American Journal of Infection Control 42 (2014) 1270-3

Contents lists available at ScienceDirect

American Journal of Infection Control

journal homepage: www.ajicjournal.org

Major article

Successful containment of carbapenem-resistant *Enterobacteriaceae* by strict contact precautions without active surveillance

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Key Words:
Carbapenem resistance
Enterobacteriaceae
Contact precaution

Background: Carbapenem-resistant *Enterobacteriaceae* (CRE) are a growing problem worldwide. Guidelines focus on carbapenemase-producing organisms, and little is known about whether strict adherence to infection control measures is effective for CRE without carbapenemase. During 2009, CRE increased markedly in a tertiary hospital, and enhanced infection control measures without active surveillance were adopted.

Methods: Beginning in April 2010, enhanced antimicrobial stewardship, strict contact precautions, and cohort isolation were adopted. After September 2010, hand hygiene performance was prospectively monitored by active surveillance, and results were monthly fed back to medical personnel. Available carbapenem-resistant *Escherichia coli* (ECO) and carbapenem-resistant *Klebsiella pneumoniae* (KPN) isolated during 2008-2010 were characterized. Imipenem and meropenem minimal inhibitory concentrations were confirmed by E-test (AB biodisk, Solna, Sweden). Phenotypic screening assays and polymerase chain reaction (PCR) amplification of known β-lactamase and carbapenemase genes were performed.

Results: From 3,511 ECO and 2,279 KPN, 44 (0.76%) were CRE (3 ECO, 41 KPN). CRE incidence rates rose from 1.61 in 2008 to 5.49 in 2009; they rose further to 9.81 per 100,000 patient days in early 2010. After adoption of strict infection control measures, CRE frequency fell back in 2011 and remained at baseline afterward. Phenotypic screening and PCR showed AmpC β-lactamase and extended spectrum β-lactamases with or without loss of porins; carbapenemases were not detected.

Conclusion: Enhanced infection control measures, even without active surveillance, seem effective to prevent further spread of CRE in a low-prevalence setting with mainly carbapenemase-nonproducing CRE.

In the last decade, carbapenem-resistant *Enterobacteriaceae* (CRE) have been increasing worldwide. Invasive infections caused by these organisms are associated with high mortality and pose a major threat to clinicians because of limited therapeutic options.[1] Therefore, preventing the acquisition and reducing the spread of CRE is of the utmost importance.

In South Korea, carbapenem resistance is still noted in <1% of *Enterobacteriaceae* isolated from clinical specimens, and carbapenemase production is only detected in a minority of isolated CRE.[2] Although carbapenemases are occasionally reported,[2,3] previous studies suggest AmpC overproduction with porin loss as the main mechanism of carbapenem resistance in South Korea.[3,4]

Guidelines for the control of CRE published in March 2012 by the Korea Centers for Disease Control and Prevention[5] are, in principle, similar to other guidelines issued by governmental agencies,

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Previous presentation: This study was presented in part at the 49th Annual Meeting of the Infectious Diseases Society of America; October 21, 2011; Boston, Massachusetts.

Funding/support: This study was supported by research grant 03-2011-020 from Seoul National University Bundang Hospital (Seongnam, South Korea).

Conflicts of interest: None to report.

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http://dx.doi.org/10.1016/j.ajic.2014.09.004

including the U.S. Centers for Disease Control and Prevention, Public Health Agency of Canada, and Public Health England.[6-10] The strategies suggested in the guidelines focus on the control of carbapenemase-producing *Enterobacteriaceae*; however, little is known about whether strict adherence to infection control measures is effective in CRE with different resistance mechanisms.[10,11]

In 2009 and early 2010, CRE increased markedly among clinical isolates in our institution. We describe the results of an enhanced infection control program without active surveillance, which was introduced beginning in April 2012 and maintained thereafter to contain the spread of CRE and the characteristics of carbapenem-resistant (CR) *Escherichia coli* (ECO) and *Klebsiella pneumoniae* (KPN) isolates.

METHODS

Hospital settings

Our institution is a 900-bed, tertiary care, university-affiliated teaching hospital in South Korea. It has 20 general (12 surgical, 8 medical) wards, 3 intensive care units (ICUs) with 43 beds (16 in the medical ICU, 9 in the cardiovascular ICU, 18 in the surgical ICU), and an emergency department. Most bedrooms on the general wards are facilitated with 4-6 beds, a common bathroom with a sink, and a separate sink beside the door. Chlorhexidine-based antiseptic handwash and soap are provided on every sink, and alcohol-based handrubs are mounted on every bed and in corridors.

