

ORIGINAL PAPER
INFECTIOUS DISEASES

Impact of the multidisciplinary antimicrobial stewardship team intervention focusing on carbapenem de-escalation: A single-centre and interrupted time series analysis

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Abstract

Background: As a result of the constant increase in carbapenem resistance amongst gram-negative bacteria in several countries, the inappropriate use of carbapenems must be reduced. Antimicrobial stewardship programmes (ASPs) aim to improve carbapenem usage by implementing interventions, including the promotion of the de-escalation (DE) strategy. Thus, this study aimed to evaluate the impact of this strategy on carbapenem use based on a clear definition of DE.

Methods: The post-prescription review and feedback (PPRF) strategy, which is used to optimise carbapenem use, was implemented by the antimicrobial stewardship team (AST). We compared the DE rate during the pre-AST intervention period (from April 2017 to March 2018) and post-AST intervention period (from April 2018 to March 2019).

Result: A total of 1500 patients ($n = 771$ in the pre-AST intervention period and $n = 729$ in the intervention post-AST period) were admitted to the hospital. The average duration of antibiotic therapy decreased from 9.9 to 7.7 days. The DE rate significantly increased in the post-AST intervention period compared with the pre-AST intervention period (51.4% vs 40.3%; $P < .001$).

Conclusion: The PPRF strategy implemented by the AST could improve the carbapenem usage by increasing the DE rate of carbapenem.

1 | INTRODUCTION

Considering the continuous increase in carbapenem resistance amongst gram-negative bacteria in several countries, the appropriate use of carbapenems and other types of antibiotics must be implemented to solve this problem.^{1,2} Antimicrobial stewardship programmes (ASPs) aim to address carbapenem resistance by

implementing interventions that improve carbapenem use, which include promoting the de-escalation (DE) strategy.^{3,4} Limiting the unnecessary use of carbapenem in hospitals can reduce resistance rates amongst problematic gram-negative bacteria, including *Pseudomonas aeruginosa*.⁵

When carbapenem is inappropriately used in some patients, including those who received prolonged therapy, the DE strategy

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is recommended for cost-saving and preventing antimicrobial resistance (AMR) when susceptible bacteria are identified. Although the strategy is considered beneficial in terms of patient safety and prevention of AMR, it has not been utilised in diverse clinical settings.⁶⁻⁸ Furthermore, although this strategy is widely recommended, it does not have a clear definition and is difficult to sufficiently evaluate.⁹⁻¹¹

Thus, a multidisciplinary antimicrobial stewardship team (AST) comprising trained pharmacists who focus on carbapenem stewardship with the use of the post-prescription review and feedback (PPRF) strategy was established.^{12,13} Thus, this study aimed to evaluate the impact of this strategy on the DE, duration, and use of carbapenem based on a clear definition of DE.

2 | MATERIALS AND METHODS

2.1 | Study design and setting

This study was conducted at Showa University Fujigaoka Hospital, a 584-bed tertiary care centre with a 14-bed intensive care unit, in Japan. A quasi-experimental uncontrolled intervention was provided to determine the impact of the ASP on carbapenem treatment. The study was approved by the institutional review board (no. F2018C25) of the institution, and the need for informed consent was waived because of the retrospective design of the study.

From April 2018 to March 2019, the AST implemented an intervention that promotes DE strategies for patients treated with carbapenem. This analysis included consecutive patients who were admitted to any department of the hospital and received carbapenems. The control group only received carbapenem therapy from April 2017 to March 2018. Carbapenem therapy included both definitive therapy for documented infection and empirical therapy for suspected infection.

2.2 | Data collection

Data, including demographic information of patients (eg, age, serum creatinine, granulocyte count, and weight), antimicrobial regimen, and days of therapy (DOT) per 100 patient-days in the hospital, were collected retrospectively from electronic charts. The clinical data of mortality, antibiotic prescription (category, dose, and duration), blood culture results of individuals who received carbapenem treatments, recommendations made by the AST, and acceptance rate were obtained. The susceptibility rates of gram-negative bacteria to meropenem were calculated as the proportion of susceptible isolates to total isolates of each bacteria detected during the period. The isolated bacteria were counted per patient and specimen in hospital in-patients during the period. Drug susceptibility was interpreted according to Clinical and Laboratory Standards Institute document M100-S22.

