Risk factors for the acquisition of carbapenem-resistant *Escherichia coli* in a tertiary care hospital in South Korea : A matched case-control study

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Risk factors for the acquisition of carbapenem-resistant *Escherichia coli* in a tertiary care hospital in South Korea : A matched case-control study

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ABSTRACT

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Background: Carbapenem resistance among Gram-negative bacilli has become an emerging threat worldwide. The objective of this study was to identify risk factors for the acquisition of carbapenem-resistant *Escherichia coli* (CRE).

Methods: We conducted a matched case-control study involving 57 cases with acquisition of CRE and 114 controls (1:2 matched) selected among patients with carbapenem-susceptible *E. coli* between January 2006 and December 2010 in a 2,000-bed tertiary care hospital in South Korea. The two groups were matched for the site and date of *E. coli* isolation.

Results: In univariate analysis, previous use of carbapenem (p<0.001),

fluoroquinolone (p=0.001), and glycopeptide (p<0.001), total number of previous antibiotic treatments (p=0.004), and length of hospital stay (p=0.047) were significantly associated with CRE acquisition. However, the year of isolation, attending healthcare workers, department or ward at the time of isolation, and the existence of CRE during the hospital stay were not associated with CRE acquisition. In multivariate analysis, previous use of carbapenem [odds ratio (OR) 4.56, 95% confidence interval (CI) 1.44-14.457, p=0.009] and previous use of fluoroquinolone (OR 2.81, 95% CI 1.137-6.991, p=0.0253) were independent risk factors for CRE acquisition.

Conclusions: In this institute, antibiotic selective pressure seems to be more important for CRE acquisition than nosocomial transmission.

Key words: carbapenem-resistant *Escherichia coli,* risk factor

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I. INTRODUCTION

Enterobacteriaceae are the most common pathogens in humans, causing various diseases from simple cystitis to severe infections such as bacteremia, peritonitis, and meningitis. Carbapenems have served as important antimicrobial agents for the treatment of these organisms. Until recently, resistance to carbapenems has been uncommon; however, use of carbapenems has been increasing gradually over past decades, and as a result, carbapenem-resistant *Enterobacteriacae* have emerged[1,2].

Until 2006 the resistance rate of *K. pneumoniae* to carbapenems in the United States was reported as only 0.3%, but in 2008, it increased to 10%[3].

Given these circumstances, the clinical outcomes and risk factors of carbapenem-resistant *K. pneumoniae* infections have been extensively studied[4-6].

Similarly, the emergence and spread of carbapenem-resistant *Escherichia coli* (CRE) has also increased to 4%[7]. Because *E. coli* is a much more common clinical isolate than *K. pneumoniae*, CRE provides more challenging problems for physicians.

The mechanism of carbapenem resistance in *E. coli* is mostly attributable to an outer membrane porin deficiency combined with the presence of CMY-2-/CMY-4-related AmpC enzymes[8,9], CTX-M/SHV-12 type extended spectrum β-lactamase (ESBL), or IMP-8-type metallo-b-lactamase[8,10]. Recently, OXA-48-like carbapenemases and outer-membrane protein loss were also reported.[1]

To date, the risk factors for CRE acquisition have not been well described, and there are only limited observational data and clinical reports of the treatment of infections caused by CRE. Because CRE represents a significant potential threat to hospital infection control[11], we conducted a matched case-control study to identify potential risk factors for the acquisition of CRE.

II. MATERIALS AND METHODS

1. Study design and patients

This case-control study was conducted at Severance Hospital in Seoul,

Korea, a 2,000-bed tertiary care medical center. In this retrospective study, microbiology laboratory databases were reviewed to identify all clinical cultures positive for CRE between January 2006 and December 2010. All identified patients were enrolled, and their medical charts were reviewed. For patients with more than one episode of infection with *E. coli*, only data relevant to the first episode were collected and analyzed.

