



Abrupt Increase in Rate of Imipenem Resistance in *Acinetobacter baumannii* Complex Strains Isolated from General Hospitals in Korea and Correlation With Carbapenem Administration During 2002–2013

Young Ah Kim, M.D.¹, Yoon Soo Park, M.D.², Taemi Youk, M.D.³, Hyukmin Lee, M.D.⁴, and Kyungwon Lee, M.D.⁴

Department of Laboratory Medicine¹, National Health Insurance Service Ilsan Hospital, Goyang; Department of Internal Medicine², National Health Insurance Service Ilsan Hospital, Goyang; Department of Statistics³, Korea University, Seoul; Department of Laboratory Medicine and Research Institute of Bacterial Resistance⁴, Yonsei University College of Medicine, Seoul, Korea

Dear Editor,

Acinetobacter baumannii is a cause of healthcare-associated infections and one of the most important pathogens found in intensive care units (ICUs). The recent dramatic spread of carbapenem-resistant *A. baumannii* complex (CRAB) in Korea has raised substantial concern in medical practice owing to the lack of adequate therapeutic options [1, 2]. It is well-known that the selective pressure of antibiotics contributes to emergence of new resistant strains [3]. However, there is no sufficient evidence for the association between carbapenem administration and emergence of imipenem-resistant *A. baumannii*. The rate of imipenem resistance in *A. baumannii* isolates from general hospitals in Korea markedly increased from 27% in 2007 to 72% in 2010, according to data from a nationwide multicenter study conducted by the Korean Antimicrobial Resistance Monitoring System (KARMS) [4], representing major public threat in Korea. In addition to antibiotic selection pressure, other factors could affect the spread of resistant organisms, such as new antimicrobial resistance mechanisms, virulence, host factors, and the infection control policy. In this study, we aimed to elucidate the potential

explanation for this abrupt increase in imipenem resistance in *A. baumannii* in Korea, focusing on the antibiotic selection pressure nationwide.

Carbapenem is usually considered a treatment option for extended-spectrum β -lactamase (ESBL)-producing *Enterobacteriaceae*. The rate of cefotaxime resistance in *Klebsiella pneumoniae* isolates increased from 18% in 2003 to 41% in 2009, and that of *Escherichia coli* increased from 10% in 2004 to 21% in 2008, in Korea [4]. It is mainly attributed to the spread of ESBL producers, which could be a main driver of carbapenem usage because carbapenem is the last resort for treatment of these infections.

This study was approved by the National Health Insurance Service Ilsan Hospital Institutional Review Board, as required by the local hospital policy (NHIMC 2017-03-025), with permission from the National Health Insurance Service-National Sample Cohort (REQ0000007622). The antibiotic usage data in Korea for 12 years (from 2002 to 2013) were acquired from the National Health Insurance Service-National Sample Cohort (NHIS-NSC) database [5]. The systemic prescription of antibiotics based

Received: June 19, 2017

Revision received: August 11, 2017

Accepted: October 23, 2017

Corresponding author: Hyukmin Lee

Department of Laboratory Medicine and Research Institute of Bacterial Resistance, Yonsei University College of Medicine, 211 Eonju-ro, Gangnam-gu, Seoul 06273, Korea
Tel: +82-2-2019-3530, Fax: +82-2-2057-8926
E-mail: hmlee.labmed@gmail.com

© Korean Society for Laboratory Medicine.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

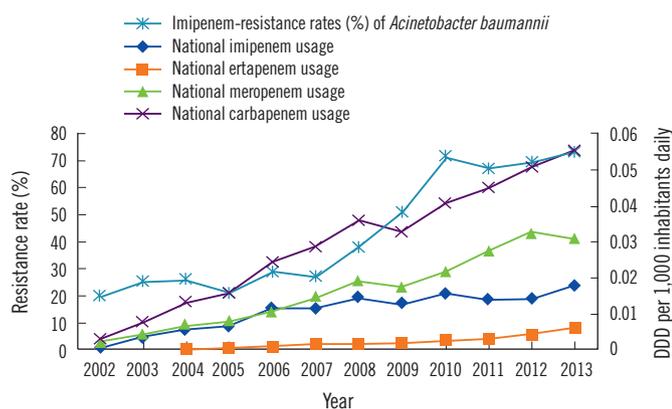


Fig. 1. Correlation of national carbapenem usage with rate of imipenem resistance in *Acinetobacter baumannii* (IMP-R-ABA) strains isolated from general hospitals in Korea from 2002 to 2013. Correlation of imipenem usage with IMP-R-ABA (correlation coefficient $r=0.93$, $P<0.0001$); correlation of meropenem usage with IMP-R-ABA ($r=0.93$, $P<0.0001$); correlation of ertapenem usage with IMP-R-ABA ($r=0.92$, $P=0.0002$); correlation of total carbapenem usage with IMP-R-ABA ($r=0.94$, $P<0.0001$).

on Anatomical Therapeutic Chemical (ATC) classification is standardized according to the daily defined dose (DDD) per 1000 inhabitants [6]. The data were analyzed using SAS software version 9.2 (SAS Institute, Cary, NC, USA). The relationship between antibiotic use and resistance were evaluated by simple correlation analysis. The significance level was set at $P<0.05$.

