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Controlling endemic multidrug-resistant *Acinetobacter baumannii* in Intensive Care Units using antimicrobial stewardship and infection control

Shinhye Cheon[1,*], Mi-Ja Kim[2,*], Seon-Jin Yun[3], Jae Young Moon[4], and Yeon-Sook Kim[1,3]

[1]Division of Infectious Diseases, Department of Internal Medicine, Chungnam National University School of Medicine, Daejeon; [2]Department of Nursing, Daejeon Institute Science and Technology, Daejeon; [3]Department of Infection Control, Chungnam National University Hospital, Daejeon; [4]Division of Pulmonology and Critical Care Medicine, Department of Internal Medicine, Chungnam National University School of Medicine, Daejeon, Korea

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Correspondence to
Yeon-Sook Kim, M.D.
Division of Infectious Diseases, Department of Internal Medicine, Chungnam National University School of Medicine, 282 Munhwa-ro, Jung-gu, Daejeon 35015, Korea
Tel: +82-42-280-8109
Fax: +82-42-257-5753
E-mail: alice@cnuh.co.kr

*These authors contributed equally to this work.

Background/Aims: Nosocomial infections caused by multidrug-resistant (MDR) *Acinetobacter baumannii* have become public-health problem. However, few studies have evaluated the control of endemic MDR *A. baumannii* in Intensive Care Units (ICUs). Therefore, we investigated the effectiveness of antimicrobial stewardship and comprehensive intensified infection control measures for controlling endemic MDR *A. baumannii* in ICUs at a tertiary care center.
Methods: Carbapenem use was strictly restricted through antimicrobial stewardship. Environmental cleaning and disinfection was performed at least 3 times per day in addition to basic infection control measures. Isolation using plastic curtains and contact precautions were applied to patients who were colonized or infected with MDR *A. baumannii*. The outcome was measured as the incidence density rate of hospital-onset MDR *A. baumannii* among patients in the ICUs.
Results: The incidence density rate of hospital-onset MDR *A. baumannii* decreased from 22.82 cases per 1,000 patient-days to 2.68 cases per 1,000 patient-days after the interventions were implemented (odds ratio, 0.12; 95% confidence interval, 0.03 to 0.4; $p < 0.001$). The mean monthly use of carbapenems also decreased from 134.99 ± 82.26 defined daily doses per 1,000 patient-days to 94.85 ± 50.98 defined daily doses per 1,000 patient-days ($p = 0.016$).
Conclusions: Concomitant implementation of strict antimicrobial stewardship and comprehensive infection control measures effectively controlled endemic MDR *A. baumannii* in our ICUs within 1 year.

Keywords: Acinetobacter baumannii; Antimicrobial stewardship; Infection control

INTRODUCTION

Acinetobacter baumannii has emerged as a major nosocomial pathogen that causes ventilator-associated pneumonia, bacteremia, secondary meningitis, skin and soft tissue infection, and urinary tract infection in Intensive Care Units (ICUs) [1,2]. The incidence of *A. baumannii* infections has continuously increased, due to the increasing proportion of seriously ill patients who require advanced medical support [1,3,4]. The propensity of *A. baumannii* to acquire mechanisms of antimicrobial resistance, as well as the uncontrolled use of broad-spec-

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trum antibiotics, has led to increased isolation rates of multidrug-resistant (MDR) *A. baumannii* in many hospitals [5,6]. Furthermore, nosocomial outbreaks that are caused by MDR *A. baumannii* constitute a growing public-health concern, and this organism's ability to survive on dry surfaces for prolonged periods has made it endemic in many hospitals [7,8].

In Korea, the reported incidence of carbapenem-resistant *A. baumannii* infections was 82.5% in 2010, according to the surveillance that was carried out by the Korean Nosocomial Infections Surveillance System [9]. In our hospital's ICUs, a rapid increase in the isolation rates of MDR *A. baumannii* has been observed (from 55.4% in January 2012 to 94.1% in March 2013). Since 2008, we have experienced several outbreaks of MDR *A. baumannii* which were controlled using contact isolation precautions and improved hand hygiene adherence, although it has subsequently become endemic. There are numerous reports describing the successful control of nosocomial outbreaks, but there is little data regarding control of the endemic setting [10-14]. Therefore, we aimed to evaluate the effectiveness of comprehensive intensified infection control strategies for controlling endemic MDR *A. baumannii* in the ICUs at a tertiary care center.

