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ORIGINAL ARTICLE

Effects of implementation of an online comprehensive antimicrobial-stewardship program in ICUs: A longitudinal study

I-Ling Chen [a,b], Chen-Hsiang Lee [b,c,d,*], Li-Hsiang Su [b], Yu-Chin Lily Wang [a], Jien-Wei Liu [b,c,d]

[a] *Department of Pharmacy, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan*
[b] *Infection Control Team, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan*
[c] *Division of Infectious Diseases, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan*
[d] *Chang Gung University College of Medicine, Kaohsiung, Taiwan*

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Abstract *Background/purpose:* The long-term effects of antimicrobial-stewardship programs in the intensive care units (ICUs) have not been adequately examined. We evaluated the impact of an online comprehensive antimicrobial stewardship program (OCASP) on the outcomes of patients in 200-bed medical/surgical ICUs over the course of 11 years.
Methods: We analyzed the records of adult patients admitted to ICUs during the 5 years before (n = 27,499) and the 6 years after (n = 33,834) implementation of an OCASP. Antimicrobial consumption, expenditures, duration of treatment, incidence of healthcare-associated infections (HAIs), prevalence of HAIs caused by antimicrobial-resistant strains, and crude or sepsis-related mortality of patients were analyzed. Segmented regression analyses of interrupted time series were used to assess the significance of changes in antimicrobial use.
Results: Compared to the patients in the pre-OCASP period, the patients in the post-OCASP period were older, had greater disease severity, longer ICU stays, and were more likely to receive antimicrobials, but had lower antimicrobial expenditures and crude and sepsis-related mortality. The trend of overall antimicrobial use [slope of defined daily dose/1000 patient-days vs. time) increased significantly before OCASP implementation ($p < 0.001$), but decreased significantly after implementation ($p < 0.01$). The administration duration of all classes of antibiotics were significantly shorter ($p < 0.001$) and the incidences of HAIs were significantly lower ($p < 0.001$) after implementation. However, there was an increase in the proportion of HAIs caused by carbapenem-resistant *Acinetobacter baumannii* relative to all *A. baumannii* infections.

* Corresponding author. Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, 123 Ta-Pei Road, Niao Sung District, Kaohsiung 833, Taiwan.
E-mail address: lee900@cgmh.org.tw (C.-H. Lee).

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Conclusion: Implementation of an OCASP in the ICUs reduced antimicrobial consumption and expenditures, but did not compromise healthcare quality.

Introduction

The problem of increasing antimicrobial resistance is especially critical for patients in the intensive care unit (ICU), because they are more susceptible to healthcare-associated infections (HAIs).[1,2] Antibiotic resistance may be particularly severe in ICUs, because the patients are critically ill and often severely immunocompromised, have undergone medical or surgical procedures or instrumentation, or receive multiple antimicrobials conferring selection pressure of antimicrobial-resistant pathogens. Furthermore, effective infection-control programs may not be in place.[3] Previous research indicated that ICU patients are five to 10 times more likely to acquire HAIs than patients in general wards.[4] Moreover, HAIs caused by antimicrobial-resistant isolates are associated with increases of medical costs, prolongation of ICU stays, and greater morbidity and mortality.[5] Several approaches may potentially reduce antimicrobial resistance. For example, use of shorter courses of broad-spectrum antimicrobials may reduce selection pressure on bacterial flora and prevent the emergence of resistance.[6] In general, antimicrobial-stewardship programs may help combat the emergence of antimicrobial resistance, improve clinical outcomes, and reduce medical costs by limiting the inappropriate use of antimicrobials.[7,8]

Previous research indicated that 30—50% of antimicrobial use in hospitals is unnecessary or inappropriate[9] and that, among all hospital departments, ICUs have the greatest use of antimicrobials.[1] Therefore, antimicrobial stewardship is particularly important for ICU settings. Previous research examining the impact of antimicrobial stewardship in ICUs indicated that changes in antimicrobial use were associated with decreased antimicrobial resistance.[3,8,10] While implementation of an antibiotic stewardship program requires considerable human resources, especially in large institutions, the increased computerization of hospitals in recent years provided new opportunities for development of such programs. A recent study in a large hospital setting examined the impacts of an online, comprehensive, facility-wide antimicrobial-control system on healthcare quality and economic burden.[11] However, the long-term effects of computerized programs for implementation of antimicrobial review in ICU patients have not been adequately explored.

