Impact of an Infectious Disease Specialist-Led Postprescription Carbapenem Intervention on Prescribing Behavior in a Japanese Tertiary Hospital: a Before-After Study

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Abstract

Background: There are a few infectious disease (ID) specialists in Japan. A solution to promote the implementation of antimicrobial stewardship activities under these resource-limited settings is required.

Methods: We compared carbapenem consumption between a 24-month baseline and 12-month intervention periods. During the intervention period, an ID specialist provided daily advises through a chart review and ID consultation service to prescribers against all prolonged carbapenem use (≥ 14 days). Additionally, we send an aggregated table containing the weekly point prevalence amount of each departmental carbapenem use for 7–13 and ≥ 14 days through e-mail to all doctors.

Results: Among the 1,241 carbapenem courses during the intervention period, the ID specialist provided a total of 96 instances of feedback regarding carbapenem use for ≥ 14 days, and the feedback acceptance rate was 76%. After the initiation of the intervention, the trend in monthly carbapenem consumption changed (coefficient: -0.62; 95% CI: -1.15 to -0.087, $p = 0.024$), and its consumption decreased (coefficient: -0.098; 95% CI: -0.16 to -0.039, $p = 0.002$) without an increase in the consumption of broad-spectrum antimicrobials or in-hospital mortality. Interestingly, the monthly number of carbapenem courses, but not the duration of carbapenem use, significantly decreased (coefficient: -3.02; 95% CI: -4.63 to -1.42, $p = 0.001$). The carbapenem-related annual estimated savings after the intervention was \$83,745, with a 22% cost reduction.

Conclusions: Our ID specialist-led daily intervention with weekly feedback regarding long-term carbapenem use was effective in reducing antimicrobial consumption. Such feedback may be useful in changing the prescribing behavior and promoting appropriate antimicrobial usage even in resource-limited settings.

Background

Antimicrobial resistance is a serious global health threat, and the annual antimicrobial resistance-related death is predicted to be 10 million people in 2050 [1]. Given this threatening substantial issue, reducing the use of inappropriate antimicrobials is an urgent task. In acute care hospital, approximately 20–50% of overall antimicrobials are estimated to be unnecessary or inappropriate [2], and antimicrobial stewardship programs (ASPs) are advocated as key elements in optimizing antimicrobial use in healthcare settings [3]. Among various ASPs, the importance of infectious disease (ID) specialist-led ASPs has been highlighted in recent years [4], involving preprescription authorization (PPA) and postprescription review with feedback (PPRF) as core strategies of ASPs [3, 5]. However, in Japan, there are only a few board-certified ID specialists (1.18 per 100,000 people in Japan versus 2.56 per 100,000 people in the USA) [6–8]; therefore, a lack of human resources is one of the major barriers for the implementation of these evidence-based ASPs. Further, although the Japanese government issued a national action plan on antimicrobial resistance in 2016, only 14.6% of overall Japanese medical institutions, including 41% of hospitals with > 500 beds, had an approved formal antimicrobial

stewardship team (AST) in 2018, and most staff members were not full-time equivalent (FTE) [9]. Thus, at present, the Japanese guidance for implementing ASPs has recommended the PPRF strategy instead of the time-consuming PPA [10].

In Japan, third-generation cephalosporin-resistant *Enterobacteriaceae* has increased in national surveillance data [11]. In our hospital, third-generation cephalosporin-resistant *Escherichia coli* has been recently identified in approximately 30% of total *E. coli* cases; therefore, carbapenem consumption increased from a median of 2.19 defined daily doses (DDDs) per 100 patient-days in 2012 to 3.73 DDDs per 100 patient-days in 2016. Despite this alarming increase, we have insufficient protected time to devote to the implementation of PPA and early PPRF, and thus, there is a need for a solution. Hence, the aim of this study was to assess the effectiveness of an ID specialist-led, hospital-based ASP against prolonged carbapenem use in resource-limited settings using weekly feedback and daily intervention.