METHODS

Hospital setting

Chungnam National University Hospital is a 1,275-bed, teaching hospital that is located in Daejeon, South Korea. It has 40,673 annual admissions and three ICUs, including a medical ICU (19-bed), a surgical ICU (20-bed) and a second surgical ICU (7-bed). Each ICU is multi-bed open ward with one isolation bed. All of the ICUs are located on the same floor, although the surgical ICUs are clustered together and the medical ICU is physically removed from the surgical ICUs. The distance between the beds in each ICU is < 1 m. The nurse-to-patient ratio was 1:4 when this study's intervention measures were implemented. One infectious disease physician and three infection control nurses evaluated the case patients in the ICUs throughout the study.

Preexisting hospital infection-control practices included wearing gloves and gowns when health care workers (HCWs) take care of patients colonized or infected with MDR *A. baumannii* and cleaning the environment using 0.01% sodium hypochlorite once a day. There was no restriction on using antibiotics in ICUs before these interventions.

The study interventions were implemented by a multidisciplinary team that consisted of an infection control practitioner, an infectious diseases physician, an ICU physician, the head nurses of ICUs, and three infection control nurses. The study period was divided into baseline investigation phase (April 1 to 30, 2013), an intervention phase (May 1, 2013 to February 28, 2014), and a follow-up phase (March 1 to 31, 2014).

Definition

MDR *A. baumannii* was defined as any *A. baumannii* isolate that is resistant to representative antibiotics of at least three different classes of antimicrobial agents, including carbapenems but excluding polymyxin B (colistin) and tigecycline. Case patients were defined as patients in the ICUs who developed nosocomial colonization or infection with MDR *A. baumannii*. Nosocomial colonization with MDR *A. baumannii* was defined as the acquisition of this pathogen at least three nights after the hospital admission [15]. Nosocomial infection with MDR *A. baumannii* was defined using the Centers for Disease Control and Prevention definitions of nosocomial infections [16]. The antibiotic use densities were recorded as the total weight of drug, and the value was converted into defined daily doses (DDD) per 1,000 patient-days, in accordance with the World Health Organization (WHO)'s recommendations [17]. The incidence density rate of hospital-onset MDR *A. baumannii* was defined as the per-patient number of first MDR *A. baumannii* isolates from clinical specimens (regardless of specimen source) and active surveillance testing at > 3 calendar days after admission to ICU, after excluding patients with history of colonization or infection [15].

Microbiology

Identification and antimicrobial susceptibility testing of *A. baumannii* isolates were performed using VITEK II (bioMerieux, Marcy L'Etoile, France). Hand cultures from HCWs were also evaluated for those who worked in the ICUs. Environmental cultures were done for a diverse group of sites, including respiratory equipment,

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ventilator tubes, suctioning equipment, surrounding curtains, bedrails, bedside tables, computer keyboards, and monitors, blood pressure cuffs, infusion pumps, stethoscopes, and washbasins. The environmental and hand cultures were sampled using a sterile pre-moistened cotton swab, which was inoculated onto MacConkey agar plates.

Intervention

The comprehensive intensified infection control strategy was implemented to control the spread and colonization of MDR *A. baumannii* (in addition to the routine control measures). The infection control strategy consisted of antimicrobial stewardship, hospital staff education, active surveillance cultures, contact precautions, environmental cleaning and disinfection enforcement, and hand hygiene promotion.

Antimicrobial stewardship

This hospital adopted a computerized antibiotic prescription system. This system automatically stops the prescription of the specific antibiotics if an infectious disease specialist does not approve there prescriptions. The antibiotics under the control are as follows: carbapanems (ertapenem, imipenem, meropenem, doripenem), glycopeptides, linezolid, tigecycline, colistin, voriconazole, posaconazole, echinocandins, and liposomal amphotericin. However, due to the insufficient number of infectious diseases specialists, the antimicrobial stewardship was not strictly implemented before this intervention. Many clinicians used these antibiotics for systemic inflammatory response syndrom conditions with noninfectious causes (such as acute pancreatitis) and continued these antibiotics for infections with confirmed pathogens which were susceptible to many other antibiotics.

