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Major article

Successful control of carbapenem-resistant *Acinetobacter baumannii* in a Korean university hospital: A 6-year perspective

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Background: This study evaluated the effect of infection control interventions on the incidence of carbapenem-resistant *Acinetobacter baumannii* (CRAB) in a tertiary hospital over a 6-year period.
Methods: Multiple interventions, including cohorting, promotion of hand hygiene, active surveillance in the intensive care units, and environmental cleaning, were implemented from 2007 through 2009 (period 1). From 2009 through 2012 (period 2), infection control programs were enhanced by the introduction of an onsite education and hand hygiene campaign in preparation for hospital accreditation. To assess the efficacy of the infection control intervention programs, the nosocomial incidence density of CRAB, consumption of alcohol-based hand gel, and consumption of antimicrobials during the study period were measured.
Results: The incidence density of CRAB increased from 0.35 to 0.46 per 1000 patient-days (PD) during period 1, but decreased to 0.06 per 1000 PD in period 2 ($P = .011$). The consumption of alcohol-based hand gel increased from 5.6 L to 11.9 L per 1000 PD during the study period ($P < .001$). There was a significant association between the incidence density of CRAB and carbapenem use ($P = .008$).
Conclusions: Education for infection control programs, hand hygiene campaign, and the judicious use of carbapenem may decrease the nosocomial incidence of CRAB.

Acinetobacter baumannii has emerged as an important nosocomial pathogen, and infection caused by multidrug-resistant *A baumannii* (MDR-AB) is currently considered the most difficult to control.[1-3] Several studies have reported variable degrees of success in controlling MDR-AB using such interventions as promotion of hand hygiene, isolation and contact precautions, environmental cleaning, targeted active surveillance, and temporary unit closures.[1,3,4] The Korean Nosocomial Infection Surveillance System data identified *A baumannii* as an increasing cause of nosocomial infections in intensive care units (ICUs), accounting for 32% of gram-negative bacilli infections in 2011.[5] Moreover, the incidence of carbapenem-resistant *A baumannii* (CRAB) increased from 1% in 1997 to 51% in 2009.

Although controlling the transmission of CRAB is a high priority for tertiary care hospitals, there is little information available about CRAB control measures in Korea.[2] In this study, we evaluated the long-term effects of infection control interventions on the incidence of CRAB and the association between CRAB isolation and the consumption of different antimicrobials.

METHODS

Gyeongsang National University Hospital, an 890-bed teaching hospital located in Jinju, Republic of Korea, has a 19-bed medical ICU, a 14-bed surgical ICU, and 4 cohort rooms (16 beds) on general

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wards for isolating patients with multidrug-resistant organisms (MDROs). Owing to an increase in the incidence of CRAB infection or colonization since 2007, various infection control programs were introduced sequentially or simultaneously according to clinical necessity. To assess the effect of these intervention programs, we analyzed 2 time periods retrospectively: period 1, from July 2007 to June 2009, and period 2, from July 2009 to December 2012.

Infection control measures

During period 1, multifaceted infection control programs were implemented. All patients with a culture positive for CRAB were managed with contact precautions and isolation in single or cohort rooms, whenever possible. Entry into the rooms of patients with a CRAB-positive culture was permitted only after white coats were removed and disposable gloves and gowns were donned. Hand hygiene using alcohol-based hand gel (ABHG) was promoted, and environmental cleaning of the cohort areas was performed daily using a sodium dichloroisocyanurate (NaDCC)- containing solution. All patients admitted to the ICUs were screened for CRAB via nasal swabs within 24 h of admission and weekly thereafter if CRAB was identified.

During period 2, the following infection control measures were added to the baseline protocol owing to an increase in CRAB infection or colonization. Onsite education was conducted biweekly by the infection control team after July 2009. Starting in July 2010, we monitored and promoted infection control measures to prepare for hospital accreditation by the Ministry of Health and Welfare, which occurred on April 26, 2011. The accreditation program assessed the essential activities of infection control and demanded >80% compliance with hand hygiene in clinical practice.

Microbiological studies

Swab specimens from each patient were obtained from both anterior nares using sterile transport swabs (Copan Diagnostics, Murrieta, CA). Specimens were immediately cultured on 5% sheep's blood agar plates and incubated overnight in air at 37°C. All clinical and surveillance samples underwent species identification and antibiotic susceptibility testing using the Vitek-2 system (bioMérieux, Durham, NC). Susceptibility results were interpreted according to the Clinical and Laboratory Standards Institute guidelines.[6] Microorganisms were defined as CRAB if *A baumannii* with a minimum inhibitory concentration of >4 μg/mL for imipenem or meropenem was identified.