Methods

Study design and setting

This uncontrolled before-after study was designed to compare carbapenem consumption in a 24-month baseline period (from August 2015 to July 2017) to that in a 12-month intervention period (from August 2017 to July 2018). The study was conducted at the Iizuka Hospital (AIH), a tertiary care hospital with 1048 inpatient beds and an adult/neonatal intensive care unit in Fukuoka, Japan. The data for this study were obtained via a medical database at the AIH linking a microorganism database in the microbiology laboratory, a prescription database in the pharmacy department, a patient database from the AST, and a chart review.

This study was approved by the Institutional Review Board at the AIH (approval no. 17183) and conducted according to the principles expressed in the Declaration of Helsinki. The need for informed consent was waived because this study only used data collected from clinical practice.

Feedback and intervention

AST members included a physician, clinical pharmacist, nurse, and microbiology laboratory technician who performed ASP duties since April 2015. We restricted antimicrobial prescription of daptomycin, linezolid, and tedizolid as PPA but did not restrict against carbapenem prescription. Every weekday during the baseline period, two ID-trained pharmacists performed a prospective audit for all carbapenem prescription from the initiation to discontinuation of the prescription with a FTE of 1.1. They predominantly provided dosing optimization feedback to carbapenem prescribers through the patient charts. Moreover, they recorded a template document in the patient charts on the day of carbapenem prescription initiation and after use for 7 days, recommending the proper use of antimicrobials. Indication and duration of carbapenem use was up to the prescribing doctors because their feedback contained neither an alternative prescription choice nor a suggestion for discontinuation.

During the intervention period, we additionally initiated an intervention by a board-certified ID specialist against all carbapenem use for ≥ 14 days. The ID specialist provided daily ID consultation through face-to-face or telephone conversations with prescribers and recorded the recommendation in the patient's chart. In addition, we reported an aggregated table involving the weekly point prevalence surveillance indicating the amount of departmental carbapenem use for 7–13 days and ≥ 14 days through e-mail to all medical doctors at the AIH.

Outcome measure and definition

The primary endpoint of this study was the trend in monthly carbapenem consumption. Secondary endpoints were 1) change in each intravenous antimicrobial consumption which was available at the AIH, and 2) the trend in the detection of hospital-acquired microorganisms/infections including methicillin-resistant *Staphylococcus aureus* (MRSA), extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae*, carbapenem-resistant organisms (CROs), *Candida* spp. bloodstream infections, and *Clostridioides difficile* infections (CDI). Additionally, we extracted data for all-cause in-hospital mortality and length of hospital stay from the medical database at the AIH.

Monthly aggregated hospital antimicrobial consumption was measured as days of therapy (DOTs) per 100 patient-days and DDDs per 100 patient-days. The incidence of microorganism detection was calculated as the number of clusters per 1000 patient-days. A microorganism recovered from a previously enrolled patient (e.g., continuous bacteremia) within the same month was excluded. Hospital-acquired microorganism/infection was defined as a microorganism/infection identified > 48 hours after admission. ESBL-producing *Enterobacteriaceae*, including *Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, and *Proteus mirabilis* was identified using the Cica β -test (Kanto Chemical Co., Tokyo, Japan) and the disc diffusion method. CRO was defined as an imipenem-resistant organism based on the Clinical Laboratory Standard Institute (CLSI) M100-S29. CDI was defined as a patient with diarrhea and a stool specimen positive for glutamate dehydrogenase plus toxin assay (C. DIFF QUIK CHEK COMPLETE from 2015–2017; Alere Medical Co., Tokyo, Japan, and GE Test Immunochromato-CD GDH/TOX from 2017–2018; Nissui Pharmaceutical Co., Tokyo, Japan).

The acceptance rate was defined as the number of feedback accepted by prescribers divided by the total number of feedback made by an ID specialist. Acceptance or nonacceptance was decided by chart review within 24 hours after the recommendations were made. A carbapenem-related annual cost reduction and estimated savings were calculated based on the annual cost of purchasing carbapenem. The cost of purchasing carbapenem was adjusted to the cost of branded meropenem in 2018 considering fluctuations in drug prices and cost differences between brands and generics. The exchange rate of 1 USD to 110 JPY in 2019 was used.

