American Journal of Infection Control 42 (2014) 621-5

Contents lists available at ScienceDirect

American Journal of Infection Control

journal homepage: www.ajicjournal.org

Major article

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

Jin Young Ahn MD [a], Je Eun Song MD [a], Min Hyung Kim MD [a], Heun Choi MD [a], Jae Kyung Kim MD [a], Hea Won Ann MD [a], Jung Ho Kim MD [a], Yongduk Jeon MD [a], Su Jin Jeong MD, PhD [a], Sun Bean Kim MD [a], Nam Su Ku MD [a,b], Sang Hoon Han MD, PhD [a,b], Young Goo Song MD, PhD [a,b], Dongeun Yong MD, PhD [c], Kyungwon Lee MD, PhD [c], June Myung Kim MD, PhD [a,b], Jun Yong Choi MD, PhD [a,b,*]

[a] *Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea*
[b] *AIDS Research Institute, Yonsei University College of Medicine, Seoul, Korea*
[c] *Department of Laboratory Medicine and Research Institute of Bacterial Resistance, Yonsei University College of Medicine, Seoul, Korea*

Key Words:
Carbapenem resistance
Antibiotic selective pressure

Background: Carbapenem resistance among gram-negative bacilli is 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 comprising 57 cases of acquisition of CRE and 114 controls (1:2 matched) selected from patients with a culture of carbapenem-susceptible *E coli* between January 2006 and December 2010 at a 2000-bed tertiary care center in South Korea.

Results: On univariate analysis, previous use of carbapenem ($P < .01$), fluoroquinolone ($P < .01$), and glycopeptide ($P < .01$), as well as length of hospital stay ($P < .05$), were significantly associated with CRE acquisition. On multivariate analysis, previous use of carbapenem (odds ratio [OR], 4.56; 95% confidence interval [CI] 1.44-14.46; $P = .01$) and previous use of fluoroquinolone (OR, 2.81; 95% CI, 1.14-6.99; $P = .03$) were independent risk factors.

Conclusions: At this institute, the antibiotic selective pressure of carbapenems and fluoroquinolones was shown to be an important risk factor for the acquisition of CRE.

Enterobacteriaceae, the most common pathogen to humans, causes various diseases ranging from simple cystitis to severe infections, such as bacteremia, peritonitis, and meningitis. Carbapenems have served as an important antimicrobial agent against these organisms. Until recently, resistance to carbapenems was uncommon; however, increased use of carbapenems over the past few decades has led to the emergence of carbapenem-resistant Enterobacteriaceae.[1,2]

In the United States, the rate of resistance of *Klebsiella pneumoniae* to carbapenems was reported as only 0.3% as late as 2006, but had increased to 10% by 2008.[3] The clinical outcomes of and risk factors for carbapenem-resistant *K pneumoniae* infections have been well studied.[4-6] 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 presents a much greater challenge to physicians.

The mechanism of carbapenem resistance in *E coli* mainly involves an outer membrane porin deficiency combined with AmpC β-lactamase[8,9] and acquired class A carbapenemases, including *K pneumoniae* carbapenemase[10] and metallo-β-lactamases (eg, imipenem-hydrolyzing β-lactamase [IMI], Verona integron-encoded β-lactamase [VIM], New Delhi metallo-β-lactamase [NDM]).[11] Recently, oxacillinase (OXA)-48–like carbapenemases and outer membrane protein loss have been reported as well.[1]

* Address correspondence to Jun Yong Choi, MD, PhD, Department of Internal Medicine and AIDS Research Institute, Yonsei University College of Medicine, 50 Yonsei-ro, Seodaemun-gu, Seoul 120-752, Korea.
E-mail address: seran@yuhs.ac (J.Y. Choi).

This work was supported by BioNano Health-Guard Research Center funded by the Ministry of Science, ICT, and Future Planning of Korea as a Global Frontier Project (Grant H-GUARD_2013M3A6B2078953).
Conflict of interest: None to report.

0196-6553/$36.00 - Copyright © 2014 by the Association for Professionals in Infection Control and Epidemiology, Inc. Published by Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.ajic.2014.02.024

The risk factors for CRE acquisition have not been well described to date. Nevertheless, CRE poses an enormous threat to hospital infection control.[12] Accordingly, we conducted a matched case-control study to identify potential risk factors for the acquisition of CRE.

MATERIALS AND METHODS

Study design and patients

This case-control study was conducted at Severance Hospital in Seoul, Korea, a 2000-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 studied, and their medical charts were reviewed. For patients with multiple episodes of infection with *E coli*, only data relevant to the first episode were collected and analyzed.

For each patient with CRE acquisition, we selected 2 matched control patients from the pool of patients with carbapenem-susceptible *E coli* acquisition. Because clinical manifestations and treatment are affected by the acquisition site and the time of *E coli* isolation, the 2 groups were matched for the site of and date of *E coli* acquisition.

