Carbapenem-resistant Enterobacteriaceae: Prevalence and Risk Factors in a Single Community-Based Hospital in Korea

Hyo-Jin Lee¹,², Jae-Ki Choi¹,², Sung-Yeon Cho¹,², Si-Hyun Kim¹,², Sun Hee Park¹,², Su-Mi Choi¹,², Dong-Gun Lee¹,², Jung-Hyun Choi¹,², and Jin-Hong Yoo¹,²

¹Division of Infectious Diseases, Department of Internal Medicine, College of Medicine, The Catholic University of Korea; ²Vaccine Bio Research Institute, College of Medicine, The Catholic University of Korea, Seoul, Korea

Background: Carbapenemase-producing Enterobacteriaceae (CPE) are Gram-negative bacteria with increasing prevalence of infection worldwide. In Korea, 25 cases of CPE isolates were reported by the Korea Centers for Disease Control and Prevention in 2011. Most CPE cases were detected mainly at tertiary referral hospitals. We analyzed the prevalence and risk factors for carbapenem-resistant Enterobacteriaceae (CRE) in a mid-sized community-based hospital in Korea.

Materials and Methods: We retrospectively analyzed all consecutive episodes of Enterobacteriaceae in a mid-sized community-based hospital from January 2013 to February 2014. CRE was defined as organisms of Enterobacteriaceae showing decreased susceptibility to carbapenems. Risk factors for CRE were evaluated by a case–double control design. Carbapenemase was confirmed for CRE using a combined disc test.

Results: During 229,710 patient-days, 2,510 Enterobacteriaceae isolates were obtained. A total of 41 (1.6%) CRE isolates were enrolled in the study period. Thirteen species (31.7%) were Enterobacter aerogenes, 8 (19.5%) Klebsiella pneumoniae, 5 (12.2%) Enterobacter cloacae, and 15 other species of Enterobacteriaceae, respectively. Among the 41 isolates, only one (2.4%) E. aerogenes isolate belonged to CPE. For evaluation of risk factors, a total of 111 patients were enrolled and this included 37 patients in the CRE group, 37 in control group I (identical species), and 37 in control group II (different species). Based on multivariate analysis, regularly visiting the outpatient clinic was a risk factor for CRE acquisition in the control group I (P = 0.003), while vascular catheter and Charlson comorbidity index score ≥3 were risk factors in control group II (P = 0.010 and 0.011, each). Patients with CRE were more likely to experience a reduced level of consciousness, use a vasopressor, be under intensive care, and suffer from acute kidney injury. However, CRE was not an independent predictor of mortality compared with both control groups.

Conclusion: In conclusion, the prevalence of CRE was higher than expected in a mid-sized community-based hospital in Korea. CRE should be considered when patients have a vascular catheter, high comorbidity score, and regular visits to the outpatient clinic. This study suggests the need for appropriate prevention efforts and constant attention to CRE infection control in a mid-sized community-based hospital.

Key Words: Carbapenems; Enterobacteriaceae; Risk factors; Prevalence; Drug resistance
Introduction

Enterobacteriaceae family includes Escherichia coli, Klebsiella pneumoniae, Citrobacter freundii, Morganella morganii, Proteus mirabilis, Enterobacter species, and Serratia species, to name a few. They are responsible for various infectious diseases such as intra-abdominal infection, urinary tract infection, bloodstream infection and respiratory tract infection [1]. Carbapenem is the main treatment for severe infections caused by Enterobacteriaceae, because they have various resistance mechanisms to overcome extended spectrum beta-lactam [2]. Recently, carbapenem-resistant Enterobacteriaceae (CRE) has become one of the leading infectious concerns worldwide, resulting in high mortality in infected patients [3-6].

In the United States, the first outbreak of CRE was reported in New York in 2003. Since this report, the presence of CRE has increased in healthcare facilities [7]. In Asia, the first case of K. pneumoniae carbapenemase was reported in China in 2004, and more cases have been increasingly detected in Taiwan, Korea, and Singapore [3, 4]. In Korea, most of the reported multi-drug resistant (MDR) microorganisms were found at tertiary referral hospitals, and CRE was also detected predominantly at tertiary hospitals [8-10]. However, the prevalence and risk factors of CRE acquisition have not been well described in small or mid-sized community-based hospital settings. Therefore, we performed an analysis of epidemiologic characteristics and risk factors for CRE in a mid-sized community-based hospital in Korea.