This longitudinal study reported the results of an online, comprehensive, antimicrobial-stewardship program (OCASP) implemented in 2005 that was developed to guide the use of antimicrobial agents in the ICUs of a 2700-bed medical center in southern Taiwan. The specific objectives were to examine the long-term effects of OCASP on antimicrobial use and expenditures, duration of antimicrobial treatment, incidence of HAIs, prevalence of HAIs caused by antimicrobial-resistant pathogens, and outcomes of patients admitted to the ICUs.

Methods

Study design and setting

The Kaohsiung Chung Gang Memorial Hospital (KSCGMH) is a medical center in southern Taiwan, with 2700 beds, 43 non-critical wards, and 18 ICUs that included nine medical and six surgical ICUs (a total of 200 beds) for adults. This retrospective study was conducted with a waiver of the need for informed consent of participants, and was approved by the Institutional Review Board (Ethics Committee) of Chang Gung Memorial Hospital, Kaohsiung, Taiwan (Document no. 97-1694B).

All data for patients aged 18 years or older who were admitted to any medical or surgical ICU from January 2000 to December 2010 were retrospectively reviewed. The data included age, sex, duration of ICU stay, use of parenteral antimicrobials, and duration of antimicrobial treatment. Disease severity was evaluated by Acute Physiology and Chronic Health Evaluation (APACHE) II score[12] or Glasgow Coma Scale (GCS)[13] upon ICU admission. All patients readmitted to an ICU after discharge were classified as new patients.

OCASP in ICUs

The OCASP was implemented in the ICUs of the KSCGMH in January 2005, wherein all antimicrobial agents prescribed to ICU patients required approval from infectious diseases (ID) physicians. The OCASP is built into the Health Information System and is linked to comprehensive electronic medical records. All inpatient settings were allocated and preassigned to 10 ID physicians practicing in the hospital. Each ID physician was notified when the antimicrobial was prescribed to patients admitted to his or her preassigned ICU or ward. All of the above information was entered into OCASP automatically, and a remind message was sent to the ID physician by mobile phone if the prescription was not reviewed within 48 hours. The prescribing physicians were required to provide necessary supporting clinical data that included clinical history, laboratory reports, culture results, and images for online review by the ID physicians. After review, the ID physicians would briefly discuss the case with the intensivists prior to rendering a decision. If a prescription was disapproved, the antimicrobial would be discontinued by the pharmacy unit-dose delivery system within 48 hours, and the prescriber would be immediately notified to modify the regimen. When necessary, the ID

physicians could suggest a formal consultation if on-site patient evaluation was deemed necessary.

Measures of antimicrobial use, duration, and costs

The parenteral antimicrobials listed in the electronic database of the hospital pharmacy were: carbapenems group 1 (ertapenem), carbapenems group 2 (imipenem and meropenem), non-extended-spectrum cephalosporins (cefazolin, cefuroxime), extended-spectrum cephalosporins (ceftriaxone, flomoxef, ceftazidime, cefpirome, and cefepime), natural penicillin (penicillin G), aminopenicillins (ampicillin and amoxicillin), antipseudomonal penicillins (piperacillin and piperacillin-tazobactam), aminopenicillins/β-lactamase inhibitor (amoxicillin/clavulanate and ampicillin/sulbactam), aminoglycosides (gentamicin and amikacin), fluoroquinolones (ciprofloxacin, levofloxacin, and moxifloxacin), glycopeptides (vancomycin and teicoplanin), other antibacterial agents (colistin, tigecycline, linezolid, daptomycin), and antifungal agents (caspofungin, micafungin, voriconazole, and fluconazole). Among these antimicrobial agents, ertapenem, levofloxacin, piperacillin-tazobactam, colistin, tigecycline, linezolid, daptomycin, and micafungin were introduced to the KSCGMH during the period following OCASP implementation. The other antimicrobial and antifungal agents were available both before and after OCASP implementation. Consumption of each antimicrobial was expressed as the defined daily dose (DDD) per 1000 inpatient days for each prescribed antibiotic and the semester categorized prescription to which the antibiotic belonged.[14,15] The duration of antibiotic administration was defined by the start and stop dates. The costs of antimicrobial agents were not standardized, because they changed significantly during the 11-year study period. Expenditures were summed to calculate the total cost of antimicrobials and/or pharmaceuticals. The expenditures of consumed antimicrobials were calculated as a percentage of all pharmaceuticals used during the ICU stay of the patient.