For each patient with CRE acquisition, we selected two matched control patients from the pool of patients with carbapenem-susceptible *E. coli* acquisition. The two groups were matched for the site and the date of *E. coli* isolation.

2. Microbiological tests

Antimicrobial susceptibilities were determined using the disc-diffusion method or a VITEK-2 N131 card (bioMerieux, Hazelwood, MO., USA). The results were interpreted according to CLSI 2010/2011 guidelines[12,13]. Resistance to carbapenem was defined as an MIC to imipenem or meropenem exceeding 4 μg/mL or disk diffusion less than 19 mm.

3. Collected data and definitions

The data collected included: age, sex, underlying disease, culture specimens, date of culture, admission ward at the time of culture, duration of hospital stay before isolation of *E. coli*, procedures received, prior antimicrobial therapy regimen, and the antimicrobial susceptibility of *E. coli.* The presence of the following comorbid conditions was documented: neutropenia, admission to intensive care unit (ICU), use of an

immunosuppressive agent within 30 days prior to *E. coli* isolation, and postoperative conditions. In addition, we assessed data with regard to the presence of a central venous catheter, foley catheter, or mechanical ventilation.

Epidemiological types of *E. coli* were classified as community-acquired (CA), hospital-acquired (HA), or healthcare-associated (HCA)[14,15]. HA was defined as acquisition of *E. coli* more than 48 hrs after admission or within 10 days of discharge from an acute care hospital. HCA was defined by a history of hospitalization for two or more days in the previous 90 days, receipt of intravenous medication or home wound care in the previous 30 days, receipt of hemodialysis, or residence in a nursing home or long-term care facility[13,14]. CA was defined as the first acquisition of *E. coli* less than 48 hrs after admission in the absence of any risk factors for HCA acquisition of *E. coli*[13,14].

Neutropenia was defined as an absolute neutrophil count below 500/μL. Corticosteroid use was noted only if the patient had recently received the equivalent of 30 mg of prednisone daily for at least seven days or 20 mg each day for 14 days. Receipt of immunosuppressant was defined as use of any immunosuppressive drug (e.g., cyclosporine, antineoplastic chemotherapy) in the previous 30 days. Previous exposure to various antibiotic agents was also reported. Exposure to a specific antimicrobial agent was considered relevant only if the antibiotics had been administered for at least three consecutive days within one month before acquisition of *E. coli*.

Exposure to various risk factors was taken into consideration in the

analysis only if it occurred before the acquisition of *E. coli*.

4. Statistical analysis

Continuous variables are presented as mean ± SD, and categorical variables are presented as numbers and percentages. For continuous variables, Student's t-test or Wilcoxon test was used, depending on the validity of the normality assumption. Chi-square test or Fisher's exact test was used to test categorical variables. Multivariate analysis was performed using logistic regression to identify factors that independently and significantly affected the outcome. Variables with a p-value less than 0.05 in univariate analysis were considered for inclusion in a multivariate model. A p value <0.05 was considered significant. All statistical analyses were performed using the SPSS program.

III. RESULTS

1. Number of patients with CRE during the study period

From January 2006 to December 2010, a total of 171 patients were included in this study (57 cases with CRE and 114 controls with carbapenem-sensitive *E. coli*). The two groups were matched for the site and date of *E. coli* isolation. During the five-year study period, CRE was isolated from 57 patients: six patients in 2006, nine in 2007, 18 in 2008, 17 in 2009, and seven in 2010. There were no outbreaks of CRE during the study period. The hospital wards in which CRE was isolated were not

clustered.