Materials and Methods

1. Study design and subjects

We retrospectively reviewed the medical records of all consecutive episodes of Enterobacteriaceae from hospitalized patients at Bucheon St. Mary’s Hospital, a 607-bed, university-affiliated, community-based general hospital from January 2013 to February 2014. During the study period, surveillance cultures were not performed. The microbial data were obtained from the clinical microbiology laboratory for the purpose of analyzing the prevalence of CRE and comparing antimicrobial resistance profiles with carbapenem-susceptible Enterobacteriaceae (CSE).

The risk factors for patients with CRE were evaluated by using a case-double control design. The case group included all adult patients (age ≥16 years) who were found to have any CRE organism (hereinafter referred to as the CRE group). Only first positive culture data from patients who had multiple cultures for Enterobacteriaceae organisms were included. The case group was randomly matched to two control groups by sites of culture, time needed to collect a microbiological specimen from admission day (± 6 days), and length of stay (>2 days).
**Table 1. Antibiotic resistance of carbapenem-resistant Enterobacteriaceae**

| Antibiotic resistance | CRE (n = 41) n (%) | CSE (n = 2,469) n (%) | OR (95% CI) | P       |
|-----------------------|---------------------|------------------------|-------------|---------|
| Amikacin              | 9 (22.0)            | 105 (4.3)              | 6.31 (2.94–13.56) | <0.001  |
| Ceftazidime           | 22 (53.7)           | 901 (36.5)             | 2.01 (1.08–3.73)  | 0.024   |
| Cefepime              | 17 (41.5)           | 795 (32.2)             | 1.55 (0.82–2.91)  | 0.173   |
| Aztreonam             | 19 (46.3)           | 889 (36.0)             | 1.60 (0.85–2.98)  | 0.140   |
| Ciprofloxacin         | 19 (46.3)           | 934 (36.0)             | 1.56 (0.71–2.98)  | 0.267   |
| Tigecycline           | 8 (19.5)            | 331 (13.4)             | 1.56 (0.71–2.98)  | 0.267   |
| TMP-SMX               | 13 (31.7)           | 709 (28.7)             | 1.15 (0.59–2.23)  | 0.678   |

CRE, carbapenem-resistant Enterobacteriaceae; CSE, carbapenem-susceptible Enterobacteriaceae; OR, odds ratio; TMP-SMX, trimethoprim-sulfamethoxazole.