Statistical analysis

We used segmented regression analysis of an interrupted time series to evaluate trends in monthly antimicrobial consumption calculated by DOTs per 100 patient-days and trends in the incidence of detected microorganisms, which was represented as a change in level due to the initiation of the

intervention and change in trend between two periods [12]. The monthly antimicrobial consumption using DDDs per 100 patient-day, number of detected hospital-acquired microorganisms/infections, all-cause in-hospital mortality, and length of hospital stay were compared between the two periods using the chi-squared (χ^2) test for nominal variables and Mann-Whitney U test for continuous variables. A two-tailed p-value of < 0.05 was regarded as statistically significant, and the 95% confidence interval (95% CI) was used. All analyses were performed using Stata/SE v. 14.2 (StataCorp, College Station, TX, USA).

Results

Impact of the intervention on carbapenem consumption

During the study period, 90,076 patients were admitted to the AIH, including 59,195 in the baseline period and 30,881 in the intervention period. Out of these, 3,935 patients received carbapenem (meropenem and doripenem) injection: 2,694 in the baseline period and 1,241 in the intervention period. Among the 1,241 courses of carbapenem in the intervention period, an ID specialist provided a total of 96 instances of feedback against carbapenem use for ≥ 14 days. The predominant content of the feedback was carbapenem discontinuation ($n = 45$), followed by further investigation ($n = 25$), and change to other antimicrobials ($n = 22$) (Table 1). The overall acceptance rate of the ID specialist's feedback was 76%, and the ID specialist devoted an average FTE of 0.16 to the intervention. After the initiation of the intervention, the trend in monthly carbapenem consumption (DOTs per 100 patient-days) changed in level (coefficient: -0.62; 95% CI: -1.15 to -0.087, $p = 0.024$, Fig. 1), and its consumption decreased (coefficient: -0.098; 95% CI: -0.16 to -0.039, $p = 0.002$). Interestingly, the monthly number of courses of carbapenem significantly decreased (Fig. 2), changing in level (coefficient: -18.6; 95% CI: -34.2 to -3.05, $p = 0.021$) and in trend (coefficient: -3.02; 95% CI: -4.63 to -1.42, $p = 0.001$). However, the trend in monthly average duration of carbapenem use did not significantly decrease (coefficient: -0.033; 95% CI: -0.16 to 0.095, $p = 0.61$). The adjusted annual costs of purchasing carbapenem in the latest baseline period (from August 2016 to July 2017) and in the intervention period (from August 2017 to July 2018) were \$386,861 and \$303,116, respectively. Namely, the carbapenem-related annual estimated savings after the intervention was \$83,745, with a cost reduction of 22%. There was no change in in-hospital mortality (3.8% versus 3.7%, $p = 0.53$) or length of hospital stay (median 14.5 [interquartile range (IQR) 14.2–14.8] versus 14.3 [IQR 14.0–14.6] days, $p = 0.52$) between the baseline and intervention periods.

Table 1
Content and acceptance rate of feedback made by an ID specialist against carbapenem use for ≥ 14 days

Recommendations (n = 96)	Intervention (n)	Acceptance (n)	Acceptance rate (%)
Carbapenem discontinuation	45	37	82
Further investigation	25	16	64
Change to other antimicrobials	22	17	77
Source control	3	2	67
Dosing optimization	1	1	100
Total	96	73	76

Change in monthly intravenous antimicrobial consumption

Comparing the two periods, monthly overall intravenous antimicrobial consumption increased after the intervention (median 37.1 [IQR 35.6–40.8] versus 41.4 [IQR 40.8–42.4] DDDs/100 patient-days, $p = 0.02$), whereas monthly carbapenem consumption decreased (median 2.28 [IQR 2.04–2.58] versus 1.79 [IQR 1.66–2.02] DDDs/100 patient-days, $p < 0.001$, Table S1). Among all available intravenous antimicrobials at the AIH, consumption of piperacillin-tazobactam (median 1.90 [IQR 1.72–2.21] versus 2.32 [IQR 2.03–2.56] DDDs/100 patient-days, $p = 0.002$), first-generation cephalosporins (median 2.41 [IQR 2.21–2.80] versus 3.24 [IQR 3.08–3.35] DDDs/100 patient-days, $p < 0.001$), and third-generation cephalosporins (median 1.72 [IQR 1.63–2.17] versus 2.34 [IQR 2.18–2.46] DDDs/100 patient-days, $p < 0.001$) predominantly increased after the intervention. There was no significant increase in the consumption of fourth-generation cephalosporins ($p = 0.097$) and fluoroquinolones ($p = 0.42$).