HAIs and the prevalence of HAIs caused by antimicrobial resistance

HAIs, defined as infections that were not present and for which there was no evidence of prior incubation at the time of admission, were identified based on Centers of Disease Control diagnostic criteria for nosocomial infections.[16]

There were no changes in microbiological laboratory techniques during the 11-year study period. All isolated microorganisms were identified using standard biochemical tests and were verified by a Vitek System (bioMérieux, Marcy-l'Etoile, France). Susceptibility testing was performed following the guidelines of the Clinical Laboratory Standards Institute (CLSI) for susceptibility testing, and the results were interpreted according to the CLSI at the time of the tests.[17] Isolates with intermediate susceptibility were considered resistant. The resistance of each antimicrobial agent was calculated as the number of antimicrobial-resistant isolates divided by the total number of tested pathogens. The prevalence of HAIs caused by antimicrobial-resistant strains included carbapenem (represented by imipenem)-resistant *Acinetobacter baumannii* (CRAB) and carbapenem (represented by imipenem)-resistant *Pseudomonas aeruginosa* (CRPA).

End-point measurements

There were several end-points in this study. First, the total consumption, expenditures, and durations of antimicrobial use before and after OCASP implementation were compared. Second, the incidence of HAIs and prevalence of HAIs caused by antimicrobial-resistant pathogens during ICU stays was assessed. Finally, the ICU readmission rate was calculated as the number of patients who were readmitted to ICUs within 48 hours of discharge divided by the number of patients who were discharged from ICUs. The crude mortality was defined as the all-cause mortality occurring during ICU stay. Sepsis-related mortality was defined as death of a patient occurring within 14 days after the onset of the sepsis, with a clinical course suggestive of persistently active infection without other obvious explanation.

Statistical analysis

Patient characteristics, expenditures for antimicrobials, durations of antimicrobial treatments, and biannual HAI-incidence rates before (from 1 January 2000 to 31 December 2004) and after (from 1 January 2005 to 31 December 2010) OCASP implementation were compared. Categorical and continuous data are presented as a number (percentage) and as a mean [95% confidence interval (CI)] or median (inter-quartile range), respectively. Categorical variables were compared with the Chi square test or the Fisher's exact test. Quantitative continuous variables were compared using the *t* test or the Mann—Whitney *U* test for normally and non-normally distributed variables, respectively. For multiple comparisons, *p*-values were calculated by applying a Bonferroni correction. A segmented regression analysis of interrupted time series was used to assess changes in antimicrobial consumption before and after OCASP implementation. Autocorrelation must be considered in order to avoid bias in these estimates. In this study, autocorrelation was measured using a Durbin-Watson test, where values between 1.5 and 2.5 indicated no serial correlation. We used a segmented linear regression model with least squares fitting to estimate biannual antimicrobial consumption in ICU patients:

$$Y_t = \beta_0 + \beta_1 \times \text{time}_t + \beta_2 \times \text{policy}_t + \beta_3 \times \text{time after}_t + \varepsilon_t, \quad (1)$$

where β_0 was the mean baseline level of antimicrobial use during the pre-OCASP period, β_1 was the change in antimicrobial use during the pre-OCASP period, β_2 was the mean antimicrobial use after OCASP implementation, β_3 was the change in antimicrobial use after OCASP implementation, and ε_t represented an error term describing random variability not explained by the model.[18] All statistical analyses were performed using SAS software version 9.3 for Windows (SAS Institute Inc., Cary, NC, USA).

Results

Study population

There were 27,499 admissions before and 33,834 admissions after OCASP implementation. Comparison of these groups indicated that patients during the post-OCASP period were older, had longer ICU stays, and were more likely to have severe disease and receive antimicrobials (Table 1).