**Table 2. Patient characteristics according to carbapenem susceptibility of Enterobacteriaceae**

| Variables                                      | CRE (n = 37) | CSE I (n = 37) | P       | CSE II (n = 37) | P       |
|------------------------------------------------|--------------|----------------|---------|-----------------|---------|
| Age, median (range)                            | 68 (31-90)   | 66 (42-88)     | 0.806   | 65 (16-91)      | 0.344   |
| Male                                           | 21 (56.8)    | 21 (56.8)      | 1       | 16 (43.2)       | 0.245   |
| Length of stay, median (IQR)                   | 24 (12-46)   | 16 (6-35)      | 0.245   | 14 (8-32)       | 0.266   |
| Colonization with VRE                          | 4 (10.8)     | 0 (0)          | 0.115   | 1 (1.4)         | 0.358   |
| Non fermenter                                  | 13 (35.1)    | 11 (29.7)      | 0.619   | 7 (18.9)        | 0.116   |
| MDR speciesa                                    | 8 (21.6)     | 2 (5.4)        | 0.041   | 1 (1.4)         | 0.028   |
| Colonization of Enterobacteriaceae only        | 21 (56.8)    | 21 (56.8)      | 1       | 14 (37.8)       | 0.103   |
| Comorbidities                                  |              |                |         |                 |         |
| Diabetes                                       | 18 (48.6)    | 11 (29.7)      | 0.056   | 10 (27.0)       | 0.055   |
| Heart failure                                  | 3 (8.1)      | 4 (10.8)       | 1       | 1 (1.4)         | 0.304   |
| Renal failure                                  | 0 (0)        | 1 (2.7)        | 1       | 4 (10.8)        | 0.327   |
| Malignancy                                     | 8 (21.6)     | 9 (24.3)       | 0.782   | 5 (13.5)        | 0.359   |
| CVA                                            | 13 (35.1)    | 12 (32.4)      | 0.806   | 11 (29.7)       | 0.619   |
| Decubitus ulcer                                | 8 (21.6)     | 5 (13.5)       | 0.359   | 5 (13.5)        | 0.359   |
| CCI ≥3                                         | 32 (86.5)    | 29 (78.4)      | 0.359   | 23 (62.2)       | 0.017   |
| Healthcare risk factors                        |              |                |         |                 |         |
| LTCF permanent residence                       | 8 (21.6)     | 10 (27)        | 0.588   | 6 (16.2)        | 0.553   |
| Hospitalized for > 2 d before culture          | 21 (56.8)    | 14 (37.8)      | 0.103   | 17 (45.9)       | 0.352   |
| Regular visits to the OPDb                      | 25 (67.6)    | 13 (35.1)      | 0.005   | 17 (45.9)       | 0.060   |
| Hospitalized in past 3 mo                      | 14 (37.8)    | 8 (21.6)       | 0.127   | 9 (24.3)        | 0.209   |
| Recent events                                   |              |                |         |                 |         |
| Mechanical ventilation                         | 14 (37.8)    | 11 (29.7)      | 0.461   | 8 (21.6)        | 0.127   |
| Vascular catheter                              | 23 (62.2)    | 13 (35.1)      | 0.020   | 9 (24.3)        | 0.001   |
| Urinary catheter                               | 27 (73.0)    | 24 (64.9)      | 0.615   | 19 (51.4)       | 0.093   |
| Use of antibiotics in preceding 3 mo           | 13 (35.1)    | 12 (32.4)      | 0.806   | 12 (32.4)       | 0.806   |

CRE, carbapenem-resistant Enterobacteriaceae; CSE, carbapenem-susceptible Enterobacteriaceae; OR, odds ratio; TMP-SMX, trimethoprim-sulfamethoxazole.

aMDR species includes multi-drug resistant *Pseudomonas aeruginosa* and carbapenem-resistant *Acinetobacter baumannii*.

bRegular visits to the outpatient department are defined as visiting to outpatient department once a month on average.

CRE, carbapenem-resistant Enterobacteriaceae; CSE, carbapenem-susceptible Enterobacteriaceae; IQR, inter-quartile range; VRE, vancomycin-resistant *Enterococci*; MDR, multi-drug resistant; CVA, cerebrovascular accident; CCI, Charlson comorbidity index; LTCF, long-term care facility; OPD, out-patient department.
Control group I (hereinafter referred to as the CSE group I) was matched to the identical species of the CRE group. Control group II (hereinafter referred to as the CSE group II) was matched to the different species among Enterobacteriaceae compared with the CRE group. The clinical characteristics, risk factors for acquisition of CRE, and clinical outcomes of the case group were evaluated by comparing with those of the control groups. The following variables were reviewed from the medical records: age, sex, hospital length of stay, colonization of microorganisms, co-morbidities, Charlson comorbidity index [12], use of health care facilities, use of invasive devices, antibiotics treatment, morbidity, and mortality. This study was approved by the Institutional Review Board of Bucheon St. Mary's Hospital with a waiver of informed consent (No. HC16RISI0038).

