ORIGINAL ARTICLE

Antimicrobial stewardship with once-weekly follow-up reduced carbapenem prescriptions in an acute care hospital

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Background: Antimicrobial stewardship programs (ASP) should be performed daily. However, it is often difficult for smaller hospitals. Thus, we started an ASP for carbapenem therapy with once-weekly follow-up by ward pharmacists in 2015.

Methods: To assess the outcomes of the ASP with once-weekly follow-up by a ward pharmacist, we assessed three groups of patients in 2014, 2015, and 2016. Additionally, we measured the following outcomes: number of de-escalations, number of intravenous to oral conversions, duration of therapy, susceptibility of P. aeruginosa, carbapenem consumption, and death within 30 and 60 days.

Results: Defined daily doses (DDD) (3 and 2 DDD per 100 patient-days (PD) in 2014 and 2016, $P < 0.01$) and days of therapy (DOT) (6 and 4 DOT per 100 PD in 2014 and 2016, $P < 0.01$) in carbapenem decreased with interventions. The death rates within 30 and 60 days were not significantly different between the three groups. Multivariate regression analysis showed that de-escalations were associated with interventions by both AST and ward pharmacists (OR, 2.63; 95% CI, 1.34–4.93). AST interventions had a negative association with the duration of carbapenem therapy (adjusted R^2 of 0.006).

Conclusions: ASP with once-weekly follow-up by a ward pharmacist is a simple and beneficial method that can be adopted by smaller hospitals with limited human resources.

KEY WORDS:

Antimicrobial stewardship programs, once-weekly, ward pharmacistAbstract

INTRODUCTION

A systematic review and meta-analysis reported that antimicrobial stewardship programs (ASP) can improve the quality of antimicrobial use, reduce the use of antibiotics, and shorten the length of hospital stay without increasing mortality rates (1,2). Additionally, ASP interventions safely reduce the unnecessary use of antibiotics in hospitals, although the most effective behavior change techniques are not generally used (1).

Prospective audits and feedback should be performed daily in ASP (3). However, it is often difficult for smaller hospitals to achieve this, mainly due to limited human resources (4). Therefore, an alternative, simpler method would be beneficial for many local clinical settings. Vettese et al. (5) reported that a thrice-weekly, pharmacist-driven ASP can reduce antimicrobial expenditure, shorten the duration of therapy, and decrease the use of carbapenems, vancomycin, and levofloxacin. We started

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a once-weekly prospective audit and feedback program in October 2010. However, de-escalation was not recommended in some cases, because bacterial susceptibility had not yet been identified. In these cases, we suggested de-escalation the following week, although we thought that a once-weekly ASP was insufficient. However, it is difficult for busy physicians to maintain an ASP twice weekly or more frequently. Hence, we started an ASP with once-weekly follow-up by ward pharmacists in 2015. In this program, when de-escalation was not proposed by the ASP, the ward pharmacist could follow-up and subsequently suggest de-escalation to the patient's physician. Thus, this study aimed to assess the outcomes of the ASP with once-weekly follow-up by a ward pharmacist.

METHODS

A three-year retrospective study was conducted involving all patients admitted to Kaetsu Hospital (Niigata, Japan), a 261-bed hospital with six wards, who were administered intravenous carbapenems (imipenem, meropenem, doripenem, and biapenem) between 1 January 2014 and 31 December 2016. The study protocol was approved by the Ethics Committee of Kaetsu Hospital.

The antimicrobial stewardship team (AST) consisted of four healthcare providers: a respiratory physician, board-certified infection control pharmacist, microbiology laboratory technician, and board-certified infection control nurse. A once-weekly ASP was commenced from October 2010. The AST pharmacist reviewed the medical charts of patients to whom carbapenems were administered every Monday excluding holidays, and identified cases that might need changes to the antimicrobial regimen and those with complicated infections. The AST gave feedback (e.g., de-escalation, withdrawal of antimicrobials, performance of bacterial screening, and other suggestions) based on the medical charts. In addition, the AST was notified of carbapenem use from November 2014. Specifically, physicians voluntarily informed the AST of the diagnosis and reason for carbapenem use. An ASP with once-weekly follow-up by ward pharmacists commenced from January 2015. Specifically, when the AST could not suggest de-escalation in a case because the susceptibility of the bacteria had not been identified, the AST pharmacist provided information about the patient to the ward pharmacist. Subsequently, the ward pharmacist monitored the susceptibility of the bacteria by daily review of medical charts. When bacterial susceptibility was identified, the ward pharmacist would suggest the possibility of de-escalation to the patient's physician.

To determine the efficacy of an ASP with once-weekly follow-up by the ward pharmacists, we assessed three groups in 2014, 2015, and 2016. Outcome measures were the number of de-escalations, number of intravenous to oral conversions, duration of carbapenem therapy, antimicrobial susceptibility of *P. aeruginosa*, carbapenem consumption, and death within 30 and 60 days. Intervention was defined as feedback to the patient's physician by the AST or ward pharmacist. Interventions were recorded via electronic medical charts. Interventions by the ward pharmacists were performed by talking directly or sending the electronic medical chart to the physician. De-escalation was defined as a change in prescription from a carbapenem to another antimicrobial, including antipseudomonal penicillins and cephalosporins (6). To determine the susceptibility of *P. aeruginosa* to carbapenems, we collected data about the number of isolates and the number of susceptible isolates of *P. aeruginosa* to imipenem and meropenem. Data on bacteria isolated within <48 h of hospitalization, bacteria obtained from stool, and duplicate isolates from the same patient were excluded. Antimicrobial susceptibility testing was performed using broth microdilution according to the guidelines for MIC testing from the National Committee for Clinical Laboratory Standards. MICs of <2 μg/mL indicated *P. aeruginosa* susceptibility to imipenem and meropenem. Information about the total intravenous antimicrobial and intravenous carbapenem doses was collected, and the defined daily dose (DDD) and days of therapy (DOT) were assessed using the Japan Antimicrobial Consumption Surveillance system (7). The DDD was based on the WHO recommendation for each year. DOT was defined as the administration of a single agent on a given day regardless of the number of doses administered. DDD and DOT was normalized to 100 patient-days (PD). All data were recorded in electronic medical charts.