Data collection and analysis

The epidemiologic and clinical data of all patients from whom CRAB was isolated were reviewed between 2007 and 2012. The nosocomial incidence density of CRAB was defined as the number of patients newly infected or colonized with CRAB more than 48 hours after admission per 1000 patient-days (PD). Multiple positive samples from the same patient were counted as a single episode. The nosocomial incidence density of extended-spectrum β-lactamase–producing *Escherichia coli* and *Klebsiella pneumoniae* (ESBL-EK) was used as a control to evaluate the impact of the infection control programs, because patients affected with ESBL-EK were managed only with standard precautions.[7] ABHG consumption was calculated as liters per 1000 PD and used as a surrogate marker for hand hygiene compliance.

Antimicrobial consumption was calculated as the defined daily dose (DDD) per 1000 PD following the recommendations of the World Health Organization.[8] The 6 classes of antimicrobial agents analyzed in this study were antipseudomonal penicillins (piperacillin), β-lactam/β-lactamase inhibitor combinations (piperacillin-tazobactam, ticarcillin-clavulanate, and cefoperazone-sulbactam), extended-spectrum cephalosporins (cefotaxime, ceftriaxone, ceftazidime, and cefepime), carbapenems (imipenem and meropenem), fluoroquinolones (ciprofloxacin and levofloxacin), and aminoglycosides (gentamicin, amikacin, and tobramycin). Total antimicrobial consumption was determined based on the sum of the aforementioned broad-spectrum antimicrobials.

The χ^2 test for trend was used to examine the rates of CRAB, ESBL-EK, and ABHG consumption during the study period. Segmented regression analysis was used to examine significant changes in the level and trend of the incidence density of infection or colonization by CRAB and ESBL-EK. The Spearman rank-correlation test was used to determine the association between ABHG or antimicrobial consumption and the incidence density of CRAB. All tests were 2-tailed, and a P value $<.05$ was considered to indicate statistical significance. Analyses were performed using SPSS version 21 (IBM, Armonk, NY). This study was approved by the Institutional Review Board of Gyeongsang National University Hospital.

RESULTS

During the 6-year study period, a total of 1,658,999 patients were admitted, of whom 588 were positive for CRAB (0.35 CRAB-affected patients per 1000 admissions). Of these 588 patients, 530 (90%) had nosocomial acquisition of CRAB and were included in the present study. Of these 530 patients, 111 (21%) were diagnosed with true CRAB infection (ie, pneumonia, 76%; primary bacteremia, 10%; others, 14%). Of the 342 patients with CRAB-positive cultures in ICUs, 60 (18%) had a positive active surveillance culture. Of these 60 patients, 13 (22%) were detected only by surveillance culture, and 47 were detected by both surveillance and clinical cultures.

The nosocomial incidence density of CRAB increased from 0.35 per 1000 PD in 2007 to 0.46 per 1000 PD in 2010 ($P=.096$), but then decreased to 0.06 per 1000 PD in 2012 ($P<.001$). The nosocomial incidence density of ESBL-EK increased gradually from 0.59 per 1000 PD in 2007 to 1.00 per 1000 PD in 2012 ($P<.001$) (Fig 1). Using segmented regression analysis, we found a significant change in the trend (-0.013; $P=.011$) and level (0.340; $P=.001$) of the monthly incidence density of CRAB between periods 1 and 2; however, we found no significant change in the trend (-0.004; $P=.451$) or level (-0.157; $P=.166$) of the monthly incidence density of ESBL-EK between periods 1 and 2.

ABHG consumption increased gradually from 2007 to 2012, with the following usage reported per 1000 PD: 5.6 L in 2007, 5.5 L in 2008, 9.6 L in 2009, 7.5 L in 2010, 11.2 L in 2011, and 11.9 L in 2012 ($P<.001$). ABHG consumption was not significantly correlated with the decreased incidence density of CRAB ($r=-0.310$; $P=.141$) (Fig 1).