The interrupted time series analysis showed that the trend in monthly piperacillin-tazobactam consumption temporarily increased after the initiation of the intervention, but the level change was not significant (coefficient: 0.25; 95% CI: -0.30 to 0.79, $p = 0.36$, Fig. 3). Thereafter, the trend in piperacillin-tazobactam consumption decreased (coefficient: -0.094; 95% CI: -0.17 to -0.017, $p = 0.019$). The monthly cefepime consumption did not change in level (coefficient: -0.080; 95% CI: -0.10 to 0.26, $p = 0.37$) or in trend (coefficient: -0.013; 95% CI: -0.037 to 0.010, $p = 0.25$).

Change in hospital-acquired microorganisms/infections

Hospital-acquired MRSA and ESBL-producing *Enterobacteriaceae* were more frequently detected in the intervention period than in the baseline period ($p = 0.001$ and $p < 0.001$, respectively) (Table 2). However, after the initiation of the intervention, the trend in monthly incidence of MRSA (coefficient: -0.023; 95% CI: -0.069 to 0.023, $p = 0.32$) and ESBL-producing *Enterobacteriaceae* (coefficient: -0.0048; 95% CI: -0.027 to 0.018, $p = 0.66$) did not significantly change (Fig. S1). The CROs, *Candida* spp. bloodstream infections, and CDI were detected with similar frequency between the two periods (Table 2).

Table 2

Detection of hospital-acquired microorganisms/infections and all-cause in-hospital mortality among hospitalized patients before and after the intervention

	Baseline period (n = 59195)	Intervention period (n = 30881)	p-value
In-hospital death, n (%)	2247 (3.8)	1146 (3.7)	0.53
MRSA, n (%)	714 (1.21)	452 (1.46)	0.001
ESBL-producing <i>Enterobacteriaceae</i> , n (%)	323 (0.55)	302 (0.98)	< 0.001
CROs [‡] , n (%)	124 (0.21)	65 (0.21)	1.00
<i>Candida</i> spp. bloodstream infections, n (%)	32 (0.054)	19 (0.062)	0.66
CDI*, n (%)	145 (0.24)	94 (0.30)	0.102
[‡] CRO was defined as an imipenem-resistant organism based on the CLSI M100-S29.			
*CDI was defined as a patient having diarrhea with positive for glutamate dehydrogenase plus toxin assay.			
MRSA, methicillin-resistant <i>Staphylococcus aureus</i> ; ESBL, extended-spectrum beta-lactamase; CROs, carbapenem-resistant organisms; CDI, <i>Clostridioides difficile</i> infection			

Discussion

In this before-after study, we evaluated the impact of an ID specialist-led daily postprescription carbapenem intervention with weekly feedback for long-term carbapenem users. Our intervention was effective in reducing carbapenem consumption without causing a change in in-hospital mortality or an increase in the consumption of alternate broad-spectrum antimicrobials. We found that the number of courses of carbapenem, but not the duration of carbapenem use, decreased, indicating a possible beneficial effect of our intervention on improving prescribing behavior.

The present study has three important findings. First, it is noteworthy that our study demonstrates the positive effect of our ASP even in a resource-limited setting. There is limited information on in-hospital ASP in Asia, and resources and settings are diverse among each country and hospital [9, 13, 14]. In Japan, the resources were generally insufficient to meet the demands for implementing an ideal ASP [15], and therefore there is a necessity in developing ID-trained pharmacists and ID specialists [9]. Although PPRF is a well-established intervention, there are few resource-rich Japanese hospitals implementing early PPRF against overall antimicrobial use for 48–72 hours. Therefore, we must make a practical plan to implement the stewardship according to available institutional resources: e.g., focusing on broad-spectrum antimicrobials and/or longer duration of use, and providing once-weekly intervention [16–19]. In our hospital, the number of ID physicians was particularly insufficient; there were no ID fellows, and one (part time) and two (full time and part time) ID specialists worked in the baseline and intervention

periods, respectively. As a result, only an FTE of 0.16 was devoted to the additional stewardship activity by an ID specialist; however, it is noteworthy that our strategy had a positive effect on reducing carbapenem consumption. Hence, we highlight the positive impact of our ASP strategy, which may be a reasonable and acceptable alternative, particularly in resource-limited settings.