Antimicrobial consumption, treatment duration, and expenditure

The numbers of ID physician disagreements with the treating clinicians consisted of 2059 cases (35.2%) in 2005, 2123 cases (32.4%) in 2006, 2446 cases (30.6%) in 2007, 2739 cases (27.4%) in 2008, 2880 cases (28.5%) in 2009, and 3056 cases (29.8%) in 2010 (Figure 1). We analyzed the changes in antimicrobial use (DDD) over time using segmental linear regression of interrupted time series. The overall antimicrobial use (slope of DDD/1000 patient-days vs. time) increased significantly before OCASP implementation ($p < 0.001$), but decreased significantly after implementation ($p < 0.01$). We performed the same analysis for individual classes of antimicrobials (Table 2). Consumption of extended-spectrum cephalosporins, glycopeptides, carbapenem group 2, and aminopenicillins/β-lactamase inhibitors increased significantly before OCASP implementation ($p < 0.001$ for all), but decreased significantly after implementation ($p < 0.05$ for all). Consumption of antifungal agents increased significantly before OCASP implementation ($p = 0.04$), but did not change significantly after implementation ($p = 0.42$). Consumption of antipseudomonal penicillins did not change significantly before OCASP implementation ($p = 0.33$), but increased significantly after implementation ($p < 0.01$). Consumption of nonextended-spectrum cephalosporins ($p = 0.04$) and aminoglycosides ($p < 0.001$) decreased significantly before OCASP implementation, but did not change significantly after implementation. The consumption trend of fluoroquinolones and natural penicillin/aminopenicillins did not change significantly during either period. Comparison of the intercepts of the time series indicated positive values for overall antimicrobial use and for each class of antimicrobial and antifungal agents before OCASP implementation ($p < 0.05$ for all; Table 2). After OCASP implementation, most of the individual drug classes exhibited no significant changes in the intercepts; however, there were significant decreases in the intercepts associated with antifungal agents ($p = 0.02$), natural penicillin/aminopenicillins ($p = 0.02$), antipseudomonal penicillins ($p < 0.01$), and glycopeptides ($p < 0.001$), but there was a significant increase in the intercept associated with aminopenicillins/β-lactamase inhibitors ($p < 0.01$).

We also analyzed the effect of the OCASP on the duration of antimicrobial administration (Table 3). Analysis of the individual drug classes of antimicrobials indicated that all classes of antimicrobial-treatment durations were significantly shorter ($p < 0.001$) after OCASP implementation, except that the treatment duration of antifungal agents did not differ between the two time periods ($p = 0.05$). The antimicrobial expenditures as a percentage of all pharmaceuticals [mean (95% CI)] were significantly less after OCASP

Table 1 Patient demographics, antibiotic expenditures, and clinical outcomes before and after OCASP implementation.

	Before OCASP implementation (n = 27,499)	After OCASP implementation (n = 33,834)	p*
Age, y	60.8 (60.6–61.0)	62.0 (61.8–62.2)	< 0.001
Gender, female/male	10,626/16,873	12,955/20,879	0.37
Length of intensive care units stay, d	4 (2–10)	5 (2–11)	< 0.001
ICU type			< 0.001
Medical	8830 (32)	11,924 (35)	
Combined medical-coronary	3269 (12)	3336 (10)	
Combined medical-surgical	15,400 (56)	18,575 (55)	
ICU re-admission rate	418 (1.5)	372 (1.1)	< 0.001
High disease severity[a], A/B (%)	8973/14,743 (60.9)	15,687/23,089 (67.9)	< 0.001
Patients with antibiotics prescriptions	15,099 (54.9)	20,366 (60.2)	< 0.001
The expenditures of antibiotics among all pharmaceuticals, %	49.0 (46.8–51.1)	42.7 (41.6–43.8)	< 0.001
Incidence of healthcare-associated infections (events/1000 inpatient-days/6 months)[a]	15.1 (13.4–16.7)	11.0 (10.3–11.8)	<0.001
Sepsis-related mortality, C/D (%)	2977/15,099 (19.7)	3360/20,366 (16.5)	< 0.001
Crude mortality	5090 (18.5)	5037 (14.9)	< 0.001

[a] High disease severity is defined as patients with APACH II scores >15 or Glasgow Coma Scales <9.
Data are presented as n (%), or median (inter-quartile range), or mean (95% confidence interval).
*Because of the large patient sample, we defined statistical significance as $p < 0.001$.
A = number of patients; B = number of patients with available data; C = number of patients with sepsis-related mortality; D = number of patients with sepsis; ICU = intensive care unit; OCASP = online comprehensive antimicrobial stewardship program.