The consumption pattern of antimicrobial is shown in Figure 2. The DDD per 1000 PD of total antimicrobials, β-lactam/β-lactamase inhibitor combinations, extended-spectrum cephalosporins, quinolones, and carbapenems increased from 2007 to 2009. In contrast, the DDD per 1000 PD of total antimicrobials, β-lactam/β-lactamase inhibitor combinations, carbapenems, and aminoglycosides decreased from 2010 to 2012. The consumption of total antimicrobials ($r=0.722$; $P<.001$) and carbapenems ($r=0.530$; $P=.008$) was significantly associated with the incidence density of CRAB.

DISCUSSION

This study analyzed factors contributing to the decreased incidence density of nosocomial CRAB infection or colonization over a 6-year study period. The introduction of onsite education for infection control programs and promotion of hand hygiene during the preparation for hospital accreditation appear to have been

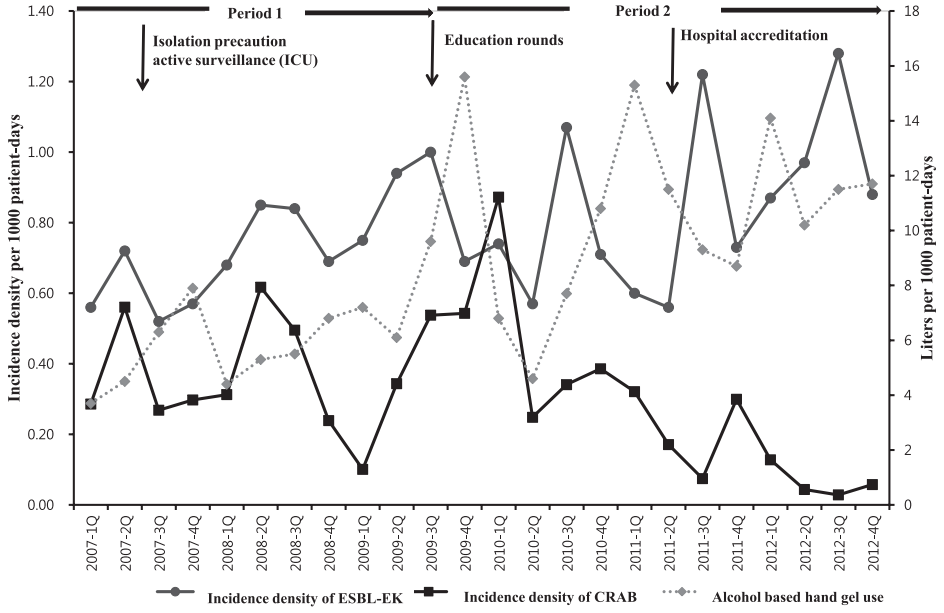

Fig 1. Trends in nosocomial incidence density of CRAB and ESBL-EK per 1000 PD and in ABHG consumption in liters per 1000 PD from 2007 to 2012.

effective in controlling CRAB infection and colonization in our hospital.

The isolation precautions and active surveillance cultures for CRAB in the ICUs were ineffective in controlling CRAB infection and colonization during period 1. Active surveillance culture allows the early detection of patients with MDROs at hospital admission or during hospitalization to apply contact precautions and reduce person-to-person transmission.[9] In contrast to other MDROs, the appropriate surveillance sampling method for MDR-AB has not yet been determined.[9] A study that reported low (~55%) MDR-AB surveillance culture sensitivity even when cultures were obtained from 6 sites recommended obtaining cultures from multiple sites for MDR-AB detection.[10] Because sampling of multiple sites is costly and increases the workload, nasal swabs were used for CRAB active screening cultures in our hospital, which may be inappropriate for detecting CRAB carriers. Nonetheless, the findings of the present study are in line with previous studies that found a lack of effect from active surveillance cultures for CRAB.[11,12] In addition, compliance with the infection control interventions in the present study might have been suboptimal during period 1. After a brief lag, there was a significant decrease in the incidence density of CRAB during period 2. We assumed that the hand hygiene campaign instituted in advance of the hospital accreditation program during period 2 greatly enhanced compliance, which led to a twofold increase in ABHG consumption.

