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■ Case Report

Four Cases of Carbapenem-Resistant *Enterobacteriaceae* Infection from January to March in 2014

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Infection with carbapenem-resistant *Enterobacteriaceae* (CRE) and other multidrug resistant bacteria has increased rapidly in Korea. The Korea Centers for Disease Control and Prevention reported 1,609 cases of CRE infection in the country in 2013. The risk factors for CRE infection include history of treatment with antibiotics such as cephalosporins or carbapenem, trauma, diabetes, cancer, and history of ventilator support. Herein, we report four cases of CRE infection seen during a 3-month period in our hospital in 2014. CRE infection is associated with a high mortality rate of 30% to 50%, even with combination antibiotic therapy. Prevention of CRE infection in hospital settings is fundamental to controlling its transmission. Key preventive measures include, contact precautions, hand hygiene, education of healthcare personnel, screening for CRE when indicated, and exercising discretion in prescribing carbapenem or cephalosporins.

Keywords: Carbapenemase; *Enterobacteriaceae*; *Enterobacter cloacae*; Drug Resistance, Bacterial

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INTRODUCTION

Carbapenem was developed from thienamycin in 1980 and has a broad antibacterial spectrum that includes gram-negative and gram-positive bacteria such as *Pseudomonas aeruginosa* and *Enterobacteriaceae*. Its resistance to extended-spectrum beta-lactamase (ESBL) and the increasing incidence of cephalosporin-resistant *Enterobacteriaceae* strains since the 1990s are the two main reasons for its increasing use. However, the rampant use of carbapenem has in turn led to emergence of resistance against it among *Enterobacteriaceae*, due to which its therapeutic value has been decreasing. Carbapenem-resistant *Enterobacteriaceae* (CRE) also show resistance to other antibiotics such as aminoglycosides and quinolones. These multidrug-resistant bacteria have been rapidly spreading worldwide. According to the Korea Centers for Disease Control and Prevention, the number of cases of CRE infection increased 2-fold from 816 cases in 2012 to 1,609 in 2013.[1)]

Resistance to carbapenems may be due to the production of carbapenemases or the production of an ESBL or AmpC β-lactamases, combined with porin-loss.[2)] CRE with carbapenemase expression are referred to as carbapenemase-producing *Enterobacteriaceae* (CPE). CPE require separate consideration in the context of patient treatment and infection control, as carbapenemase-expressing strains are more virulent and carry a higher risk of contagion, while resistance conferred by AmpC β-lactamase/ESBL associated with porin loss is relatively less contagious. Therefore, CPE is considered more important than CRE for purposes of infection control.[3)] CPE are more likely to be isolated from patients with a history of carbapenem treatment, diabetes mellitus (DM), decreased immunity, history of ventilator support; elderly and critically sick patients requiring intensive care; and organ transplant recipients.[1)] We present four cases of CRE infection encountered in our hospital during a 3-month period in 2014.

CASE REPORTS

1. Case 1

The patient was a 28-year-old man who was hospitalized for extradural hemorrhage, skull and rib fractures, and an open leg wound sustained in a road traffic accident. There was no significant medical or travel history. He underwent craniectomy and open-reduction and internal fixation of fracture, and was admitted to the intensive care unit (ICU). He developed pneumonia on the 5th day and was treated with teicoplanin and piperacillin/tazobactam. The pneumonia showed signs of resolution on the 15th day, but his fever persisted. The central line catheter was removed, and a blood culture was performed. The antibiotic regimen was changed from piperacillin/tazobactam to doripenem. Results of the blood culture including the central line sample were positive for *Enterobacter cloacae* resistant to amoxicillin/clavulanic acid, aztreonam, cefazolin, cefoxitin, gentamicin, trimethoprim/sulfamethoxazole, cefotaxime, tigecycline, piperacillin/tazobactam, and ertapenem, and susceptible to amikacin (minimum inhibitory concentration 16), ciprofloxacin (minimum inhibitory concentration 1), cefepime (minimum inhibitory concentration ≤1), and imipenem (minimum inhibitory concentration 0.5). As the infecting organism was resistant to ertapenem, a carbapenemase gene test was performed, which was positive for the Verona imipenemase (VIM) II, a Carbapenem-Hydrolyzing Metallo-β-Lactamase gene. The patient was diagnosed with carbapenemase-producing *Enterobacter cloacae*, and Doripenem was changed to colistin. Subsequently, his condition improved with normalization of body temperature and C-reactive protein (CRP) level. Treatment was continued for 3 weeks. He recovered fully and was discharged with on-going follow-up in an outpatient clinic.