2. Demographic and clinical characteristics of subjects

The demographics and characteristics of the two groups are shown in Table 1. The mean age was 65.26 years in the CRE group and 62.78 years in the control group, and the patients were predominantly female (52.6% vs. 55.3%). Patients in both groups had predominantly hospital-acquired infection, but the proportion of hospital-acquired *E. coli* was higher in the CRE group than in the control group (61.4% vs. 45.6%). CRE was most frequently confirmed in urinary specimens (35.1%), followed by blood (24.6%), gastrointestinal specimens (17.5%), skin and soft tissue (13%), surgical site aspiration (3.5%), respiratory secretions (3.5%), and throat aspirates (3.5%). The CRE group had a longer average hospital stay than the control group (26.63 days vs. 13.11 days, p=0.047). There was no statistically significant difference in other demographic factors.

3. Risk factors for the acquisition of CRE

The results of univariate analysis of the two groups regarding risk factors for acquisition of CRE are listed in Table 2. There was no statistically significant difference in underlying co-morbidities, predisposing factors, or type of procedures undergone in the CRE group compared with the control group except for bronchoscopy (5.3% vs. 0%, p=0.013). However, the total number of prior antibiotic treatments was greater in the CRE group than the control group (1.98 vs. 0.99, p=0.004). Compared with the control group, a larger proportion of patients in the CRE group were

treated with fourth-generation cephalosporins (7.0% vs. 0.9%, p=0.025), fluoroquinolones (31.6% vs. 11.5%, p=0.001), glycopeptides (26.4% vs. 4.4%, p<0.001), or carbapenems (28.1% vs. 5.3%, p<0.001) before acquisition of *E. coli*. Investigation of 28-day overall mortality showed no statistical difference in the clinical courses of the two groups (14.8% vs. 10.2%, p=0.388).

Multivariate analysis showed that prior use of carbapenems [odds ratio (OR) 4.56, 95% confidence interval (CI) 1.44-14.46, p=0.0099] and fluoroquinolones [OR 2.82, CI 1.14-6.99, p=0.0253) were independent risk factors for the acquisition of CRE (Table 3).

The antimicrobial sensitivities of *E. coli* were also investigated (Table 4). Resistance to ampicillin/sulbactam, piperacillin/tazobactam, aztreonam, cefoxitin, cefotaxim, ceftazidime, cefepime, fluoroquinolone, and amikacin were more frequent in patients with CRE, but there was no significant difference between the two groups in the proportion of extended spectrum β-lactamase (ESBL)-producing *E. coli.*

Table 1. Demographics and clinical characteristics

Factors	Total N=171	CRE Group N=57	Control Group N=114	*p* value
Demographic factors				
Sex (male)	78(45.6)	27(47.4)	51(44.7)	0.745
Age	64 ± 13.92	65.26 ± 14.30	62.78 ± 13.71	0.273
BMI (kg/m^2)	22.01 ± 3.90	21.55 ± 3.51	22.35 ± 4.07	0.222
Length of stay (d)	18.23 ± 40.55	26.63 ± 37.89	13.11 ± 41.30	0.047*
Type of acquisition				
Community-acquired	41(23.98)	9(15.8)	32(28.1)	0.109
Hospital-acquired	87(50.88)	35(61.4)	52(45.6)	
Health-care associated	43(25.14)	13(22.8)	30(26.3)	
Site of culture				
Urine	60(35.09)	20(35.1)	40(35.1)	
Blood	42(24.56)	14(24.6)	28(24.6)	
Gastrointestinal origin	30(17.54)	10(17.5)	20(17.5)	
Skin and soft tissue	21(12.28)	7(13.2)	14(13.2)	
Surgical site infection	6(3.50)	2(3.5)	4(3.5)	
Sputum	6(3.50)	2(3.5)	4(3.5)	
Ear, eye, throat	6(3.50)	2(3.5)	4(3.5)	