What is known

- Antimicrobial stewardship (AS) improves the optimisation of antibiotic prescription using the post-prescription review and feedback (PPRF) strategy.
- Carbapenem is a wide-spectrum antibiotic, and its use must be limited to maintain biological sensitivity.
- Because de-escalation is not well defined, the prescription after de-escalation is not evaluated.

What is new

- The PPRF strategy improves the optimal utilisation of antimicrobials and reduces carbapenem use by enhancing de-escalation therapy.
- Based on the definition of de-escalation, the prescription trend of carbapenem was assessed.
- The rate of switching to narrow-spectrum β -lactams significantly increased in the post-AST intervention period.
- The trend of carbapenem use significantly decreased by switching to narrow-spectrum antibiotics and by shortening the duration of carbapenem treatment.

2.3 | Intervention

The AST had a conference on patients receiving carbapenems once a week. The PPRF strategy aims to optimise antimicrobial use by encouraging a prescriber to comprehensively engage in blood culture, microbial examination, imaging or blood examination, and antibiotic selection and to follow the appropriate dose or frequency as scheduled, discontinuation of treatment, and duration of therapy. The AST then provided recommendations to the attending physicians regarding the aforementioned interventions according to the data obtained from the medical charts. If the prescriber does not follow the recommendation after 3-5 days, the physician in the AST discussed the situation with the prescriber and made recommendations via telephone. More than one recommendation could be made per patient.

The members of the AST in this study included physicians (respiratory and emergency physicians and paediatricians) and a full-time pharmacist, infection control nurse, and microbiology technologist. The carbapenem PPRF strategy implemented by the AST was used by physicians during conference, decision-making, and recommendations (with a total full-time equivalent [FTE] of 0.05); by the pharmacist when selecting patients and checking the prescription and patient's condition every weekday, attending conferences, and performing follow-ups after recommendations (FTE of 0.5); by the microbiology laboratory technician when assessing biological data (FTE of 0.1); and by the infection control nurse when evaluating primary disease and medical device (FTE of 0.05). The FTEs of each health care worker did not include other AST activities, such as infectious disease consultation, infection control implementation, and provision of education to hospital staff.

The AST collaborated with a ward-based clinical pharmacist (CP) if needed. The CP confirmed the dosage to the physician based on renal function and blood culture results. The AST follows and supported the recommendation of the CP.⁸ Moreover, the team focused on educating all medical staff, new staff, nurses, pharmacists, and medical residents. The leader physician of the AST had a discussion with the head of the medical department about treatment policy and importance of blood culture. In the pre-AST intervention period, we had no intervention strategy of antimicrobial stewardship against any antibiotics prescription including carbapenems.

2.4 | Definitions

We performed an evaluation of carbapenem therapy, which was classified into the following groups based on prescription status within 7 days: (a) discontinuation of treatment: inhibition of carbapenem therapy because of the absence of proven bacterial infection^{11,14-17}; (b) switch to a narrow-spectrum antibiotic: changing to narrower-spectrum β -lactams, such as the penicillin, piperacillin/tazobactam, and cephem groups or a combination of these groups^{14-16,18}; (c) continuation of treatment: continuous treatment with carbapenem over 7 days; (d) Change to other classes: switching to non- β -lactam antibiotics: switching to non- β -lactam antibiotics¹⁶; and (e) oral route: switch from parenteral to any oral antibiotics. DE was defined as either discontinuation, narrowing of therapy, or switch to oral route.^{11,14,19,20}

2.5 | Outcome

The primary outcome was the DE rate between the pre- and post-AST intervention periods. The secondary outcomes included DOT per 100 bed-days for carbapenems, length of carbapenem therapy, 30-day mortality, and in-hospital mortality.

2.6 | Statistical analysis

Categorical and continuous variables were compared using Pearson's chi-squared test or Fisher's exact test and Student's *t*-test, respectively. All statistical analyses were two-tailed, and $P < .05$ were considered statistically significant.

An interrupted time series analysis was performed to identify the effect of the intervention on the DOT of carbapenem. A total of 24 monthly data points in the pre- and post-AST intervention periods were available for analysis. The model included an intercept (β_0), baseline trend (β_1), level change after the start of the intervention (β_2), and trend change after initiating the intervention (β_3).

Statistical analyses were performed using the Statistical Package for the Social Sciences software version 23.0 (IBM Japan).

3 | RESULTS

3.1 | Characteristics of the participants

In total, 1500 in-patients were treated with carbapenem during the 12-month pre-AST intervention period ($n = 771$) and the 12-month post-AST intervention period ($n = 729$). The characteristics of the patients at baseline were similar between the pre- and post-AST periods, except in those who were on renal replacement therapy and who presented with neutropenia (Table 1).