Second, our study indicates that a predominant factor in the decrease of carbapenem consumption might be in behavior change among prescribers. In our study, ESBL-producing *Enterobacteriaceae* strains were more frequently identified in the intervention period than in the baseline period, a trend similar to that seen in national and local surveillance data in Japan [11]. Therefore, it is meaningful that carbapenem consumption decreased in the intervention period, despite being one of the first-line agents for ESBL-producing *Enterobacteriaceae*. Interestingly, although we did not provide alternate empirical antimicrobial choices or restrict carbapenem prescription, empirical carbapenem use decreased, which suggests that our intervention was indirectly or comprehensively relevant to changing prescribing behavior. Prescription trends of all available intravenous antimicrobials at our facility showed that the monthly trend in piperacillin-tazobactam consumption increased only temporarily before decreasing, but the change in level was not significant after the initiation of the intervention. There was no compensatory increase in the other antipseudomonal agents including fourth-generation cephalosporins, fluoroquinolones, and aminoglycosides (Table S1). Further, carbapenem-sparing agents such as ceftazidime-avibactam and ceftolozane-tazobactam were not available in our hospital during the study period. As a result, the comprehensive evaluation enables us to know that our intervention might promote optimal use of antimicrobials—that is, reduce unnecessary empirical carbapenem use and using narrow-spectrum antimicrobials such as first- and third-generation cephalosporins—without a change in in-hospital mortality. Thus, we emphasize that not only a reduction in carbapenem consumption but also the positive impact of ASPs on optimizing the use of antimicrobials; the concepts supported by several previous reports [19, 20].

Third, our study suggests that, in addition to intervention made by the ID specialist, several factors comprehensively affected the reduction in carbapenem consumption and optimal use of antimicrobials. We only provided direct intervention for 96 (7.7%) of 1,241 courses of carbapenem, and the duration of carbapenem use was not influenced by this. Similar to our weekly feedback, weekly e-mail-based notification alone failed to show a positive impact on reducing carbapenem consumption in a previous study [19]. However, by adding the weekly feedback to the daily intervention on carbapenem use for ≥ 14 days, synergistic positive effects and a competitive mindset among departments may occur. Further, a hospital president approved our intervention and announced the importance of the intervention and information on antimicrobial resistance to all medical staff at the facility before the initiation of our intervention. The credit and education might yield a further positive influence on growing awareness problems on antimicrobials and changing prescribing behavior. Moreover, leadership of ID consultation services changed from hospitalists to the ID specialist since April 2017 (four month before the initiation of our intervention). We conducted several in-hospital notifications to increase the use of ID consultation services. The campaign and daily ID consultation service without ASP activities might achieve a positive impact on optimal use of antimicrobials. We believe that, in addition to daily intervention, the weekly

feedback, president's credit, education of medical staff, and campaigns of using ID consultation services all comprehensively and synergistically contributed to a reduction in carbapenem consumption and optimal use of antimicrobials. Hence, we believe that taking action is important without giving up ASP activities in resource-limited settings.

This study has several limitations. First, this is a single-center study in Japan, and thus, it is uncertain whether our hospital-based ASP strategy can be applicable worldwide. Schweitzer et al described that only 48% and 23% of studies evaluating antimicrobial stewardship interventions reported clinical and microbiological outcomes, respectively [21]. However, we evaluated these outcomes, and it is noteworthy that our ASP strategy led to a decrease in carbapenem consumption with prescribing behavior change in a resource-limited setting. Second, we could not investigate the length of hospital stay among patients with infectious diseases and infectious disease-related total medical cost reduction. However, we would like to emphasize the impact on cost reduction that our ASP accomplished on overall intravenous antimicrobial-related saving of \$255,352 in addition to annual estimated carbapenem-related savings (\$83,745) on the basis of the annual purchasing cost. Third, there is evidence that the implementation of hospital-based ASP had a positive influence on microbiological outcomes [13, 22, 23]; however, our study did not show the positive microbiological impact on the hospital-acquired multidrug-resistant pathogens and infections. This may be because of the insufficient number of events and short observation period. Further, several studies showed a synergistic effect of hand-hygiene improvement combined with ASP on microbiological outcomes in the hospital [14, 24]. Thus, we should promote the implementation of hospital-based ASP with hand-hygiene intervention as well as a local-regional ASP to improve microbiological outcomes, and continue further outcome evaluation.