Since April 1 2013, the use of carbapenems has been closely monitored and restricted through antimicrobial stewardship. One consultant physician (CP) from the Department of Infectious Diseases reviewed and approved the use of carbapenems, and carbapenems could not be prescribed for > 5 days without the CP's approval. According to CP's clinical decisions, alternative therapeutic agents were recommended to avoid the unnecessary use of cabapenems.

Education

Hospital staff education was emphasized to improve their perception of and adherence to hand hygiene protocols, as well as to improve their understanding regarding the importance of controlling MDR *A. baumannii* dissemination. This education was focused on when and how to perform hand hygiene. At the beginning of this study, all hospital staffs who were involved in ICU care were educated by an infectious disease physician. Monthly education of new staff was subsequently performed by infection control nurses.

Active surveillance cultures

Since the start of this intervention, all patients who were admitted to the ICUs were screened for MDR *A. baumannii* at admission, and subsequently underwent surveillance cultures twice weekly. Tracheal aspirate was collected if the patient was intubated or tracheostomized. Nasopharyngeal swabs or sputa were collected if the patient was not intubated.

Contact precautions

Any patient with a culture that was positive for MDR *A. baumannii* was cohorted to a designated area in each unit and contact precautions were implemented. All of these patients' caregivers wore gloves and gowns when they touched the patient or were in their immediate vicinity. When possible, all medical equipment was used exclusively for the infected or colonized patients. We used plastic curtains for each patient to prevent cross-transmission between these patients in the ICUs. When suction was performed through an endotracheal tube, the plastic curtains were kept closed to prevent respiratory droplets from disseminating to other patients or the surrounding environment. Closed suction systems were used for patients whose respiratory secretion contained MDR *A. baumannii*.

Environmental cleaning and environmental cultures

Environmental cleaning was reinforced, and disinfectants were applied for an adequate period to achieve sterilization, based on the manufacturer's guidance. Contaminated medical equipment was meticulously disinfected. The nursing staff also wiped the environments surrounded colonized or infected patients at least 3 times per day, using a cloth that was soaked with

1:100 diluted bleach or quaternary ammonium chloride wipes (NewGenn Science, Roudham, UK). An additional worker was assigned to perform an additional 2 hours of environmental cleaning per day. Environmental cultures were performed for most sites in the ICUs, and were repeated each month during the intervention period. The results were reported to the head ICU nurses, and environmental cleaning was subsequently focused on any near-patient hand-touch sites and the sites that tested positive for MDR *A. baumannii*.

Hand hygiene promotion

An alcohol-based hand rub was available at all bed sides in ICUs, and a non-alcoholic hand rub was distributed to any HCWs who were allergic to alcohol. Education of the hospital staffs and campaigns to increase hand hygiene adherence were also conducted. During the campaigns, posters, flyers and videos were openly used to promote hand-hygiene performance among the HCWs, and some of these materials were exhibited in the ICUs. All hospital computers were equipped with screensavers that contained hand hygiene guidelines, which were downloaded from the WHO website. Hand hygiene adherence was continuously monitored by blinded nurses who were working in each ICU. Monthly hand cultures were also performed, and the individual results were reported to each HCW and the administration staff.

Statistical analysis

The chi-square test for trend (Mantel-Haenszel extension) was used to compare the incidence density of MDR *A. baumannii* and hand hygiene adherence. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using Epi-Info version 6.0 (Centers for Disease Control and Prevention, Atlanta, GA, USA). The mean monthly use of carbapenems was compared using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). Differences with a $p < 0.05$ were considered statistically significant.

RESULTS

Incidence density rate of nosocomial MDR *A. baumannii*

The monthly incidence density rates of nosocomial MDR *A. baumannii* colonization/infection are shown in Fig. 1. During the investigation phase, the incidence density rate was 22.82 cases per 1,000 patient-days. After the interventions were implemented, the incidence density rates decreased to 3.9 cases per 1,000 patient-days (OR, 0.17; 95% CI, 0.05 to 0.51; $p < 0.001$) and to 2.68 cases per 1,000 patient-days during the follow-up phase (OR, 0.12; 95% CI, 0.03 to 0.4; $p < 0.001$).