2. Microbiology

The microbial organism identification and antimicrobial susceptibility profiles were determined using the Vitek 2 system (bioMérieux, Hazelwood, MO, USA) in accordance with the manufacturer’s instruction. Minimum inhibitory concentrations (MIC) for imipenem, meropenem, and ertapenem were determined by CLSI M100-S22 guidelines [13]. Morganella, Providencia, and Proteus species were tested against ertapenem and meropenem rather than imipenem because of their intrinsic resistance to imipenem [14]. CRE was defined as organisms of Enterobacteriaceae showing decreased susceptibility to carbapenems (MIC for imipenem ≥2 µg/mL, meropenem ≥2 µg/mL, or ertapenem ≥1 µg/mL) and resistance to all third-generation cephalosporins regardless of carbapenemase production [15, 16]. For organisms showing reducing susceptibility to carbapenem, a modified Hodge test was performed [17]. For CRE organisms, a carbapenemase confirmation test was conducted using a combined disc test (Rosco Diagnostica, Taastrup, Denmark) [17].

3. Statistical analysis

To evaluate statistical significance, categorical variables were analyzed using the $\chi^2$ or Fisher’s exact test and continuous variables were analyzed using the Student’s t-test or the Mann–Whitney U-test. Statistical studies were performed with the Statistical Package for the Social Sciences version 13.0 (SPSS, Inc., Chicago, IL, USA). For multivariate analysis, logistic regression analysis was used. Variables with a P-value...
of <0.20, on univariate analysis, were entered into the model selection procedure using a stepwise backward process. Variables were two-sided, and P-values <0.05 were considered statistically significant.

Results

1. Microbiologic data

During 229,710 patient-days, 41 (1.6%) isolates of CRE organisms were obtained from among 2,510 Enterobacteriaceae isolates. CRE was cultured from sputum (41.5%), urine (29.3%), surgical wound (17.1%), soft tissue (7.3%), and blood (4.9%). The distribution of CRE species is shown in Figure 1. Only one case of Enterobacter aerogenes showed metallo-β-lactamase based on the combined disc test. Antimicrobial resistance of Enterobacteriaceae is shown in Table 1. In the most cases, the antimicrobial resistance proportions were higher in the CRE group than those of the CSE group. Amikacin and ceftazidime were statistically different between the CRE and CSE groups (P < 0.001 and P = 0.024, respectively).

2. Demographic data and risk factors for acquisition of CRE

During the study period, a total of 111 patients were enrolled including 37 patients in the CRE group, 37 in the CSE group I (identical species) and 37 in the CSE group II (different species). Four of 37 CSE patients had two species of CRE organisms. CSE group II isolates were comprised of 12 of E. coli, 12 of K. pneumoniae, 5 of Enterobacter cloacae, 3 of Serratia marcescens, 2 of Klebsiella oxytoca, and one each of Citrobacter koseri, E. aerogenes, and M. morganii. The median age of patients in the study cohort was 65.6 years (range, 16–91 years). There were 58 men (52.3%) in the study. The demographic and clinical characteristics of CRE and CSE patients are summarized in Table 2. Based on univariate analysis, the risk factors for acquisition of CRE were MDR Pseudomonas aeruginosa and carbapenem-resistant Acinetobacter baumannii colonization, regular visits to the out-patient clinic, and vascular catheter in CSE group I. The risk factors were MDR P. aeruginosa and carbapenem-resistant A. baumannii colonization, Charlson comorbidity index score ≥3, and vascular catheter in CSE group II. The results of multivariate analysis in each control group are shown in Table 3. In CSE group I, regular visits to the outpatient clinic was an independent risk factor for patients with CRE (P = 0.003). MDR species and vascular catheters, however, demonstrated tendencies associated with CRE acquisition (P = 0.056 and P = 0.057, respectively). In the CSE group II, vascular catheter and Charlson comorbidity index score ≥3 were risk factors for CRE (P = 0.010 and P = 0.011, respectively).

3. Clinical outcomes associated with CRE

The clinical outcomes of the CRE patients are summarized in Table 4. Those in the CRE group showed more severe disease progression than those of the CSE groups. Only 56.3% patients received susceptible antibiotics for CRE when infection was suspected. The patients with CRE were more likely to experience a reduced level of consciousness, use a vasopressor, be under intensive care, and suffer from acute kidney injury. However, CRE was not an independent predictor of mortality compared with CSE controls. There was no difference in additional hospitalizations in 6 months between case and control groups.