3.2 | Process measures

During the intervention, the AST gave 447 recommendations for 218 patients. Figure 1 shows the type of interventions provided by the AST and the proportion of patients who accepted the treatment. The total acceptance rate was 68.7% (307/447). The proportion of patients receiving carbapenem treatment who underwent blood culture was higher in the post-AST intervention period than in the pre-AST intervention period (74.9% vs 54.5%; $P < .05$).

3.3 | Primary outcome

The DE rate was significantly higher in the post-AST intervention period than in the pre-AST intervention period (51.4% vs 40.3%; $P < .001$) (Table 2). Notably, the rate of switching to narrower-spectrum β -lactams increased; the occurrence of prolonged carbapenem therapy decreased.

3.4 | Secondary outcomes

No significant differences were observed in in-hospital mortality and 30-day mortality between the pre- and post-AST periods (19.5% vs 20.3%, $P = .681$ and 14.3% vs 15.0%; $P = .707$, respectively).

Table 3 shows the susceptibility rates of gram-negative bacteria during the periods. No significant differences were observed in the susceptibility between the pre- and post-AST intervention periods.

3.5 | Trend analysis of carbapenem use

The trend of carbapenem use increased during the pre-AST intervention period ($\beta_1 = 0.101$, $P = .007$). After the AST intervention, the level ($\beta_2 = -0.686$, $P = .049$) and the slope decreased ($\beta_3 = -0.211$, $P < .001$) (Figure 2). DOT per 100 patient-days was reduced in the post-AST intervention period compared with the pre-AST intervention period (2.95 vs 3.59). The mean (\pm standard deviation) days of carbapenem therapy was significantly shorter during the

TABLE 1 Characteristics of the patients (n = 1500)

Variables	All patients (n = 1500)	Pre-AST intervention period (n = 771)	Post-AST intervention period (n = 729)	P value
Age, y	67.1 ± 20.2	67.5 ± 19.3	66.7 ± 21.1	.444
Body weight, kg	52.7 ± 14.7	52.5 ± 15.0	52.9 ± 14.5	.367
Renal replacement therapy	130 (8.7)	81 (10.5)	49 (6.7)	.009
Creatinine clearance, mL/min ^a	73.7 ± 47.6	72.3 ± 47.8	75.1 ± 47.4	.275
Neutropenia, granulocytes <500/ μL	195 (13.0)	78 (10.1)	117 (16.0)	.001
Carbapenems				
Meropenem	1298 (86.5)	642 (83.3)	656 (90.0)	<.001
Doripenem	52 (3.5)	35 (4.5)	17 (2.3)	.019
Imipenem/ cilastatin	50 (3.3)	40 (5.2)	10 (1.4)	<.001
Panipenem/ betamipron	37 (2.5)	20 (2.6)	17 (2.3)	.744
Biapenem	63 (4.2)	34 (4.4)	29 (4.0)	.677
Combination therapy	256 (17.1)	131 (17.0)	125 (17.1)	.936
β-lactam agent				
Penicillin G	1 (0.1)	1 (0.1)	0 (0.0)	1.000
Third-generation cephalosporins	9 (0.6)	6 (0.8)	3 (0.4)	.508
Aminoglycosides	52 (3.4)	22 (2.9)	30 (4.1)	.041
Macrolides	8 (0.5)	7 (0.9)	1 (0.1)	.070
Quinolones	24 (1.6)	18 (2.3)	6 (0.8)	.020
Anti MRSA agents	164 (10.9)	78 (10.1)	86 (11.8)	.297
Others	14 (0.9)	9 (1.2)	5 (0.7)	.332
Intensive care unit	133 (8.9)	72 (9.3)	61 (8.4)	.509
Mortality				
30-day	219 (14.6)	110 (14.3)	109 (15.0)	.707
In-hospital	298 (19.9)	150 (19.5)	148 (20.3)	.681

Note: Data were presented as mean ± standard deviation or n (%).

Abbreviations: AST, antimicrobial stewardship team; MRSA, methicillin-resistant *Staphylococcus aureus*.

^aThe creatinine clearance values of patients who had received renal replacement therapy were not included.

post-AST intervention period than in the pre-AST intervention period (7.7 ± 4.8 vs 9.9 ± 8.5; $P < .001$).