Although data on the efficacy of our infection control interventions are mixed, and the impact of our hospital's accreditation on infection control remains to be determined, the findings of the present study suggest that the educational intervention and hospital accreditation process may have influenced adherence to infection control measures, especially hand hygiene.[13,14] Our data support the findings of a survey of Japanese hospitals that identified a significant association between infection control performance scores and hospital accreditation status.[15]

Regardless of hand hygiene compliance, we assumed that the cohorting of patients colonized or infected with CRAB in the present study still had a significant impact on reducing the transmission of CRAB. Because the occupancy of cohort rooms by CRAB-isolated patients was not being monitored, the incidence density of

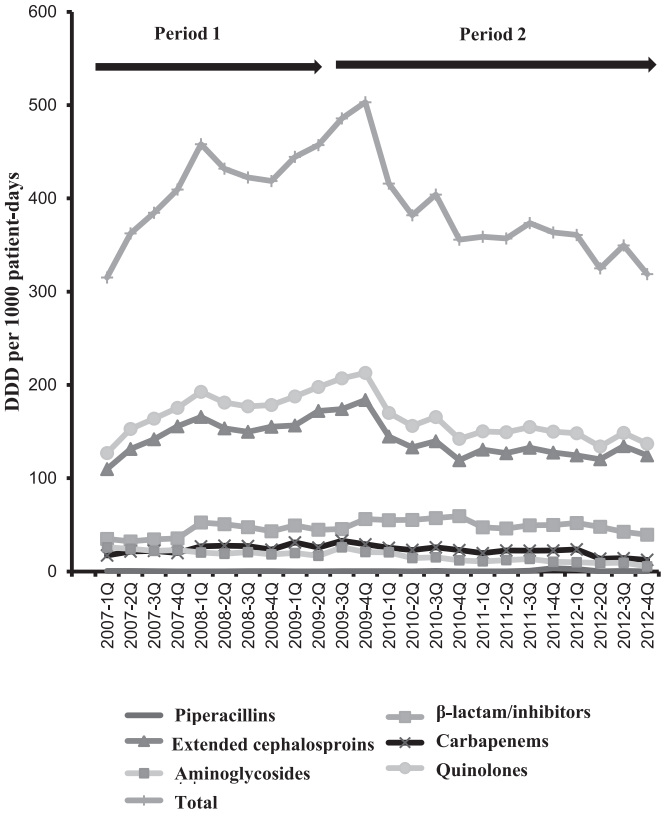

Fig 2. Consumption of antimicrobials during the study period. Data are presented as DDD per 1000 PD.

ESBL-EK served as a control to evaluate the impact of isolation precautions on infection control measures, similar to a study by Cheng et al.[7] Despite the increased ABHG consumption following onsite education and hand hygiene promotion during period 2, the nosocomial incidence density of ESBL-EK increased slightly, in contrast to that of CRAB. Although we were unable to determine the

proportion of reduced CRAB incidence density attributable to decreased patient-to-patient transmission, we propose that cohorting improved compliance with infection control measures including hand hygiene, which is consistent with previous studies demonstrating the efficacy of isolation precautions for patients with CRAB infection or colonization.[4,15,16] There may be other reasons for the increasing incidence density of ESBL-EK, however. Active screening for ESBL-EK was not performed, and the proportion of patients already colonized with ESBL-EK at the time of hospital admission might have affected the nosocomial incidence density of ESBL-EK.[7] In addition, Harris et al[17] determined by pulsed-field gel electrophoresis that only 3 of 23 patients (13%) who acquired ESBL-producing *E coli* in the ICU acquired the bacteria through patient-to-patient transmission, suggesting that patient-to-patient transmission is not a common method of acquisition of ESBL-producing *E coli*.

Despite the lack of specific antimicrobial control measures in place during the study period, the consumption of total antimicrobials and carbapenems decreased after 2010. Although we were unable to evaluate the causal relationship between antimicrobial consumption and the incidence density of CRAB, our findings suggest that the reduction in CRAB rates was related to the level of antimicrobial consumption, consistent with previous reports.[1,2,18] The proportion of antibiotic resistance attributable to antibiotic use versus patient-to-patient transmission could not be determined in the present study, however.

This study has several limitations. The individual effect of each intervention was not evaluated, because several interventions were introduced simultaneously or sequentially. Compliance with the various interventions during the study period could not be verified, owing to the retrospective study design. Molecular typing of the CRAB isolates was not performed, and thus the role of patient-to-patient transmission in the acquisition of CRAB could not be determined.

In conclusion, the present study suggests that adherence to infection control protocols by onsite education, hand hygiene campaign, and the judicious use of carbapenem may be important in decreasing the nosocomial incidence density of CRAB.

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