated that presence of central venous catheter, tracheostomy, mechanical ventilator use, and abdominal invasive intervention were identified as the risk factors for CRE (Wang et al., 2016; Jiao et al., 2015; Mittal et al., 2016; Giannella et al., 2014). A study conducted in Turkey identified the risk factors of carbapenem resistance as the use of invasive devices and total parenteral feeding duration (Budak et al., 2014). Another study indicated that the use of urinary catheters, invasive procedures and prolongation of mechanical ventilation were risk factors for CRE development (Yigit et al., 2001). Similar findings with the literature were obtained in the present study and endotracheal intubation, ventilation, catheter, usage, and tracheostomy were identified as the risk factors for CRE development.

Intensive care units (ICU), where a large number of patients are observed simultaneously and underlying diseases are common, are critical for the development and spread of antimicrobial resistance due to frequent invasive procedures on patients and to the regularly used antimicrobials (Brusselaers et al., 2011). Papadimitriou-Olivgeris et al. conducted a study in 2012 and determined that 13% of patients admitted to intensive care units were colonized by *Klebsiella pneumoniae* (KPC). The same authors conducted another study in 2013 and found that 75% of the patients were colonized by KPC during their stay at the ICU (Papadimitriou-Olivgeris et al., 2012; Papadimitriou-Olivgeris et al., 2013). The present study also found that prolonged total ICU and hospital stay were found to be risk factors for CRE. Currently, antibiotic resistance is gradually increases due to the increased consumption of antibiotics in the community and in health care units and increased number of patients with an impaired immune system.

In Turkey, Dizbay et al. conducted a study in 2014 and determined that use of antibiotics in the last three months, especially imipenem and cefoperazone /sulbactam, was an independent risk factor for CRE development (Dizbay et al., 2014). Hyle et al. conducted a study in the United States in 2010 and concluded that the use of β-lactam antibiotics and carbapenem in the last 30 days was a risk factor for CRE (Hyle et al., 2010). The present study investigated the relationship between antibiotics and duration of CRE and determined that piperacillin/tazobactam, carbapenem, glycopeptide and colistin uses were risk factors. Several studies reported mortality rates between 24% and 65% in patients infected with CRE strains, and resistance to carbapenems was found to be an independent risk factor for mortality (Daikos and Markogiannakis, 2011; Deshpande et al., 2006; Schwaber et al., 2008). 39 of the 70 patients, in the patient group of the present study, were infected with CRE and died, thus the mortality rate in the present study was high, with 55.7%. Treatment options for CRE are limited and various combination treatments are provided based on the antibiogram results. One of the major reasons for such high mortality rate is the lack of an effective treatment option. It is also considered that continuous drug revisions due to side effects these drugs such as colistin, which is used in the treatment of CRE, lead to an increase in mortality.

CONCLUSION

CRE infections were considered an important factor among the causative agents of recent hospital infections. The way to prevent these infections; Indications of invasive procedures should be well established, unnecessary invasive procedures should be avoided and invasive procedures should be terminated as soon as the indications disappear. In order to reduce infections caused via the CRE agents, surveillance results should regularly be monitored, recommendations of the infection control committee should be taken into consideration, and standard precautions, especially hand hygiene and the isolation and infection control guidelines should be followed in case of contact with patients. This article was produced from the thesis study.

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Conflict of Interest

All the authors including, Mehmet Zeki Kortak, Fatma Bozkurt, Özcan Deveci, Ciğdem Mermutlu, Recep Tekin, Mustafa Kemal Çelen, Saim Dayan declare that they have no conflict of interest.

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