4 | DISCUSSION

This study revealed that the PPRF strategy for carbapenem use that was implemented by the multidisciplinary AST promoted the DE strategy without compromising patient safety. Notably, the trend of carbapenem use was reduced by switching to narrow-spectrum antibiotics and by shortening the length of carbapenem use.

In this study, we focused on carbapenem stewardship by promoting DE using the intervention implemented by the AST. DE is considered an important strategy for ASPs and is a default practice whenever broad-spectrum antimicrobials are prescribed. Several studies have attempted to define DE. However, its definition remains unclear because of the complexity of clinical settings and limited data available.^{10,11} Moreover, we attempted to evaluate the AST intervention focusing on appropriate carbapenem use based on a clear definition of DE. Because carbapenem has the widest spectrum of antimicrobial activity, switching to other narrower-spectrum β-lactams is considered.^{6,11} Piperacillin-tazobactam is

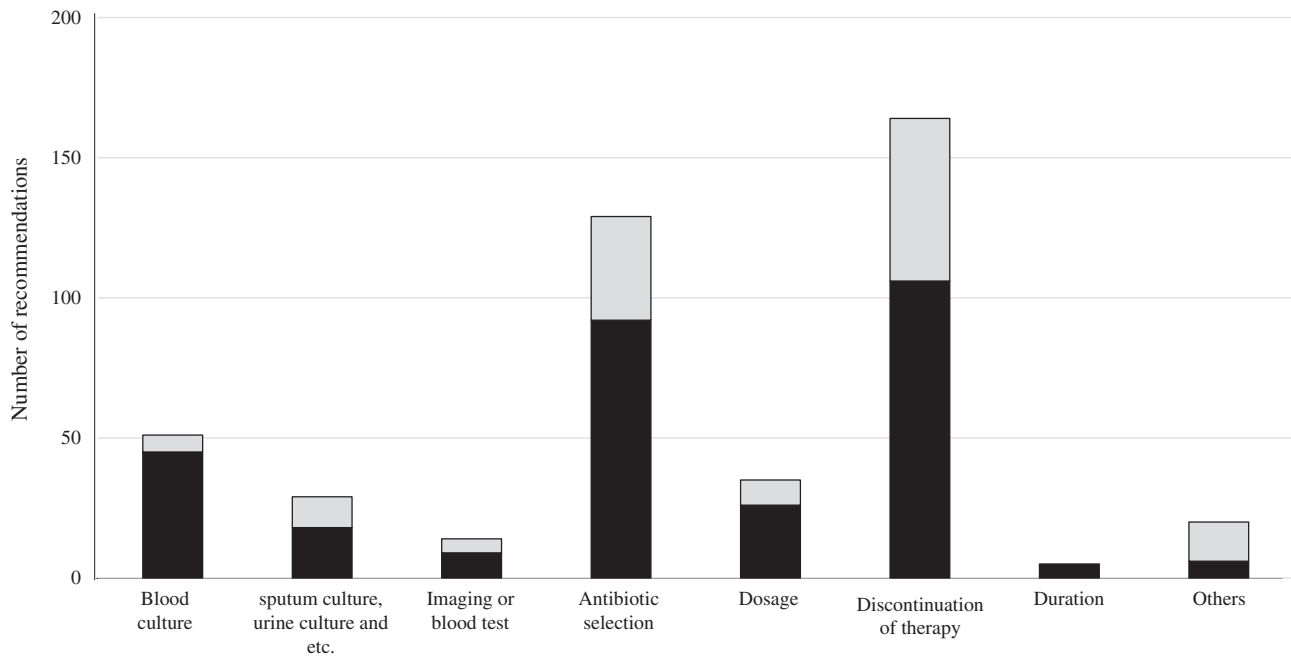


FIGURE 1 Number of recommendations made by the antimicrobial stewardship team. Black bars, recommendations that were accepted; gray bars, recommendations that were not accepted

TABLE 2 Trends of carbapenem prescription during the pre- and post-AST intervention periods