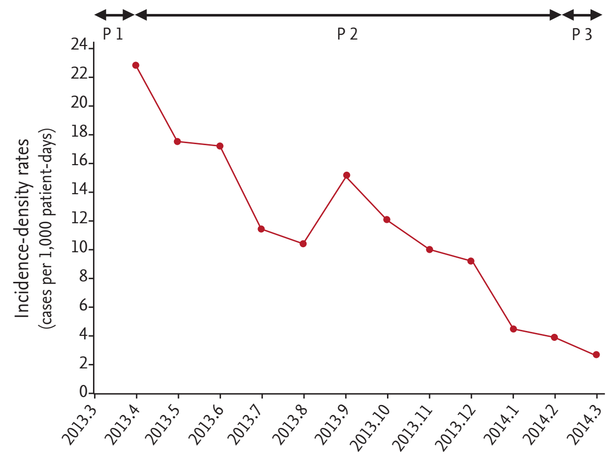

Figure 1. Incidence density rates of multidrug-resistant *Acinetobacter baumannii* during the study period. Data are recorded as the number of new nosocomial colonizations or infections per 1,000 patient-days. The infection control measures were implemented in May 2013.

During the study period, the monthly influx of MDR *A. baumannii* colonizers or infected patients to ICUs was 1.18 ± 0.98 per month (median, 1.18; range, 0 to 2). The proportion of MDR *A. baumannii* among all *A. baumannii* isolates declined from 93.16% in April 2013 to 78.26% in March 2014.

Consumption of antimicrobials

The strict control of carbapenem use was implemented at the end of March 2013, and has been maintained since that time (Fig. 2). The consumption of carbapenems was reported as monthly DDD/1,000 patient-days. During the intervention phase, the monthly mean carbapenem use decreased significantly from 134.99 ± 82.26 DDD/1,000 patient-days (April 2012 to March 2013) to 94.85 ± 50.98 DDD/1,000 patient-days (April 2013 to March 2014) ($p = 0.016$). Anti-pseudomonal carbapenems accounted for > 95% of the carbapenems that were used during the study period. Glycopeptide usage also decreased from 115.34 ± 55.70 to 89.68 ± 92.09 DDD/1,000

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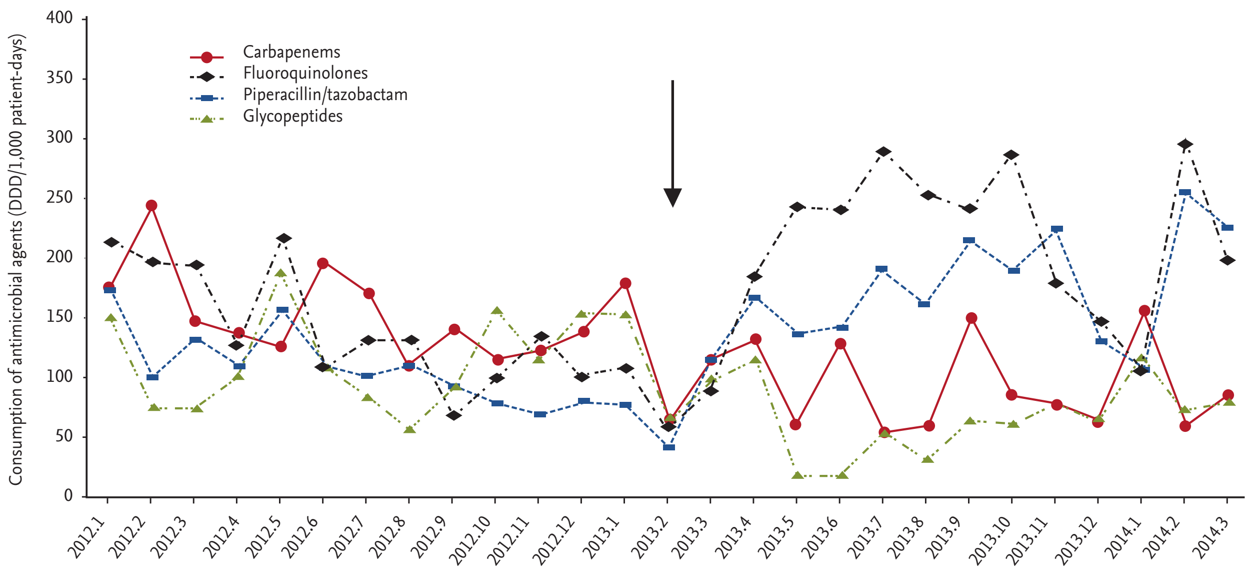