Data are presented as mean ± SD, or number of subjects; *p value < 0.05

Table 2. Risk factor analysis and outcome

Factors	Total N=171	CRE Group N=57	Control Group N=114	*p* value
Comorbidities				
Number of comorbidities	2.02 ± 1.387	2.25 ± 1.154	1.98 ± 1.487	0.243
HTN	62(36.26)	23(40.4)	39(34.2)	0.431
DM	46(26.90)	20(35.1)	26(22.8)	0.088
Cardiovascular disease	21(12.28)	6(10.5)	15(13.2)	0.621
CNS disease	30(17.54)	11(19.3)	19(16.7)	0.67
Renal disease	45(26.32)	15(26.3)	30(26.4)	1
Solid tumor	71(41.52)	23(40.4)	48(42.1)	0.826
Solid organ transplantation	6(3.50)	2(3.5)	4(3.5)	1
Lung disease	2(1.17)	1(1.8)	1(0.9)	0.615
Hematologic malignancy	15(8.77)	8(14.0)	7(6.1)	0.085
Rheumatologic disease	9(5.26)	1(1.8)	8(7.0)	0.146
Liver disease	45(26.32)	16(28.1)	29(25.4)	0.713
Predisposing factors				
Neutropenia	12(7.02)	6(10.7)	6(5.3)	0.147
Steroid use	6(4.68)	5(9.1)	3(2.6)	0.064
Immune suppressant use	9(5.26)	4(7.0)	5(4.4)	0.468
Chemotherapy	34(19.89)	8(14.0)	26(22.8)	0.175
Radiation therapy	12(7.02)	5(8.8)	7(6.1)	0.525
Prior infection	85(46.78)	30(54.5)	55(49.5)	0.669
ICU stay	17(9.94)	7(12.7)	10(8.8)	0.423
Hemodialysis	8(4.68)	3(5.3)	5(4.4)	0.352
Maintenance of central line	40(23.39)	16(28.1)	24(21.1)	0.203
Maintenance of foley catheter	50(29.24)	19(33.9)	31(27.2)	0.365
Invasive procedures				
Number receiving procedure	95(55.56)	35(61.4)	60(52.6)	0.277
Number of procedures	1.23 ± 1.542	1.47 ± 1.638	1.11 ± 1.486	0.151

Central line insertion	31(18.12)	12(21.1)	19(16.7)	0.483
Foley catheter insertion	53(30.99)	23(40.4)	30(26.5)	0.067
Endoscopy	16(9.94)	3(5.3)	13(11.4)	0.194
Cardiovascular catheterization	4(2.34)	2(3.5)	2(1.8)	0.474
Mechanical ventilator	18(10.52)	6(10.5)	12(10.5)	1
Surgery	3(1.75)	1(1.8)	2(3.6)	1
Bronchoscopy	3(1.75)	3(5.3)	0(0)	0.013*
Prior antibiotics use				
Total number of antibiotics	1.32 ± 1.814	1.98 ± 2.252	0.99 ± 0.455	0.004*
Ampicillin	8(4.68)	4(7%)	4(3.5)	0.312
Antipseudomonal penicillins	11(6.43)	5(8.8)	6(5.3)	0.386
Antistaphylococcal penicillins	2(1.17)	2(3.5)	0(0)	0.045*
1^{st}- or 2^{nd}-generation cephalosporins	12(7.02)	3(5.3)	9(8.0)	0.516
3^{rd}-generation cephalosporins	29(16.96)	10(17.5)	19(16.5)	0.905
4^{th}-generation cephalosporins	5(2.92)	4(7.0)	1(0.9)	0.025*
Carbapenems	22(12.86)	16(28.1)	6(5.3)	<0.001*
Fluoroquinolones	331(18.13)	18(31.6)	13(11.5)	0.001*
Glycopeptides	20(11.70)	15(26.4)	5(4.4)	<0.001*
Aminoglycosides	12(7.02)	4(7.0)	8(7.1)	0.988
Clindamycin	2(1.17)	1(1.8)	1(0.9)	0.62
Macrolides	4(2.34)	2(3.5)	2(1.8)	0.48
Metronidazole	28(16.37)	9(15.8)	19(16.8)	0.865
Linezolid	4(2.34)	3(5.3)	1(0.9)	0.075
28-day overall mortality	19(11.11)	8(14.8)	11(10.2)	0.388