Variables	Pre-AST intervention period	Post-AST intervention period	P value
	(n = 771)	(n = 729)	
Duration of carbapenem therapy, days	9.9 ± 8.5	7.7 ± 4.8	<.001
De-escalation	311 (40.3)	375 (51.4)	<.001
Discontinuation of therapy (within 7 days)	236 (30.6)	234 (32.1)	.534
Switch to narrow-spectrum antibiotics	63 (8.2)	120 (16.5)	<.001
Penicillin group	8 (1.0)	17 (2.3)	.050
Ampicillin	3 (0.3)	3 (0.4)	1.000
Ampicillin and sulbactam	4 (0.5)	12 (1.6)	.043
Piperacillin and tazobactam	5 (0.6)	14 (1.9)	.028
Cephem group	46 (6.0)	83 (11.4)	<.001
First generation cephem	10 (1.3)	24 (3.3)	.009
Second Generation cephem	14 (1.8)	19 (2.6)	.297
Third Generation cephem	22 (2.9)	37 (0.4)	.027
Fourth Generation cephem	0 (0.0)	3 (1.0)	.115
Combination	4 (0.5)	5 (0.7)	.465
Switch from parenteral to oral route	12 (1.6)	22 (3.0)	.057
Continuous treatment (more than 8 days)	446 (57.8)	341 (46.8)	<.001
Change to other classes ^a	14 (1.8)	12 (1.6)	.801
Anti MRSA drugs	6 (0.8)	4 (0.5)	.754
Others	7 (0.9)	5 (0.7)	.629
Combination	1 (0.1)	4 (0.5)	.170

Note: Data were presented as mean ± standard deviation or n (%).

Abbreviations: AST, antimicrobial stewardship team; MRSA, methicillin-resistant *Staphylococcus aureus*.

^aChange to other classes was defined as a switch to non-β-lactam intravenous agents.

	Pre-AST intervention period		Post-AST intervention period		P value
<i>Escherichia coli</i>	100%	(1001/1001)	100%	(1008/1008)	>.99
<i>Klebsiella pneumoniae</i>	99.1%	(583/588)	99.4%	(652/656)	.617
<i>Enterobacter cloacae</i>	89.7%	(131/146)	94.1%	(143/152)	.167
<i>Pseudomonas aeruginosa</i>	87.4%	(456/522)	88.3%	(505/572)	.638

Note: Data were presented as susceptibility rates (No. of isolates).

Abbreviation: AST, antimicrobial stewardship team.

TABLE 3 Susceptibility rates of gram-negative bacteria to meropenem during the pre- and post-AST intervention periods