2. Case 2

A 69-year-old woman with subarachnoid hemorrhage was hospitalized with the chief complaint of headache. There was no significant medical or travel history. Cerebral angiography did not reveal any evidence of aneurysm. A conservative line of treatment was followed; no embolization was performed. She showed signs of hydrocephalus, for which a cerebrospinal fluid sample was obtained via lumbar puncture for culture and routine cerebrospinal fluid testing. The cerebrospinal fluid culture was positive for *Enterobacter cloacae* resistant to amoxicillin/clavulanic acid, cefazolin, cefoxitin, cefotaxime, tigecycline, piperacillin/tazobactam, ertapenem, and imipenem; moderately susceptible to tigecycline (minimum inhibitory concentration 2) and ciprofloxacin (minimum inhibitory concentration 2); and susceptible to gentamicin (minimum inhibitory concentration ≤1), amikacin (minimum inhibitory concentration 16), trimethoprim/sulfamethoxazole (minimum inhibitory concentration ≤20), aztreonam (minimum inhibitory concentration ≤1), cefepime (minimum inhibitory concentration ≤1), and imipenem (minimum inhibitory concentration 0.5). Due to resistance to ertapenem and imipenem, a carbapenemase gene test was performed which was positive for the VIM II gene. The patient was diagnosed as having a carbapenemase-producing *Enterobacter cloacae* infection. The cerebrospinal fluid test revealed a white blood cell (WBC) count of 6 μL and red blood cell count of 1,770 μL; WBC and CRP levels were normal. Thus, infection was considered absent, especially since the patient had no fever. In the ICU, she used the same bed that was earlier used by case 1, before he was diagnosed with Carbapenem-producing enterobacteriaceae, as the culture result had not been reported at that time. The patient in this case showed a type of carbapenemase gene same as case 1. This case was considered as contamination during the sample collection. Fol-

low-up cerebrospinal fluid culture and blood tests were performed, and the patient was kept under observation without treatment, as no infection was found. The patient's condition improved, following which she was discharged and is now being followed up in the outpatient clinic.

3. Case 3

A 42-year-old female patient was admitted to the hospital with right limb paralysis caused by subarachnoid hemorrhage. She had a history of hypertension, but no significant travel history. She was admitted to the ICU after embolization for a cerebral aneurysm. She recovered well and was shifted to a general ward on the 21st day of admission. She developed fever on the 29th day, and blood and urine culture was performed along with removal of the central line catheter. Her blood sample including the central line samples was positive for methicillin-resistant *Staphylococcus aureus*. Her urine sample was positive for an *Escherichia coli* strain resistant to amoxicillin/clavulanic acid, aztreonam, cefazolin, cefoxitin, gentamicin, cefotaxime, tigecycline, piperacillin/tazobactam, ciprofloxacin, cefepime, imipenem, and ertapenem, and susceptible to trimethoprim/sulfamethoxazole (minimum inhibitory concentration ≤20), amikacin (minimum inhibitory concentration ≤2), and tigecycline (minimum inhibitory concentration ≤0.5). As the *Escherichia coli* strain was resistant to imipenem and ertapenem, a carbapenemase gene test was performed, which was positive for the New Delhi Metallo (NDM) I enzyme. The foley catheter had been continuously used, as the patient did not complain of any urinary symptoms. The catheter was removed on suspicion of asymptomatic bacteriuria and colonization, and the patient was kept under observation. Vancomycin was administered to treat the central line-associated sepsis. The patient showed improvement after 3 weeks of vancomycin treatment and is being followed up in an outpatient clinic.

4. Case 4

An 81-year-old female patient was admitted to this hospital due to an aggravated surgical wound. She underwent embolization for a ruptured cerebral aneurysm in this hospital, and had been receiving rehabilitation treatment in a specialized facility. She had a history of hypertension and DM, with no significant travel history. As she was admitted in the same ward as case 3, a stool culture was performed, which was positive for *Klebsiella pneumoniae*. The bacterial strain was ESBL-positive and was resistant to amoxicillin/clavulanic acid, trimethoprim/sulfamethoxazole, aztreonam, amikacin, cefazolin, cefoxitin, gentamicin, cefotaxime, tigecycline, piperacillin/tazobactam, ciprofloxacin, cefepime, imipenem, and ertapenem, with moderate susceptibility to tigecycline (minimum inhibitory concentration 2). Carbapenemase gene test in this case was negative and considered as CRE colonization. The patient was isolated and underwent regular stool culture. The culture results were negative for bacteria. The patient was discharged from isolation, and is being followed up.