As shown in Fig. 1, the rate of imipenem resistance in *A. baumannii* strains isolated from general hospitals showed a good correlation with the national usage data for carbapenems (including imipenem, meropenem, ertapenem, and total carbapenems). The resistance mechanism of CRAB is primarily mediated by Ambler's class D OXA-type β -lactamases. Gurung *et al* [7] investigated the clonal diversity and genetic basis of antimicrobial resistance among CRAB isolates in a Korean hospital, all of which were found to be sequence type 2 but were classified into two sequence groups and nine pulso-types. *bla*_{OXA-23}, which is a plasmid-borne gene encoding carbapenemase, was found to be largely responsible for resistance to carbapenems, and increased selection pressure of carbapenem might have facilitated the selection of dominant clones. There are some limitations of this study. Because most CRAB strains harbor not only *bla*_{OXA-23} but also multidrug resistance genes such as *armA*, *bla*_{ESBL}, and aminoglycosides-modifying enzyme genes [8], they may be co-selected by other classes of antibiotics that were not considered in this study. In addition, *A. baumannii* can survive for long periods in hospital settings, particularly on inanimate surfaces. Such environments may act as a reservoir for cross-colonization and

infection outbreaks [9]. Although the KARMS data were collected from non-duplicated first isolates, the potential effect of outbreaks of *A. baumannii* infection within healthcare facilities could not be fully eliminated. Essentially, this represents an ecological study comparing groups rather than individuals, which is associated with some intrinsic methodological problems that limit any inference on causality [10]. Nevertheless, our data was based on nationwide surveillance and the antimicrobial prescription database collected over a long period, which could provide useful information on the correlation between carbapenem administration and resistance in *A. baumannii* for practical applications. The NHIS maintains and stores all the national records for healthcare utilization and prescriptions, which could provide large-scale, extensive, and stable nationwide antimicrobial prescription data.

In conclusion, a correlation between carbapenem use and resistance of *A. baumannii* to imipenem was observed, which can offer insight into the increasing rate of imipenem-resistance in *A. baumannii* in Korea. These data can be used to develop national antibiotic usage management policies to reduce the spread of antibiotic resistance.

Authors' Disclosures of Potential Conflicts of Interest

This study was supported by grants from the National Health Insurance Service Ilsan Hospital (2016-20-001).

REFERENCES

- Lee Y, Kim YA, Song W, Lee H, Lee HS, Jang SJ, et al. Recent trends in antimicrobial resistance in intensive care units in Korea. *Korean J Nosocomial Infect Control* 2014;19:29-36.
- Jasemi S, Douraghi M, Adibhesami H, Zeraati H, Rahbar M, Boroumand MA, et al. Trend of extensively drug-resistant *Acinetobacter baumannii* and the remaining therapeutic options: a multi-center study in Tehran, Iran over a 3-year period. *Lett Appl Microbiol* 2016;63:466-72.
- Levy SB and Marshall B. Antibacterial resistance worldwide: causes, challenges and responses. *Nat Med* 2004;10(S12):S122-S9.
- KCDC, Korean Antimicrobial Resistance Monitoring System 2013 annual report. cdc.go.kr/CDC/cms/cmsFileDownload.jsp?fid=136&cid=21224&fieldname (Accessed on June 18 2017).
- Lee J, Lee JS, Park S, Shin SA, Kim KW. Cohort profile: The National Health Insurance Service-National Sample Cohort (NHIS-NSC), South Korea. *Int J Epidemiol* 2017;46:e15. doi: 10.1093/ije/dyv319
- World Health Organization Collaborating Centre for Drug Statistics and Methodology. Definitions and general considerations. http://www.whocc.no/ddd/definition_and_general_considerations/#DDDs (accessed June 18, 2017; last updated December 20, 2016).
- Gurung M, Rho JS, Lee YC, Kim HS, Moon SY, Yu BH, et al. Emergence and spread of carbapenem-resistant *Acinetobacter baumannii* sequence type 191 in a Korean hospital. *Infect Genet Evol* 2013;19:219-22.

8. Kim Y. Conditional probability analysis of multidrug resistance in Gram-negative bacilli isolated from tertiary medical institutions in South Korea during 1999-2009. *J Microbiol* 2016;54:50-6.
9. Aliramezani A, Douraghi M, Hajihassani A, Mohammadzadeh M, Rahbar M. Clonal relatedness and biofilm formation of OXA-23-producing carbapenem resistant *Acinetobacter baumannii* isolates from hospital environment. *Microb Pathog* 2016;99:204-8.
10. Morgenstern H. Ecologic studies in epidemiology: concepts, principles, and methods. *Annu Rev Public Health* 1995;16:61-81.