Discussion

This case-control study showed the high prevalence of CRE isolates in a mid-sized community-based hospital in Korea. To our knowledge, this is the first study on the prevalence and risk factors of CRE acquisition in the mid-sized community-based hospital in Korea.

The incidence and prevalence of CRE is influenced by geographical characteristics. Mexico and Uganda reported about 10% CRE prevalence [18, 19]. Asia had a lower rate of CRE (0.6%) [4]. The incidence of CRE in surveillance programs of the general population of the U.S.A. was 2.93 per 100,000 [20]. Previous studies of CRE in Korea showed diverse prevalence. A prospective bacteremia surveillance study of 13 hospitals in Korea showed 3.2% of imipenem-resistant Enterobacter spp., 0.8% of K. pneumoniae and 0.1% of E. coli [21]. From 2005–2008, CRE prevalence was 0.17% at a newly opened intensive care unit (ICU) of a tertiary university-affiliated hospital [22]. In 2012, CRE prevalence of rectal culture surveillance was reported as 0.3% in the ICU of a tertiary university-affiliated referral hospital [13]. However, Kim et al. reported a 7.5% CRE prevalence of stool culture in the ICU of a tertiary university-affiliated referral hospital in 2013 [23]. In our study, the prevalence of CRE in hospitalized patients was higher than expected (1.6%). Our study was conducted at a mid-sized community-based hospital, including not only ICU but also general ward patients. It seems that high transfer rate of long-term care facility patients and greater use of carbapenem in the community-based hospitals may influence the higher
prevalence of CRE. Carbapenemase-producing Enterobacteriaceae was only one case by combined disc test in our cohort.

There are a few treatment options for CRE. One of them is tigecycline, which has activity against CRE class A, B, or D enzymes [24]. In Europe, tigecycline showed 88.6% susceptibility against CRE [25]. CRE from the UK had 46.9% susceptibility to tigecycline [26]. In Korea, 3 cases (13.6%) among 22 CRE isolates showed resistance to tigecycline [27]. In our study, 19.5% of CRE isolates were found to be resistant to tigecycline. However, there was no statistical difference between isolates in the CRE and CSE groups.

Several risk factors for the acquisition of CRE have been reported, including previous antibiotics use, vascular device, tracheostomy, admission to ICU, abdominal invasive procedure, chemotherapy/radiation therapy, biliary drainage catheter, and prior hospital stay [3, 28-32]. Exposure to healthcare facilities is one of the most remarkable risks, especially for long-term care facilities, which are known reservoirs for CRE transmission [33]. Long-term care facility residence was not related to CRE acquisition; however, regular visits to the outpatient clinic was a risk factor for CRE acquisition in CSE group I in our study. Insertion of medical instruments is also a known risk factor for CRE infections [34]. Severely ill patients, such as those undergoing mechanical ventilation, intensive treatment, and transplantation, or those with a lengthy prior hospital stay and course of antibiotics use are at risk for acquiring CRE infection, as reported by a matched case-control study [6]. In our study, vascular catheter and Charlson comorbidity index score ≥3 were the risk factors in CSE group II, as determined by multivariate analysis.

CRE has been reported to affect functional status mortality [5, 6, 15]. In this study, CRE led to impaired consciousness, transferal to ICU, and risk of acute kidney injury in CSE groups I and II. Patients in the CRE group also showed more frequent use of vasopressor than CSE group II. However, CRE was not related to mortality in either control group. In the present study, only four patients died in the hospital. The small number of patients may not be sufficient for detecting significant differences in evaluating the effect of CRE on mortality. Not all the CRE isolates acted as a pathogen, which may also have influenced mortality.

The present study has some limitations. First, it was a retrospective study. As such, specific information about the type of antibiotics used was missing from the medical records. Second, it included a small number of patients with CRE in a single hospital. Therefore, this result cannot be generalized for the incidence and prevalence of small or mid-sized hospitals in Korea. Third, this study was a case-control design in which the level of risk factors was not equal to the expected level in the population. To minimize bias, we selected two control groups. Fourth, CRE organisms were only examined by a combined disc test for confirmation of carbapenemase. Metallo-β-lactamase and K. pneumoniae carbapenemase were evaluated; however, other carbapenemases could not be investigated. Genotypic confirmation is needed for specification of carbapenemase type.