Study period and definitions

We detected an increased incidence of CR KPN in our institution throughout 2009. As this persisted into 2010, we analyzed monthly and annual carbapenem resistance rates (CRRs) among ECO and KPN retrospectively from 2007 to September 2010 by clinical microbiology database review and prospectively after September 2010 until December 2013.

CRE were defined as isolates nonsusceptible to imipenem or meropenem according to the Clinical and Laboratory Standards Institute breakpoints, which were revised in June 2010.[12] CRR was defined as the proportion of CR ECO and CR KPN among ECO and KPN, and CRE incidence was defined as the numbers of CR ECO and CR KPN per 100,000 patient days.

Infection control measures

Beginning in April 2010, we adopted enforced antimicrobial stewardship according to the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines, and we enhanced infection control measures according to the World Health Organization and U.S. Centers for Disease Control and Prevention guidelines.[7,13] Antimicrobials prescribed for inpatients were actively monitored through an electronic surveillance system linked to the pharmacy database and electronic medical records. The prescriptions were audited within 24 hours for appropriateness by infectious diseases physicians, and the decision about appropriateness (regarding the use itself and its prescribed dosage) was promptly fed back to the prescribers. In case the restricted antibiotic was regarded as not appropriate, an alternative regimen or discontinuation (if antibiotics seem unnecessary) was recommended, and approval was denied. It was not possible to continue disapproved restricted antibiotics beyond 72 hours. The decision (approval or disapproval) was valid for 7 days, unless actively reversed.

Patients colonized or infected with CRE on the basis of clinical cultures were isolated in single rooms or in cohorts and placed on strict individual contact precautions with single-use gowns and gloves. The patients with CRE remained in isolation until 3 consequent clinical cultures of the same specimen taken at least 3 days apart were negative for CRE. Cultures for surveillance were not performed.

At the beginning of every month, medical personnel were educated repeatedly on the procedures and importance of proper hand hygiene. They were strongly encouraged to adhere to hand hygiene during contact with patients using alcohol-based handrubs mounted on every bed or using soap and water at sinks mounted in every bedroom and in corridors, as appropriate. After September 2010, the performance of hand hygiene was monitored actively by trained observers using predetermined criteria for quantitative evaluation. Hand hygiene adherence rates were fed back to medical personnel every month.

Characterization of CR ECO and CR KPN

Available CR ECO and CR KPN isolated from January 2008 to December 2010 were collected and characterized. Imipenem and meropenem minimal inhibitory concentrations were confirmed by E-test. The isolates were screened phenotypically by the modified Hodge, EDTA-synergy, Boronic acid synergy, and Clinical and Laboratory Standards Institute extended spectrum β-lactamase confirmatory tests.[12,14,15] Polymerase chain reaction amplification of known β-lactamase genes (*CTX-M*, *TEM*, *SHV*, *CMY*, *DHA*) and carbapenemase genes (*KPC*, *VIM*, *IMP*, *NDM-1*, *GES*, *OXA-48*) was performed.[16-19] Pulsed-field gel electrophoresis was carried out to assess the clonal relatedness of the isolates. Only the first CRE isolate from any given patient was included in the analysis.

Antibiotic utilization amounts

Antibiotic usage data were obtained from our pharmacy database, including the actual number of units dispensed for inpatients during 2007-2011. Antibiotic consumption levels were expressed as the number of defined daily doses (DDDs) per 1,000 patient days for each quarter. The amounts of carbapenems, β-lactam/β-lactamase inhibitor combinations, third- and fourth-generation cephalosporins, and fluoroquinolones used were analyzed.

Statistical analysis

To evaluate the impact of the intervention on CRE isolation rates over time, we adopted the generalized linear autoregressive moving average class of models using the glarma R-package (http://cran.r-project.org/web/packages/glarma/index.html). All reported P values are 2 sided, and $P < .05$ was considered statistically significant.

RESULTS

CRE incidence rates in 2007 and 2008 were 1.62 per 100,000 patient days (CRR = 0.30%, 5/1,660) and 1.61 per 100,000 patient days (CRR = 0.29%, 5/1,727), respectively. The rates increased to 5.49 per 100,000 patient days (CRR = 0.88%, 17/1,941) in 2009 and kept increasing throughout the first quarter of 2010 to 9.81 per 100,000 patient days (CRR = 1.45%, 7/481) ($P < .001$). In 2009 and 2010, CRE were identified from 39 patients (17 in 2009, 22 in 2010) who were admitted to 12 departments in 13 general (4 surgical, 9 medical) wards, 2 ICUs, and the emergency department. After strict infection control measures were adopted, resistance rates started to decline, reached baseline in 2011 ($P < .001$), and remained at this level afterward (Fig 1). CRE incidence increased gradually during the preintervention period (relative risk = 1.064) but decreased