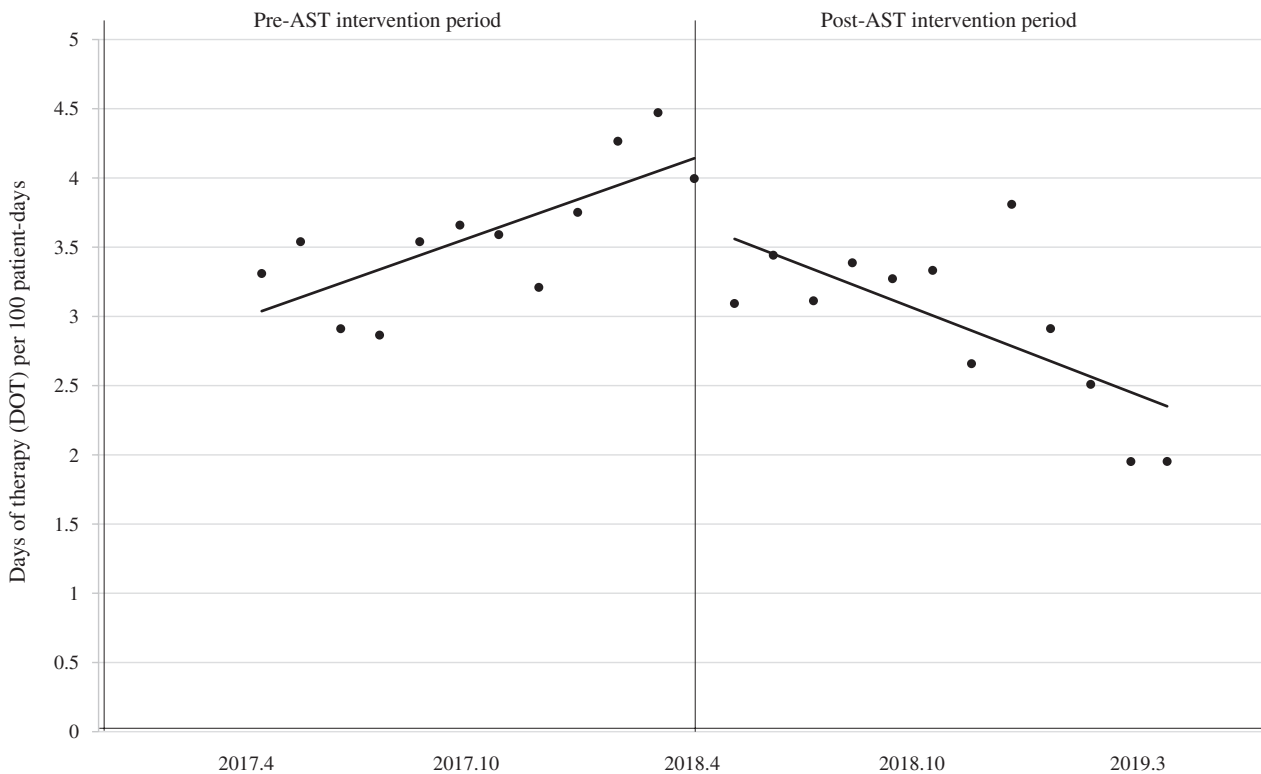


FIGURE 2 The line graph shows a segmented linear regression of therapy duration (days of therapy per 100 patient-days) during the pre- and post-AST intervention periods. The trend of carbapenem use increased during the pre-AST intervention period ($\beta_1 = 0.101$, $P = .007$). After the AST intervention, the level ($\beta_2 = -0.686$, $P = .049$) and the slope decreased ($\beta_3 = -0.211$, $P < .001$)

recognised broad-spectrum antibiotic. Piperacillin-tazobactam has been tried for use as an alternative therapy to carbapenems, from the standpoint of cost and efficacy.^{1,6} Because carbapenem has various high stable β -lactamases and high therapeutic cost, compared with piperacillin-tazobactam, we defined the switch from carbapenem to piperacillin-tazobactam as DE, according to previous studies.^{6,11}

Previous studies have defined DE as early discontinuation of antimicrobial treatment.^{17,21,22} However, the initiation of DE from the start of antimicrobial use has been controversial.^{10,11} Ideally, DE should be performed as soon as possible after obtaining culture results. Because the final blood culture results can be obtained after a week in our hospital, DE was performed within 7 days of carbapenem use. In the present study, the PPRF strategy that was evaluated and classified into five was implemented for carbapenem

stewardship. Previous studies have shown that the AST intervention is effective in decreasing the use of targeted broad-spectrum antimicrobials, including carbapenems.^{12,13} However, these studies have not assessed the outcomes based on a clear definition of DE. The implementation of interventions by promoting DE based on a clear definition is useful for the carbapenem stewardship programme in various health care facilities.

The AST without an infectious disease (ID) physician and with small FTEs for each member other than the pharmacist only had one activity per week. The AST collaborated with ward-based CPs in providing appropriate carbapenem dosage and obtaining blood culture results, which indicated a high acceptance rate of these recommendations.

In contrast, our recommendations (such as antibiotic selection and discontinuation) had low acceptance rates, which was caused by

the shortage of manpower in the AST. The attending physician often believes that carbapenem is highly effective against severe infections. Importantly, patient safety should be considered in DE.⁶ Data obtained from the MERINO trial, which supports the efficacy of carbapenem, showed that patients with bloodstream infections caused by third-generation cephalosporin-resistant gram-negative bacteria who were treated with meropenem had lower mortality than those who received piperacillin-tazobactam.²³ These therapeutic recommendations require a broad knowledge of infectious diseases, and a thorough discussion between ID specialists and prescribers is necessary to achieve successful interventions. In a Japanese nationwide survey, ID physicians and health care workers in the AST had low FTEs.²⁴ To enhance comprehensive antimicrobial stewardship that includes DE strategy, more FTE support of ID physician and ID-trained pharmacist will be needed.²⁵

The present study had several limitations. First, the effect of the strategy on AMR could not be evaluated. Preventing the unnecessary use of carbapenem along with the utilisation of infection control measures may decrease selection pressure and prevent the occurrence of AMR.²⁶ A well-designed quasi-experimental study that evaluates the effect of what on AMR must be conducted. Another limitation is the limited term of this study. ITSA requires a sufficient number of observations, which is ideally 100 points for each data in the time series.²⁷ In 2019, there was a significant shortage of various antimicrobials other than carbapenems in Japan.²⁸ The AST intervention against promoting DE in this period was challenging to evaluate.

In conclusion, the PPRF strategy implemented by the AST enhanced the carbapenem stewardship programme based on a clear definition and application of DE.

CONFLICTS OF INTEREST

All authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

All authors meet the ICMJE authorship criteria.

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