In conclusion, the incidence of CRE was higher than expected in a mid-sized community-based hospital in Korea. CRE should be considered when a patient has a vascular catheter, high comorbidity score, and regular visits to the outpatient clinic. This study suggests the need for appropriate prevention efforts and constant attention to CRE infection control. A nation-wide investigation pertaining to CRE is needed in community-based healthcare institutes.

Conflicts of Interest
No conflicts of interest.

ORCID
Jin-Hong Yoo http://orcid.org/0000-0003-2611-3399
Hyo-Jin Lee http://orcid.org/0000-0001-9351-0779
Sung-Yeon Cho http://orcid.org/0000-0001-5392-3405
Su-Mi Choi http://orcid.org/0000-0002-8187-5110
Dong-Gun Lee http://orcid.org/0000-0003-4655-0641

References
1. Wang JT, Wu UI, Lauderdale TL, Chen MC, Li SY, Hsu LY, Chang SC. Carbapenem-nonsusceptible Enterobacteriaceae in Taiwan. PLoS One 2015;10:e0121668.
2. Kaniga K, Flamm R, Tong SY, Lee M, Friedland I, Redman R. Worldwide experience with the use of doripenem against extended-spectrum-β-lactamase-producing and ciprofloxacin-resistant Enterobacteriaceae: analysis of six phase 3 clinical studies. Antimicrob Agents Chemother 2010;54:2119-24.
3. Ling ML, Tee YM, Tan SG, Amin IM, How KB, Tan KY, Lee LC. Risk factors for acquisition of carbapenem resistant Enterobacteriaceae in an acute tertiary care hospital in Singapore. Antimicrob Resist Infect Control 2015;4:26.
4. Xu Y, Gu B, Huang M, Liu H, Xu T, Xia W, Wang T. Epidemiology of carbapenem resistant Enterobacteriaceae (CRE)
during 2000-2012 in Asia. J Thorac Dis 2015;7:376-85.
5. Schwaber MJ, Klafeld-Lidi S, Navon-Venezia S, Schwartz D, Leavitt A, Carmeli Y. Predictors of carbapenem-resist-
tant *Klebsiella pneumoniae* acquisition among hospital-
ized adults and effect of acquisition on mortality. Antimi-
crob Agents Chemother 2008;52:1028-33.
6. Patel G, Huprikar S, Factor SH, Jenkins SG, Calfee DP. Out-
comes of carbapenem-resistant *Klebsiella pneumoniae* in-
fection and the impact of antimicrobial and adjunctive thera-
pies. Infect Control Hosp Epidemiol 2008;29:1099-106.
7. Patel N, Harrington S, Dhimess A, Woo B, Masoud R, Mar-
tis P, Fiorenza M, Graffunder E, Evans A, McNutt LA, Lo-
dise TP. Clinical epidemiology of carbapenem-intermedi-
ate or -resistant Enterobacteriaceae. J Antimicrob Che-
mother 2011;66:1600-8.
8. Lee K, Lee HS, Jang SJ, Park AJ, Lee MH, Song WK, Chong Y; Members of Korean Nationwide Surveillance of Anti-
microbial Resistance Group. Antimicrobial resistance surveil-
ance of bacteria in 1999 in Korea with a special reference to resistance of enterococci to vancomycin and gram-
negative bacilli to third generation cephalosporin, imipenem, and 
fluoroquinolone. J Korean Med Sci 2001;16:262-70.
9. Kwak YG, Choi SH, Choo EJ, Chung JW, Jeong JY, Kim NJ, 
Woo JH, Ryu J, Kim YS. Risk factors for the acquisition of 
carbapenem-resistant *Klebsiella pneumoniae* among hos-
italized patients. Microb Drug Resist 2005;11:165-9.
10. Lee H, Ko KS, Song JH, Peck KR. Antimicrobial activity of 
doripenem and other carbapenems against gram-negative 
pathogens from Korea. Microb Drug Resist 2011;17:37-45.