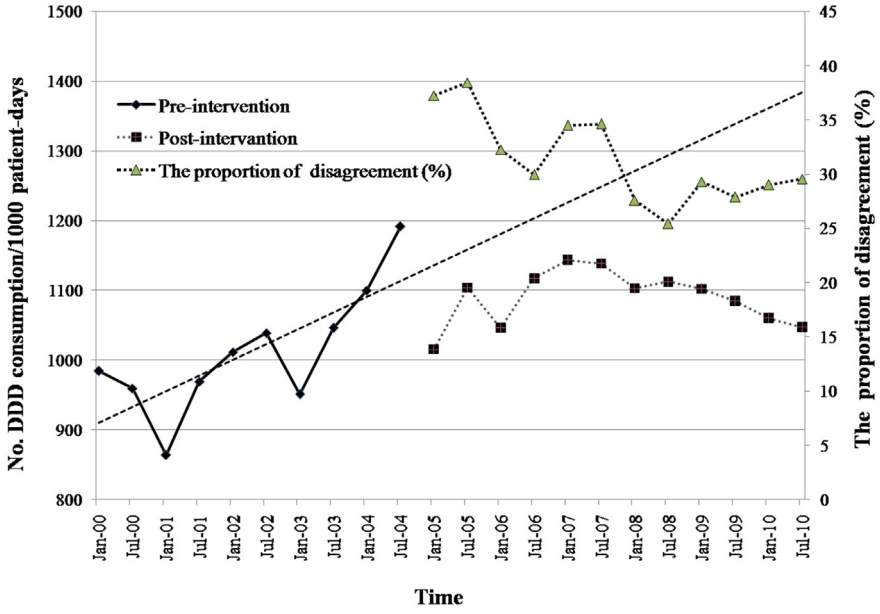

Figure 1. The main coordinate: overall use of antimicrobials (DDDs/1000 patient-days/6 months) before and after OCASP implementation. The second coordinate: the proportion of disagreement percentage (%) after OCASP implementation. DDD = defined daily dosage; OCASP = online comprehensive antimicrobial stewardship program.

implementation [49.0 (46.8–51.1)% vs. 42.7 (41.6–43.8)%, $p < 0.001$; Table 1].

Quality indicators

The ICU re-admission rate and incidence of HAIs in the ICUs were significantly lower after OCASP implementation ($p < 0.001$; Table 1). The crude mortality rate (18.5% vs. 14.9%; $p < 0.001$) and sepsis-related mortality rate (19.7% vs. 16.5%; $p < 0.001$) were both significantly reduced after OCASP implementation (Table 1). However, after implementation, there was an increase in the proportion of HAIs caused by CRAB relative to all *A. baumannii* (CRABpAB) and a decrease in the proportion of HAIs caused by CRPA relative to all *P. aeruginosa* (CRPApPA; Figure 2). Specifically, the percentage of CRABpAB infections was 0% in the first half of 2000, 72.7% in the second half of 2007, and 61.5% in the second half of 2010. The percentage of CRPApPA infections was 10.3% in the first half of 2000, 38.9% in the first half of 2004, and 25.9% in the second half of 2010.