This before-after study showed the positive impact of an ID specialist-led ASP on reductions in carbapenem consumption and antimicrobial-related cost without adversely affecting the increase of broad-spectrum antimicrobial consumption and in-hospital mortality. We believe that an important path to success in hospital-based ASP is investigating institutional/local issues of antimicrobial prescription and making a practical plan according to available institutional resources. In particular, the favorable and reliable relationship between prescribers and the AST is vital in bringing about high compliance and prescribing behavior change among prescribers, which can finally lead to optimal use of antimicrobials. Even in resource-limited settings, we advocate that taking any action is warranted even if it is not PPA and early PPRF.

Abbreviations

ID:infectious disease; ASP:antimicrobial stewardship program; PPA:preprescription authorization; PPRF:postprescription review with feedback; AST:antimicrobial stewardship team; FTE:full-time equivalent; DDDs:defined daily doses; AIH:lizuka Hospital; MRSA:methicillin-resistant *Staphylococcus aureus*; ESBL:extended-spectrum beta-lactamase; CRO:carbapenem-resistant organism; CDI:*Clostridioides difficile* infections; DOTs:days of therapy; CLSI:Clinical Laboratory Standard Institute; IQR:interquartile range

Declarations

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Author contributions

TM devised the original idea for the study. TM, YU, MU, NK, and TY collected the data. TM and HK led the analysis. TM drafted the original manuscript. All authors contributed to the study design, interpretation of the data, and revision of the manuscript for intellectual content. All authors have read and approved the final version.

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Availability of data and materials

The dataset analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board at the AIH (approval no. 17183) and conducted according to the principles expressed in the Declaration of Helsinki. The need for informed consent was waived because this study only used data collected from clinical practice.

Consent for publication

Not applicable.

Competing interests

All authors declare no conflicts of interest.

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Figures

Figure 1

Monthly trend of carbapenem consumption before and after the initiation of the intervention. The monthly trend of carbapenem consumption changed in level (coefficient: -0.62; 95% CI: -1.15 to -0.087, $p = 0.024$) and its consumption decreased (coefficient: -0.098; 95% CI: -0.16 to -0.039, $p = 0.002$) after the initiation of the intervention.

Figure 2

Monthly trend in average duration of carbapenem use (A) and the number of courses of carbapenem (B). (A) The monthly average duration of carbapenem use did not significantly change in level (coefficient: -1.24; 95% CI: -2.73 to 0.26, $p = 0.10$) or in trend (coefficient: -0.033; 95% CI: -0.16 to 0.095, $p = 0.61$). (B) The monthly number of courses of carbapenem decreased after the initiation of the intervention including changes in level (coefficient: -18.6; 95% CI: -34.2 to -3.05, $p = 0.021$) and in trend (coefficient: -3.02; 95% CI: -4.63 to -1.42, $p = 0.001$).

Figure 3

Trend in monthly piperacillin-tazobactam (A) and cefepime (B) consumption before and after the initiation of the intervention. (A) The trend in monthly piperacillin-tazobactam consumption temporarily increased but the change in level was not significant (coefficient: 0.25; 95% CI: -0.30 to 0.79, $p = 0.36$). Thereafter, the trend in piperacillin-tazobactam consumption decreased (coefficient: -0.094; 95% CI: -0.17 to -0.017, $p = 0.019$). (B) The monthly cefepime consumption did not change in level (coefficient: -0.080; 95% CI: -0.10 to 0.26, $p = 0.37$) or in trend (coefficient: -0.013; 95% CI: -0.037 to 0.010, $p = 0.25$).

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