Data are presented as mean ± SD or number of subjects (%)
HTN = hypertension; DM = diabetes mellitus; CNS = central nervous system; ICU = intensive care unit; *p value <0.05

Table 3. Multivariable analysis of risk factors for CRE acquisition

Factors	OR	95% Confidence Intervals	*p* value
Age	1.03	0.99 - 1.06	0.0828
Sex	0.92	0.43 - 1.96	0.8265
Length of stay	1.01	0.99 - 1.01	0.4015
Prior use of carbapenems	4.56	1.44 - 14.46	0.0099*
Prior use of fluoroquinolones	2.82	1.14 - 6.99	0.0253*

*p value < 0.05

Table 4. Antimicrobial sensitivity of *E.coli*

Antibiotic resistance	CRE Group N=57	Control Group N=114	*p* value
ampicillin/sulbactam	41(73.2)	38(33.8)	<0.001*
piperacillin/tazobactam	15(37.5)	2(2.7)	<0.001*
aztreonam	28(49.1)	15(13.2)	<0.001*
cefoxitin	25(43.9)	9(7.0)	<0.001*
cefotaxime	28(49.1)	24(21.1)	<0.001*
ceftazidime	24(42.1)	12(10.5)	<0.001*
cefepime	22(38.6)	9(7.9)	<0.001*
Fluoroquinolone	28(49.1)	45(39.5)	0.013 *
TMP/SMX	22(38.6)	50(43.9)	0.785
Amikacin	7(12.5)	3(2.6)	0.005*
ESBL producing	18(31.6)	28(24.6)	0.329

TMP/SMX = trimethoprime/sulfamethoxazole; ESBL = extended spectrum beta-lactamse; *p value <0.05

IV. DISCUSSION

Currently, carbapenems are the most potent agents for the treatment of serious infections with *Enterobacteriaceae* species because of their broad spectrum of antibacterial activity and their high stability to hydrolysis by most β-lactamases including extended-spectrum β-lactamases (ESBLs) and AmpC cephalosporinases.[16] However, increasing use of carbapenems has led to the emergence of carbapenem-resistant *Enterobacteriaceae* species including *E. coli*, and this is becoming an important therapeutic problem in clinical fields[17-19]. For appropriate early therapy, an understanding of patients at greatest risk for the acquisition of CRE among patients with suspected *Enterobacteriaceae* infections is critical when selecting an empirical antibiotic regimen. However, the risk factors for the acquisition of CRE have rarely been described in the English-language literature, although risk factors for carbapenem resistance to *P. aeruginosa*, *A. baumannii*, and *K. pneumoniae* have been well-documented[6,20,21].

There are only two earlier studies on risk factors of CRE infection. In the first, Jeon et al. investigated the risk factors of acquisition of CRE among hospitalized patients. A total of 46 patients with nosocomially-acquired CRE isolates were compared with 148 control patients matching the dates and wards of *E. coli* isolation[22]. Previous use of carbapenem and metronidazole, the presence of biliary drainage catheter, and prior hospital stay were associated with CRE acquisition[22]. This study used breakpoints recommended by the CLSI 2004[23], and resistance to carbapenem was

defined as an MIC to imipenem or meropenem exceeding 8 μg/mL. The second study, by Chang et al., included 17 patients with carbapenem-nonsusceptible *E. coli* (CNSE) bacteremia and 34 patients with carbapenem-susceptible *E. coli* bacteremia[24]. Prior exposure to carbapenems, uremia with regular dialysis, and chronic liver disease were independent risk factors for CNSE bacteremia, and patients with CNSE bacteremia had a higher overall in-hospital mortality rate[24]. This study followed the breakpoints recommended by the CLSI 2009[12], which were also used in our study.