Discussion

Appropriate and judicious antimicrobial use guided by an OCASP can be associated with significant benefits by reducing antimicrobial consumption and expenditure while not compromising healthcare quality in ICU settings. Recent epidemiological data indicate an increasing frequency and awareness of HAIs by antimicrobial-resistant pathogens, especially in ICUs,[1,2,19] that significantly impact clinical outcomes and economic expenditures.[5,20] Antimicrobial-stewardship programs employ diverse interventions to improve the selection of appropriate antimicrobial agents, dosing, and duration of therapy, and simultaneously seek to improve clinical outcomes and limit the emergence of antimicrobial resistance of pathogenic organisms, adverse drug events, and other negative consequences.[21] In a systematic review of the effectiveness of antimicrobial stewardship in ICUs, Kaki et al[8] suggested that most stewardship interventions were associated with a temporal decrease in either targeted or overall antibiotic use in critically ill patients. However, restricting the use of certain antimicrobial classes may be associated with a compensatory increase in the use of unrestricted antimicrobials, a phenomenon called "squeezing the balloon".[22] Furthermore, previous studies of antimicrobial-stewardship programs did not provide details about their effects on the incidence of HAIs, length of ICU stays, or mortality, and few studies demonstrated the long-term effectiveness of such programs.[8] To our knowledge, this study is the first to demonstrate that long-term implementation of an OCASP at a large institution significantly reduced antimicrobial use and expenditures without having adverse effects on healthcare quality. The increasing duration of ICU stays in our post-implementation period may be explained by the greater number of patients with more severe illnesses during this period. The increases in the intercept of consumption of aminopenicillins/β-lactamase inhibitors (amoxicillin/clavulanate and ampicillin/sulbactam), but decreases in the trend of consumption of aminopenicillins/β-lactamase inhibitors after OCASP implementation were probably due to OCASP-related de-escalation of empiric broad-spectrum antimicrobials to narrow-spectrum antimicrobials, such as aminopenicillins/β-lactamase inhibitors and use of ampicillin/sulbactam for CRAB infection, that reduced the subsequent consumption of this class of antimicrobials. Therefore, the most striking changes in trends after implementation of our OCASP were the reduced consumption of broad-spectrum antimicrobials. The increasing trend of consumption of antipseudomonal penicillins after OCASP

Table 2 Trends in the use of antibiotics (DDD/1,000 patients days/6 months) before and after OCASP implementation.

	Significant parameters of segmented regression analysis, coefficient size, & direction of effect (95% CI)								R^2	DW
	Before OCASP implementation				After OCASP implementation					
	Intercept	p*	Slope	p*	Change in intercept	p*	Change in slope	p*		
Non-extended-spectrum cephalosporins	214.6 (199.2~230.1)	< 0.001	−2.62 (−5.1~−0.1)	0.04	−5.7 (−25.0~13.5)	0.54	−2.3 (−5.4~0.8)	0.14	0.89	2.0
Aminoglycosides	205.1 (194.0~215.1)	< 0.001	−10.2 (−11.9~−8.6)	< 0.001	−0.1 (−12.9~12.7)	0.98	3.8 (−1.8~5.9)	0.18	0.98	2.2
Extended-spectrum cephalosporins	88.1 (57.5~114.6)	< 0.001	11.7 (7.1~16.3)	< 0.001	3.19 (−32.6~38.73)	0.85	−59.5 (−15.3~−3.73)	0.03	0.82	1.7
Fluoroquinolones	27.6 (13.8~41.4)	< 0.001	2.1 (−0.1~4.3)	0.06	6.4 (−10.8~23.6)	0.44	1.4 (−1.4~4.2)	0.30	0.83	1.6
Glycopeptides	32.1 (19.9~44.3)	< 0.001	9.6 (7.7~11.6)	< 0.001	−31.5 (−46.6~−16.3)	< 0.001	−6.2 (−8.7~−3.8)	< 0.001	0.92	1.6
Natural penicillin/ aminopenicillins	124.0 (109.4~139.2)	< 0.001	0.6 (−1.8~3.0)	0.6	−22.5 (−41.1~−3.9)	0.02	−6.3 (−9.3~3.2)	0.16	0.90	1.8
Antipseudomonal penicillins	52.1 (43.4~60.8)	< 0.001	−0.67 (−2.07~0.73)	0.33	−14.6 (−25.5~3.76)	0.01	3.3 (1.6~5.1)	< 0.01	0.55	1.6
Carbapenem group 2	17.2 (4.2~30.2)	0.01	8.7 (6.7~10.9)	< 0.001	−9.2 (−25.4~7.1)	0.25	−7.5 (−10.1~−4.8)	< 0.001	0.90	1.7
Aminopenicillins/ β-lactamase inhibitors	29.1 (4.4~53.8)	0.02	7.9 (3.9~11.9)	< 0.001	44.8 (14.0~75.6)	< 0.01	−11.3 (−16.3~−6.3)	< 0.001	0.82	1.6
Antifungal agents	60.1 (49.3~70.8)	< 0.001	1.8 (0.1~3.5)	0.04	−16.2 (−29.6~−2.8)	0.02	−0.8 (−3.1~1.3)	0.42	0.29	1.7
Overall antimicrobials	949.1 (873.0~1024.1)	< 0.001	24.5 (12.3~36.7)	< 0.001	−39.3 (−133.5~54.8)	0.40	−23.5 (−38.8~−8.2)	< 0.01	0.60	1.8

* The p-values represent comparisons in the time periods before or after implementation of the OCASP program, with $p < 0.05$ representing statistical significance.
CI = confidence interval; DDD = defined daily dose; DW = Durbin-Watson test; OCASP = online comprehensive antimicrobial stewardship program.