Figure 2. Consumption of antimicrobial agents during the study period. Data are presented as daily defined doses (DDD) per 1,000 patient-days. The arrow indicates the implementation of strict antimicrobial stewardship in the Intensive Care Units.

patient-days, although this decrease was not statistically significant (p = 0.157). In contrast, piperacillin/tazobactam and ciprofloxacin usage increased from 104.23 ± 65.55 to 207.91 ± 125.42 and 32.71 ± 29.68 to 191.36 ± 115.84 DDD/1,000 patient-days (p < 0.001), because these antimicrobials were one of the preferred alternatives to carbapenems.

There was no statistical difference in all-cause mortality rates, MDR *A. baumannii*-related deaths and average length of ICU stays between before and after the implementation of strict antimicrobial stewardship (data not shown).

Environmental cleaning and environmental cultures

Before the infection control interventions were implemented, MDR *A. baumannii* was isolated from numerous environmental surfaces (26 positive sites from 207 environmental sites). During this testing, MDR *A. baumannii* with different antibiograms were isolated from computer and electrocardiography monitors, infusion pumps, bedrails, computer keyboards, curtains, stethoscopes, private cups for the patients' oral hydration, and tables. After that point, environmental cleaning was reinforced and monthly cultures from an average of 313 diverse environmental sites were performed. These measures led to a marked decrease in the isolation rates of MDR *A. baumannii*, and no colonies of MDR *A. baumannii* were detected during the follow-up phase.

Hand hygiene adherence and hand cultures

A total of 245 and 126 hand hygiene opportunities were monitored during April 2013 and February 2014, respectively. Hand hygiene adherence increased significantly from 71.4% (95% CI, 65.48 to 76.72) in April 2013 to 86.5% (95% CI, 79.45 to 91.4) in February 2014 (p = 0.001). However, it subsequently decreased to 68.5% (129 of 189 opportunities) in March 2014. During the investigation phase, MDR *A. baumannii* was isolated from the hand cultures of one doctor and one nurse who were working in ICUs. However, MDR *A. baumannii* has not been isolated from hand cultures since that time.

DISCUSSIONS

MDR *A. baumannii* is one of the most difficult MDR pathogens to contain, and long-term infection control measures are needed to achieve sufficient control. However, our data indicate that our interventions resulted in a 10-fold decrease in the incidence density of nosocomial MDR *A. baumannii* within 1 year. Therefore, it appears that endemic MDR *A. baumannii* can be effectively contained through strict antimicrobial stewardship and comprehensive infection control measures.

This study highlights the importance of restricting carbapenem usage in the control of endemic MDR *A. baumannii*. In this context, carbapenems are the drug of choice for treating infections that are caused by many gram-negative bacilli. However, uncontrolled carbapenem use can result in the emergence of MDR pathogens, which renders these antimicrobials useless. Many studies have suggested that increased carbapenem use is an important risk factor for acquiring MDR *A. baumannii* [18-20]. Therefore, antimicrobial stewardship to restrict carbapenem usage has been suggested for controlling outbreaks that are caused by MDR *A. baumannii*. For example, Ogutlu et al. [21] demonstrated that carbapenem restriction reduced prevalence of *Acinetobacter* infection among ICU patients. The isolation rates of MDR *A. baumannii* at our hospital increased from 55.4% during January 2012 to 94.1% during March 2013, when the consumption of carbapenems was doubled. However, after the implementation of our antimicrobial stewardship program, the usage of carbapenems decreased, which resulted in a 10-fold decrease in the incidence density rate of nosocomial MDR *A. baumannii*. This antimicrobial stewardship program also resulted in the increased usage of piperacillin/tazobactam and ciprofloxacin, because these antibiotics were preferred as alternatives to carbapenems. Our data is contradictory to a previous study reporting that the increased use of ciprofloxacin was correlated with the acquisition of MDR *A. baumannii* [22]. Nevertheless, it seems that the increased use of carbapenems plays more important role in selecting MDR (especially carbapenem-resistant) *A. baumannii* than the other antibiotics.