Similar to the results of previous studies, our study revealed that prior use of carbapenems was an independent risk factor for the acquisition of CRE, but prior use of metronidazole, biliary procedures and drainage, uremia, and chronic liver disease were not. Unlike other studies, prior use of fluoroquinolones was also associated with the acquisition of CRE in our study. An association between prior fluoroquinolone use and carbapenem resistance was identified for *P. aerusinosa* in several studies[25,26]. Early *in vitro* studies suggested that combined resistance might occur through alterations in outer-membrane proteins that allow entry of the agents into the bacterial cell[27]. Although the main mechanism of fluoroquinolone resistance in *P. aerusinosa* is alteration of bacterial enzymes (DNA gyrase and topoisomerase IV), fluoroquinolone resistance may also occur by alteration or reduction in outer-membrane proteins or by overexpression of multidrug resistance–conferring efflux pumps that enhance excretion of fluoroquinolones and other agents from the cell[28]. Most clinical cases of carbapenem resistance are the result of either a loss

or decrease in the levels of the outer-membrane porin protein or are related to overexpression of the efflux system[8]. These mechanisms are also known to be altered in *E. coli*. In addition, the presence of fluoroquinolone-resistant proteins (Qnr) encoded by transmissible genes on plasmids is thought to play a major role in cross resistance to carbapenems[29]. In one study, plasmids associated with linked resistance to carbapenems (*bla*VIM-1) and quinolones (*qnr*S1) were found in clinical isolates of *E. coli*[29]. Therefore, changes in cell wall morphology after fluoroquinolone treatment and acquired fluoroquionolone resistance due to plasmid-encoded genes may be the mechanism of carbapenem resistance of *E. coli*.

In our results for antimicrobial sensitivity of *E. coli*, resistance to ampicillin/sulbactam, piperacillin/tazobactam, aztreonam, cephalosporin, fluoroquinolone, and aminoglycoside were more frequent in the CRE group. This can be explained by the mechanism of carbapenem resistance. Carbapenemases are members of the molecular class A, B, and D *β*-lactamases, which have the ability to hydrolyze not only carbapenems, but also penicillins, cephalosporins, and monobactams[30]. In addition, plasmid-associated linkage may cause fluoroquinolone and aminoglycoside resistance[29].

According to Yang et al., in *K. pneumoniae*, the MIC to imipenem was significantly higher in ESBL-producing pathogens than in ESBL non-producing pathogens when combined with porin loss[31]. However, ESBL production alone was not associated with carbapenem resistance in our study.

Unlike other studies, we also assessed the role of horizontal transmission. Although our study was retrospective in design, we investigated the wards in which CRE was isolated and found that the 33 patients with hospital-acquired CRE were not concentrated in the same ward but were distributed. Moreover, there was at least one year between identification of patients with CRE in the same ward (Figure 1).

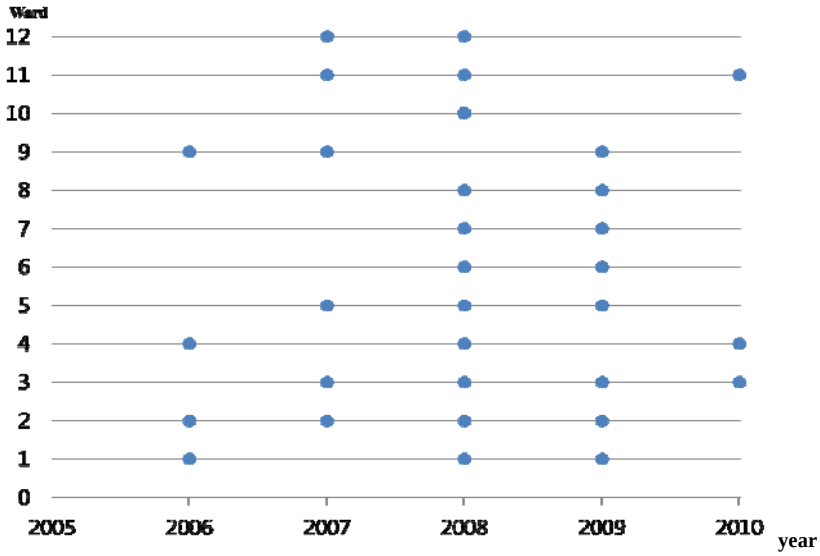
Markus et al. studied nosocomial transmission rates of ESBL-producing *E. coli* and *K. pneumoniae* and revealed that the incidence of transmission was 5.6 and 13.9 per 1000 exposure days, respectively. Thus, the incidence of ESBL-producing *K. pneumoniae* hospital transmission was significantly higher than that of ESBL-producing *E. coli* [32]. Although the Centers for Disease Control (CDC) announced guidelines for the control of carbapenem-resistant *Enterobacteriacea*[33], they emphasized their nosocomial transmission and suggested active surveillance and contact precaution. However, in our study, there were no outbreaks of CRE or nosocomial transmission. This may be associated with the lower transmission rate of *E. coli* compared with other *Enterobacteriacae* species.