Table 3 Treatment durations for different classes of antimicrobials before and after OCASP implementation.

	Before OCASP implementation	After OCASP implementation	p*
	Median (IQR, d)	Median (IQR, d)	
Aminoglycosides	3 (2–6)	3 (1–4)	< 0.001
Extended-spectrum cephalosporins	5 (2–10)	5 (2–8)	< 0.001
Fluoroquinolones	6 (2–10)	4 (2–8)	< 0.001
Glycopeptides	5 (2–10)	4 (2–8)	< 0.001
Natural penicillin/aminopenicillins	4 (2–7)	3 (1–6)	< 0.001
Antipseudomonal penicillins	5 (2–9)	4 (2–8)	< 0.001
Carbapenem groups 1 and 2	7 (3–12)	5 (2–10)	< 0.001
Non-extended-spectrum cephalosporin	3 (2–5)	3 (1–4)	< 0.001
Aminopenicillins/β-lactamase inhibitors	4 (2–8)	4 (2–7)	< 0.001
Antifungal agents	6 (3–11)	6 (3–11)	0.05

* The p values were estimated following multiple comparisons and were corrected by Bonferroni correction; $p < 0.005$ was considered significant.
IQR = inter-quartile range; OCASP = online comprehensive antimicrobial stewardship program.

implementation was possibly due to piperacillin-tazobactam being introduced in our intuition during the post-implementation period.

Our results indicated that the duration of individual classes of antimicrobial use decreased during the post-implementation period (Table 3). Specifically, the duration of broad-spectrum antimicrobial use [extended-spectrum cephalosporins, fluoroquinolones, antipseudomonal penicillins, and carbapenems (Groups 1 and 2)] was shorter during the post-implementation period, even though the patients were more likely to have severe disease during this period. After implementation of our OCASP, intensivists prescribed shorter courses of broad-spectrum antimicrobial treatment and/or de-escalated use of empirical broad-spectrum antimicrobials.

One end-point of our study involved estimation of OCASP impact on healthcare quality. Lowering ICU mortality requires optimization of ICU-service organization. Intensivists adopted the surviving ICU campaign in 2009 in response to the "international guidelines for management of severe sepsis and septic shock".[23] Infection-control nurses dedicated to the hand-hygiene program, care bundle, monitoring, and inspection of patients infected with resistant pathogens also contributed greatly to reducing the HAI rate. Pharmacists periodically monitored the consumption and expenditure of antimicrobial agents among different departments. Clinical microbiologists provided prompt data on organism identification and pathogen-susceptibility patterns. Treating clinicians can still preserve prescriber autonomy and provide opportunities for education and collaboration through audit and feedback to optimize the use of antimicrobials. As a result, the proportions of ID physician disagreement with the treating clinicians decreased over the 6 months following OCASP implementation (Figure 1). We believe that multidisciplinary teamwork along with OCASP implementation was the key to