Comprehensive infection control measures, especially those that are focused on environmental cleaning and disinfection, are critical for controlling endemic MDR *A. baumannii*. In this study, we achieved an environmental MDR *A. baumannii* positive culture rate of zero through reinforcing environmental cleaning (increasing the frequency from once to three times a day and assigning an additional worker). During nosocomial outbreaks, the colonization of the hospital environment is very important for the transmission of MDR *A. baumannii* [10,23,24], and our results of environmental cultures revealed that numerous sites in ICUs were contaminated with MDR *A. baumannii*. Several positive culture sites (such as bedrails, linen and infusion pumps) confirmed the desiccation tolerance of *A. baumannii*, but targeted environmental cleaning based on the results of environment cultures successfully controlled the contamination of these dry surfaces in our study within 3 months. However, data regarding the effectiveness of enhanced cleaning remains controversial, as Hess et al. [25] reported that enhanced cleaning in ICU rooms of patients who were colonized with methicillin-resistant *Staphylococcus aureus* or MDR *A. baumannii* did not reduce the contamination of HCWs' gowns and gloves. Contrastingly, several studies have reported the successful reduction of environmental contamination from hospital pathogens (such as vancomycin-resistant enterococci or *Clostridium difficile*), which resulted in significant reductions in the incidences of those infections [26,27]. Therefore, environmental cleaning and disinfection should be emphasized for controlling endemic MDR *A. baumannii* infections. As we do not have enough isolation rooms, we cohorted patients who were colonized with MDR *A. baumannii* into designated areas. These patients were separated using transparent plastic curtains to prevent patient-to-patient transmission, because our ICUs use a multi-bed open ward setting with < 1 m between the beds. We had previously used fabric curtains for this separation, although fabric curtains are an important reservoir for disseminating MDR *A. baumannii* [10], and so plastic curtains were used to increase the ease of cleaning and disinfection. Therefore, transparent plastic curtains may be useful for separating patients who are colonized or infected with MDR pathogens in ICUs where there are not enough isolation rooms, or where the short distance between the beds is problematic.

This study has a few limitations. First, this study did not show which intervention alone is effective for the control of MDR *A. baumannii*. We did not intend to define the effectiveness of individual intervention measures, but also assume that implementation of single infection control measures would not successfully control the endemic MDR *A. baumannii*. Therefore, we applied as many recommended infection control measures as possible. Second, the period for observation may not be enough to demonstrate how long the effectiveness of these interventions is maintained after the interventions.

In conclusion, endemic MDR *A. baumannii* was effectively controlled with strict antimicrobial stewardship and comprehensive infection control measures, includ-

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ing hospital staff education and performing active surveillance cultures, contact precautions isolation, environmental cleaning, and hand hygiene promotion. Without the application of these interventions simultaneously, it may have been difficult to achieve the successful control of MDR *A. baumannii* in our ICUs within 1 year.

KEY MESSAGE

1. Antimicrobial stewardship decreased the mean monthly use of carbapenem, from 134.99 ± 82.26 to 94.85 ± 50.98 defined daily doses/1,000 patient-days.
2. After implementing comprehensive infection control measures, adherence to hand hygiene practices increased from 71.4% to 86.5% and environmental cultures revealed no growth of multidrug-resistant *Acinetobacter baumannii*.
3. The year-long antimicrobial stewardship and comprehensive infection control measures resulted in a 10-fold decrease (from 22.82 to 2.68 cases/1,000 patient-days) in the incidence density rates of nosocomial multidrug-resistant *A. baumannii*.

Conflict of interest

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

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