One limitation of our study is the lack of molecular epidemiologic analysis, such as analysis of CRE clonality to identify the role of horizontal transmission. Other limitations of this study are its retrospective nature and the small sample size.

V. CONCLUSION

In summary, our results suggest that the acquisition of CRE may be favored by the selection pressure of carbapenems and fluoroquinolones. Furthermore, in this institute, antibiotic selective pressure seems to be a more important factor for CRE acquisition than nosocomial transmission.

Figure 1. Distribution of patients with hospital acquired CRE



Each point indicates the case of patient with CRE. Total of 33 patients with hospital acquired CRE were not concentrated in the same ward. There was at least one year in the time interval between the patients with CRE in the same ward

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ABSTRACT(IN KOREAN)

한국의 3차 병원에서 시행한 carbapenem 내성 대장균 획득의 위험인자에 대한 환자 대조군 연구

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안진영

배경 : 그람 음성 균주의 carbapenem 내성이 증가하면서 전세계적인 위협요인이 되고 있다. 본 연구의 목적은 carbapenem 내성 대장균 획득에 대한 위험인자를 확인하고자 한다.

방법 : 2006년 1월부터 2010년 12월까지 한국의 2000병상의 3차병원에 내원한 환자 중 carbapenem 내성 대장균이 검출된 환자군 57명과, 대장균의 검출 시기 및 검출된 검체가 동일한 carbapenem 감수성 대장균이 검출된 114명의 대조군을 선정하였다. 두 집단간의 기본 특성 및 기저 질환, 시술 및 수술의 시행여부, 항생제 사용력, 대장균의 항생제 감수성

결과를 비교하여 위험인자를 분석하였다.

결과 : 단변량 분석에서 carbapenem 사용력 (p<0.001), fluoroquinolone의 사용력 (p=0.001), glycopeptide의 사용력 (p<0.001), 대장균 검출 전 사용한 총 항생제의 수(p=0.004), 재원기간(p=0.047)이 carbepenem 내성 대장균 획득의 위험인자로 생각되었다. 반면, 대장균이 검출된 시기, 검출된 병동은 두 집단간에 유의미한 차이를 보이지 않았다. 다변량 분석에서 carbapenem 사용력과 [odd ratio(OR) 4.56, 95% confidence intervals(CI) 1.44-14.457, p=0.09], fluoroquinolone의 사용력 [OR 2.81, 95% CI 1.137-6.991, p=0.0253]이 carbapenem 내성 대장균이 검출된 집단에서 통계적으로 유의미하게 많은 것을 확인하였다.

결론 : carbapenem 내성 대장균의 획득에는 원내 전파보다는 항생제 사용에 의한 항생제 압력이 더욱 중요한 요소로 작용한다.

핵심되는 말 : carbapenem 내성 대장균, 위험인자