DISCUSSION

CRE infections are known to be associated with a high mortality rate even after combination antibiotic treatment. An analysis of 20 non-randomized studies showed a 50% mortality rate associated with CPE infection treated with tigecycline-gentamicin combination therapy, 64% with tigecycline-colistin combination, 67% with carbapenem-colistin combination, 57% with colistin monotherapy, and 80% with tigecycline monotherapy. Due to the high associated mortality risk, prevention of CPE infection is as important as its treatment.[4)]

Carbapenemase enzymes produced by CPE are classified into three main types based on their Amber class. Class A includes the *Klebsiella pneumonia* carbapenemase (KPC), 4 serine carbapenemases (Serratia marcescens enzyme, not metalloenzyme carbapenemase-A, imipenem-hydrolyzing, and rare Guiana extended-spectrum). Class B includes NDM, imipenemase (IMP), and VIM. Finally, class D includes the oxacillinases (OXA)-48 and OXA-181.

The KPC was first found in North Carolina in 1997 and is currently the most prevalent type of carbapenemase. Its incidence was high in 2001 in New York, and has since increased worldwide. In particular, it has been reported frequently in Greece and Italy.[4)]

The IMP was first reported in Japan in the late 1980s, and its incidence has since increased worldwide. However, its incidence rate is relatively low.[4)] The VIM was first isolated from *Pseudomonas aeruginosa* in 1997 in Italy, and was later transferred to *Klebsiella pneumoniae*. Although *Klebsiella pneumoniae* with VIM enzyme expression is less frequently observed than *Klebsiella pneumoniae* with carbapenemase, its incidence is rapidly increasing worldwide.

The NDM was first found in India. It was found in 2% to 8% of cases of *Enterobacteriaceae* infections in Indian university hospitals, and 27% of the patients hospitalized in two military hospitals in Pakistan were identified as its carriers.[4)] It has since spread to Europe, Asia, and North America via tourists and people who were treated in India.

The OXA-48 was first reported in Turkey, and was later found in the Middle East and North Africa in 2007–2008. Thereafter, it has been frequently reported in the UK, Belgium, Ireland, France, Spain, and Holland.[5,6)]

The portal of entry of CPE is similar to that of other drug-resistant gram-negative bacteria. Colonized patients are the most common reservoir of CPE in hospital settings. Horizontal transfer commonly occurs through contaminated hands of medical personnel, medical devices, and the general hospital environ-

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ment. Prevention and control of infection require hand hygiene and stringent disinfection of all media coming into contact with the patient. Sharing of medical devices between patients should be avoided, and any medical device or equipment should only be reused after sterilization. Wards should be disinfected daily to prevent infection in the hospital environment. Stool culture should be performed routinely, and CRE-positive/negative patients should be differentiated to prevent direct infection between patients. CRE-positive patients should be kept in isolation and health personnel involved in the care of such patients should be managed as a group. Whole-body disinfection using a chlorhexidine bath is known to decrease the incidence of gram-positive bacterial infections, but evidence of such an effect on the incidence of gram-negative bacterial infection is limited. Several studies have investigated the correlation between antibiotic over use and CRE incidence. It is generally suggested that reducing the total dose of antibiotics could be more helpful than restricted use of certain types of antibiotics.[7]

Early identification of CPE strains is critical for preventing the spread of infection. In case 1, the blood sample tested negative for *Enterobacter cloacae*-producing VIM II enzyme, but the delay in availability of test results led to a delay in his isolation, and the subsequent delay of the detection of the VIM II enzyme in the cerebrospinal fluid sample from case 2. Thus, a fast and accurate method for detecting carbapenemase would help combat CPE transmission.

In conclusion, the four cases described in this report are the result of an epidemiological study on CRE patients in our hospital conducted from January to March 2014. Early diagnosis, prompt isolation, and appropriate antibiotic therapy are key tenets of managing CRE infection. Patients with a history of travel and/or treatment in countries with high CRE incidence should be proactively monitored with culture studies of the relevant specimen. The duration of stay in the ICU and history of use of invasive interventions are known risk factors for CRE infection. In case 1, the CRE infection was acquired through the central line. A shorter duration of ICU stay, discretionary use of invasive instruments, and stringent antisepsis are vital for ameliorating the risk of CRE infection.[1,8]

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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