Microbiological tests

Antimicrobial susceptibility was determined using the disk-diffusion method or a VITEK-2 N131 card (bioMerieux, Hazelwood, MO). The results were interpreted according to the Clinical Laboratory Standards Institute 2011 guidelines.[13] Resistance to carbapenem was defined as an minimum inhibitory concentration (MIC) to imipenem or meropenem of $\geq$4 μg/mL or a disk diffusion of $\leq$19 mm. At this institution, susceptibility to ertapenem had not been tested as of 2012.

Collected data and definitions

We collected data on age, sex, underlying disease, cultured specimens, date of culture, admission ward at the time of culture, duration of hospital stay before isolation of *E coli*, procedures undergone, previous antimicrobial therapy, and antimicrobial susceptibility of *E coli*. The presence of the following comorbid conditions was documented: neutropenia, receipt of intensive care unit (ICU) care, use of an immunosuppressive agent within 30 days before *E coli* isolation, and postoperative condition. In addition, we assessed for the presence of a central venous catheter, indwelling urinary catheter, or mechanical ventilation.

Epidemiologic types of *E coli* were classified as community-acquired (CA), hospital-acquired (HA), or health care–associated (HCA). HA was defined as acquisition of *E coli* occurring after 48 hours from admission or by discharge from an acute care hospital within the previous 10 days. HCA was defined as a history of hospitalization for 2 or more days within the previous 90 days, receipt of intravenous medication or home wound care in the previous in 30 days, receipt of hemodialysis, or residence in a nursing home or long-term care facility.[14,15] CA was defined as acquisition of *E coli* for the first time within 48 hours after admission and the absence of risk factors for HCA acquisition of *E coli*.[14,15]

Neutropenia was defined as an absolute neutrophil count <500/μL. Corticosteroid use was recorded only if the patient had recently received the equivalent of prednisone 30 mg/day for at least 7 days or 20 mg/day for 14 days. Receipt of immunosuppressant therapy was defined as use of any immunosuppressive drug (eg, cyclosporine, antineoplastic chemotherapy) in the previous 30 days. Previous exposure to various antibiotic agents was included as well. Exposure to a specific antimicrobial agent was considered significant in our analysis only if the antibiotics had been administered for at least 3 consecutive days within 1 month before *E coli* acquisition. The exposure to various risk factors was taken into consideration in the analysis only if it occurred before *E coli* acquisition.

Table 1
Clinical characteristics and risk factor analysis for CRE acquisition

Factors	CRE group (n = 57)	Control group (n = 114)	*P* value
Demographic factors			
Male sex, n (%)	27 (47.4)	51 (44.7)	.75
Age, y, mean ± SD	65.26 ± 14.30	62.78 ± 13.71	.27
Body mass index, kg/m^2, mean ± SD	21.557 ± 3.508	22.351 ± 4.070	.22
Length of stay, d, mean ± SD	26.63 ± 37.888	13.11 ± 41.303	< .05*
Type of acquisition, n (%)			.11
Community-acquired	9 (15.8)	32 (28.1)	
Hospital-acquired	35 (61.4)	52 (45.6)	
Health-care associated	13 (22.8)	30 (26.3)	
Site of culture, n (%)			
Urine	20 (35.1)	40 (35.1)	
Blood	14 (24.6)	28 (24.6)	
Gastrointestinal origin	10 (17.5)	20 (17.5)	
Skin and soft tissue	7 (13.2)	14 (13.2)	
Surgical site infection	2 (3.5)	4 (3.5)	
Sputum	2 (3.5)	4 (3.5)	
Ear, eye, throat	2 (3.5)	4 (3.5)	
Previous antibiotic use, n (%)			
Fourth-generation cephalosporin	4 (7.0)	1 (0.9)	.03*
Carbapenem	16 (28.1)	6 (5.3)	< .01*
Fluoroquinolone	18 (31.6)	13 (11.5)	< .01*
Glycopeptide	15 (26.4)	5 (4.4)	< .01*
28-day mortality	8 (14.8)	11 (10.2)	.39

*$P < .05$.

Statistical analysis

Continuous variables are presented as mean ± SD, and categorical variables are presented as numbers and percentages. Continuous variables were tested using the Student *t* test or Wilcoxon rank-sum test, depending on the validity of the normality assumption. The χ^2 test or Fisher's exact test was used to test the categorical variables. Multivariate analysis was performed using logistic regression to identify factors that independently and significantly affected outcomes. Variables with $P < .05$ on univariate analysis were considered for inclusion in a multivariate model. A *P* value < .05 was considered significant. All statistical analyses were performed using SPSS software (version 19.0; SPSS Inc., Chicago, IL).

RESULTS

Number of patients with CRE during the study period

Between January 2006 to December 2010, a total of 171 patients were enrolled in this study, including 57 cases with CRE and 114 controls with carbapenem-susceptible *E coli*. The 2 groups were matched for the site and the date of *E coli* isolation. During the 5-year study period, CRE was isolated from 57 patients, including 6 in 2006, 9 in 2007, 18 in 2008, 17 in 2009, and 7 in 2010.

Demographic and clinical characteristics of subjects

The demographics and characteristics of the 2 groups are shown in Table 1. The mean patient age was 62.56 years in the CRE group