11. Gómez Rueda V, Zuleta Tobón JJ. Risk factors for infection with 
carbapenem-resistant *Klebsiella pneumoniae*: a case-
case-control study. Colomb Med (Cali) 2014;45:54-60.
12. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new 
method of classifying prognostic comorbidity in longitudi-
dinal studies: development and validation. J Chronic Dis 
1987;40:373-83.
13. Kim J, Lee JY, Kim SI, Song W, Kim JS, Jung S, Yu JK, Park 
KG, Park YJ. Rates of fecal transmission of extended-spect-
rum β-lactamase-producing and carbapenem-resistant 
*Enterobacteriaceae* among patients in intensive care units 
in Korea. Ann Lab Med 2014;34:20-5.
14. Clinical and Laboratory Standards Institute (CLSI). Perfor-
many standards for antimicrobial susceptibility testing: 
Twenty-second informational supplement M100-S22. 
CLSI; Wayne, PA; 2012.
15. Chang YY, Chuang YC, SiuLK, Wu TL, LinJC, LuPL, Wang 
JT, Wang LS, Lin YT, Huang LJ, Fung CP. Clinical features 
of patients with carbapenem nonsusceptible *Klebsiella 
pneumoniae* and *Escherichia coli* in intensive care units: a 
nationwide multicenter study in Taiwan. J Microbiol Im-
munol Infect 2015;48:219-25.
16. Logan LK, Renschler JP, Gandra S, Weinstein RA, Laxmi-
narayan R; Centers for Disease Control; Prevention Epi-
centers Program. Carbapenem-resistant Enterobacteria-
ceae in children, United States, 1999-2012. Emerg Infect 
Dis 2015;21:2014-21.
17. Anderson KF, Lonsway DR, Rasheed JK, Biddle J, Jensen B, 
McDougal LK, Carey RB, Thompson A, Stocker S, Limba-
obo G, Patel JB. Evaluation of methods to identify the *Kleb-
siella pneumoniae* carbapenemase in *Enterobacteriaceae*. 
J Clin Microbiol 2007;45:2723-5.
18. Ampaire LM, Katawera V, Nyehangane D, Boum Y, Bazira J. 
Epidemiology of carbapenem resistance among multi-
drug resistant enterobacteriaceae in Uganda. Br Microbiol 
Res J 2015;8:418-23.
19. Torres-Gonzalez P, Cervera-Hernandez ME, Niembro-Or-
tega MD, Leal-Vega E, Cruz-Hervert LP, Garcia-Garcia L, 
Galindo-Fraga A, Martinez-Gamboa A, Bobadilla-Del Valle 
M, Sifuentes-Osornio J, Ponce-de-Leon A. Factors associat-
ed to prevalence and incidence of carbapenem-resistant 
*Enterobacteriaceae* fecal carriage: a cohort study in a Mexi-
can Tertiary Care Hospital. PLoS One 2015;10:e0139883.
20. Guh AY, Bulens SN, Mu Y, Jacob JT, Reno J, Scott J, Wilson 
LE, Vaeth E, Lynfield R, Shaw KM, Vagnone PM, Bamberg 
WM, Janelle SJ, Dumyati G, Concannon C, Beldavs Z, Cun-
ningham M, Cassidy PM, Phipps EC, Kensey N, Travis T, 
Lonsway D, Rasheed JK, Limbago BM, Kallen AJ. Epidemi-
ology of carbapenem-resistant enterobacteriaceae in 7 US 
communities, 2012-2013. JAMA 2015;314:1479-87.
21. Huh K, Kim J, Cho SY, Ha YE, Joo EJ, Kang CI, Chung DR, 
Lee NY, Song JH, Peck KR; Korean Network for Study on 
Infectious Diseases (KONSID). Continuous increase of the 
antimicrobial resistance among gram-negative pathogens 
causing bacteremia: a nationwide surveillance study by the 
Korean Network for Study on Infectious Diseases (KONSID). 
Diagn Microbiol Infect Dis 2013;76:477-82.
22. Kim BM, Jeon EJ, Jang JW, Park J, Choi JC, Shin JW, Park 