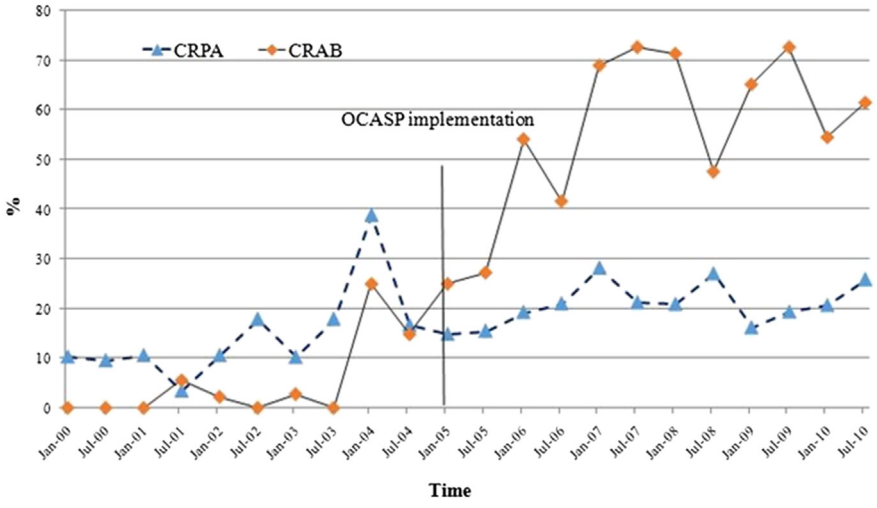

Figure 2. Percentage of HAIs caused by CRAB relative to all AB and by CRPA relative to all PA before and after OCASP implementation. AB = *Acinetobacter baumannii*; CRAB = carbapenem-resistant *Acinetobacter baumannii*; CRPA = carbapenem-resistant *Pseudomonas aeruginosa*; HAI = healthcare-associated infection; OCASP = online comprehensive antimicrobial stewardship program; PA = *Pseudomonas aeruginosa*.

the success of the ASP in terms of both process and outcome measurements. In this study, consumption and expenditure of antimicrobial agents in adult ICUs decreased after OCASP implementation without compromising healthcare quality.

Many factors other than antimicrobial-consumption patterns can potentially affect the number and resistance patterns of bacteria identified from clinical isolates. Despite the remarkable reduction in the use of antimicrobials after OCASP implementation, we noted a persistently high prevalence of CRAB and CRPA in our ICUs, despite the lack of increased CRAB or CRPA prevalence in any clinical wards or ICUs during the study period. It is possible that inappropriate carbapenem prescriptions might increase selection pressure for carbapenem-resistant bacteria.[24–26] The use and duration of carbapenem therapy in our ICU patients decreased during the post-implementation period, and, accordingly, the percentage of CRPApPA reached its peak during the pre-OCASP period, but decreased before OCASP implementation, with no increases in percentages after OCASP implementation (Figure 2). However, the percentage of CRABpAB increased throughout the entire study period. This might be because many of our patients were transferred from other healthcare institutions, which did not have antimicrobial-stewardship programs. Additionally, the global incidence of CRAB increased steadily during the 2000s,[27] and a recent longitudinal multicenter surveillance program in Taiwan indicated a significant increase in CRAB over the past 10 years.[28] The proportion of CRABpAB detection in ICU settings increased from $<$ 10% of infections in 2002 to $>$ 70% in 2010.[25] Given the commonality of risk factors for all drug-resistant microbes,[29] this supports the importance of implementation of an OCASP with strict infection-control measures to reduce the secondary spread of resistant organisms within ICUs.

A limitation of this study, as with other longitudinal uncontrolled studies that compare the effect of a newly introduced control measure, was that confounding factors may not have been adequately considered. There was no randomized allocation of stewardship intervention to different ICUs, and, therefore, we could not determine whether the changes observed were the consequences of or merely coincident with implementation of the OCASP. While randomization is not possible, bias can be minimized with the use of time-series analysis with multiple measurements during each time period as performed here. We could measure the inappropriateness of antimicrobial use, which was represented by the proportion of ID physician disagreements with the treating clinicians after OCASP implementation. Furthermore, we measured antimicrobial use and average duration of therapy. We did not consider the number of antimicrobial courses and did not focus on antimicrobials used to treat specific conditions, such as urinary tract infection or pneumonia. This limited our ability to comment on the appropriateness of the average antimicrobial treatment. Nevertheless, the duration of broad-spectrum antimicrobial use was shorter during the post-implementation period. Other interventions, such as improved hand hygiene and staff education,[30] may have confounded these results; however, these interventions were mainly instituted in our ICUs.

In summary, the results of this study indicated that OCASP provided a sustainable system for antimicrobial stewardship. In particular, the ICUs of a large medical facility indicated that an OCASP could effectively reduce the use of antimicrobials, lower antimicrobial expenditures, and shorten the duration of broad-spectrum antimicrobial therapy while exhibiting no detrimental effects on healthcare quality.

Conflicts of interest

All authors have no conflicts of interest to declare.

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