IW, Choi BW, Kim YJ. Four-year trend of carbapenem-
resistance in newly opened ICUs of a university-affili-
ated hospital of South Korea. Tuberc Respir Dis (Seoul) 
2012;72:360-6.
23. Kim DK, Kim HS, Pinto N, Jeon J, D’Souza R, Kim MS, Choi 
YJ, Yong D, Jeong SH, Lee K. Xpert CARBA-R assay for the 
detection of carbapenemase-producing organisms in in-
tensive care unit patients of a Korean Tertiary Care Hospital. Ann Lab Med 2016;36:162-5.
24. Thaden JT, Pogue JM, Kaye KS. Role of newer and re-emerging older agents in the treatment of infections caused by carbapenem-resistant Enterobacteriaceae. Virulence 2016;6:1-14.
25. Sader HS, Castanheira M, Flamm RK, Mendes RE, Farrell DJ, Jones RN. Tigecycline activity tested against carbapenem-resistant Enterobacteriaceae from 18 European nations: results from the SENTRY surveillance program (2010-2013). Diagn Microbiol Infect Dis 2015;83:183-6.
26. Livermore DM, Warner M, Mushtaq S, Doumith M, Zhang J, Woodford N. What remains against carbapenem-resistant Enterobacteriaceae? Evaluation of chloramphenicol, ciprofloxacin, colistin, fosfomycin, minocycline, nitrofurantoin, temocillin and tigecycline. Int J Antimicrob Agents 2011;37:415-9.
27. Kim SY, Shin J, Shin SY, Ko KS. Characteristics of carbapenem-resistant Enterobacteriaceae isolates from Korea. Diagn Microbiol Infect Dis 2013;76:486-90.
28. Jiao Y, Qin Y, Liu J, Li Q, Dong Y, Shang Y, Huang Y, Liu R. Risk factors for carbapenem-resistant Klebsiella pneumoniae infection/colonization and predictors of mortality: a retrospective study. Pathog Glob Health 2015;109:68-74.
29. Giannella M, Trecarichi EM, De Rosa FG, Del Bono V, Bassetti M, Lewis RE, Losito AR, Corcione S, Saffioti C, Bartoletti M, Maiuro G, Cardellino CS, Tedeschi S, Cauda R, Viscoli C, Viale P, Tumbarello M. Risk factors for carbapenem-resistant Klebsiella pneumoniae bloodstream infection among rectal carriers: a prospective observational multicentre study. Clin Microbiol Infect 2014;20:1357-62.
30. Correa L, Martino MD, Siqueira I, Pasternak J, Gales AC, Silva CV, Camargo TZ, Scherer PF, Marra AR. A hospital-based matched case-control study to identify clinical outcome and risk factors associated with carbapenem-resistant Klebsiella pneumoniae infection. BMC Infect Dis 2013;13:80.
31. Ahn JY, Song JE, Kim MH, Choi H, Kim JK, Ann HW, Kim JH, Jeon Y, Jeong SI, Kim SB, Ku NS, Han SH, Song YG, Yong D, Lee K, Kim JM, Choi JY. Risk factors for the acquisition of carbapenem-resistant Escherichia coli at a tertiary care center in South Korea: a matched case-control study. Am J Infect Control 2014;42:621-5.
32. Jeon MH, Choi SH, Kwak YG, Chung JW, Lee SO, Jeong JY, Woo JH, Kim YS. Risk factors for the acquisition of carbapenem-resistant Escherichia coli among hospitalized patients. Diagn Microbiol Infect Dis 2008;62:402-6.
33. Gupta N, Limbago BM, Patel JB, Kallen AJ. Carbapenem-resistant Enterobacteriaceae: epidemiology and prevention. Clin Infect Dis 2011;53:60-7.
34. Martirossov DM, Lodise TP. Emerging trends in epidemiology and management of infections caused by carbapenem-resistant Enterobacteriaceae. Diagn Microbiol Infect Dis 2016;85:266-75.