JMP v.9 software (SAS Institute Inc., Cary, NC) was used for all statistical analysis. Continuous variables were reported as means and standard deviation, and categorical variables as frequency and percentage. Univariate analysis was performed using one-way ANOVA followed by Tukey-Kramer post-hoc test or $\chi 2$-test. Multivariable analysis was performed using logistic regression analysis with a stepwise backward–forward selection ($P < 0.25$) procedure to identify the independent factors associated with de-escalation and intravenous to oral conversion. Additionally, multivariable analysis was performed using multiple regression analysis with a stepwise backward-forward selection ($P < 0.25$) procedure to identify the independent factors associated with the duration of carbapenem therapy. Interventions by the AST or ward pharmacists and notifications to the AST were subjected to multivariate analysis. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated in logistic regression analysis. Moreover, the partial regression coefficient (standard error) and adjusted R^2 values were calculated in multiple regression analysis. $P < 0.05$ was considered statistically significant.

RESULTS

The three groups in this study comprised 417, 415, and 361 patients administered carbapenems in 2014, 2015, and 2016, respectively. Patient backgrounds, number of interventions, and outcomes are shown in Table 1; the proportion of males was significantly different between the groups. Unknown infections were also included during diagnosis. The duration of carbapenem therapy in both 2015 and 2016 decreased by one day compared with 2014 (significant difference between 2014 and 2015, $P < 0.01$). Moreover, the number of deaths within 30 and 60 days were not significantly different between the three groups. In contrast, although notifications to the AST, total

TABLE 1: Patient backgrounds, number of interventions, and outcomes				
	2014 n = 417	2015 n = 415	2016 n = 361	*P**
Sex male, n (%)	245 (59)	277 (67)	211 (58)	0.02
Age, years (SD)	79 (13)	80 (13)	79 (13)	0.78
Body weight, kg (SD)	46 (13)	48 (12)	47 (14)	0.11
Diagnosis				
Respiratory, n (%)	125 (30)	114 (27)	117 (32)	0.32
Urinary, n (%)	61 (15)	43 (10)	42 (12)	0.16
Digestive, n (%)	58 (14)	56 (13)	48 (13)	0.97
Other, n (%)	172 (41)	202 (49)	153 (42)	0.07
Notifications to AST, n (%)	82 (20)	324 (78)	310 (86)	< 0.01
Total interventions, n (%)	16 (4)	74 (18)	63 (17)	< 0.01
Interventions by AST, n (%)	16 (4)	38 (9)	56 (16)	< 0.01
Interventions by ward pharmacists, n (%)	0 (0)	42 (10)	10 (3)	< 0.01
Number of de-escalations, n (%)	48 (12)	68 (16)	48 (13)	0.11
Number of intravenous to oral conversions, n (%)	12 (3)	14 (3)	18 (5)	0.27
Duration of carbapenem therapy, days (SD)	10 (6)	9 (6)†	9 (6)	<0.01
Death within 30 days, n (%)	79 (19)	80 (19)	84 (23)	0.26
Death within 60 days, n (%)	108 (26)	105 (25)	99 (26)	0.79

Continuous variables are reported as mean and standard deviation, and categorical variables as frequency and percentage.
Abbreviations: AST, antimicrobial stewardship team; SD, standard deviation.
* One-way ANOVA followed by Tukey–Kramer post-hoc test or $\chi 2$-test.
† Significant compared with 2014.

TABLE 2: Susceptibility of *P. aeruginosa* to imipenem and meropenem				
	2014 n = 57	2015 n = 41	2016 n = 41	*P**
Imipenem susceptibility of *P. aeruginosa* isolates, n (%)	39 (68)	28 (68)	34 (83)	0.21
Meropenem susceptibility of *P. aeruginosa* isolates, n (%)	41 (72)	30 (73)	34 (83)	0.42

* χ^2-test.

interventions, interventions by the AST, and those by the ward pharmacists increased in 2015 and 2016 compared with 2014 (significant difference between the three groups by χ^2-test, $P < 0.01$), the number of de-escalations and intravenous to oral conversions were no different between the groups. Furthermore, interventions by both the AST and ward pharmacists occurred in a few cases. The number of interventions by ward pharmacists was lower in 2016 compared with 2015 because the number of AST interventions was higher.

The susceptibility of *P. aeruginosa* to both imipenem and meropenem is shown in Table 2, and showed an increase from 70% in 2014 to 80% in 2016; however, there was no significant difference between the three groups.

Antimicrobial consumption is shown in Table 3. The DDD of all antimicrobials in 2015 and 2016 was significantly increased compared with 2014 (P <0.01); however, the DDD of carbapenems was significantly lower in 2015 (2 DDD per 100 PD, $P = 0.02$) and 2016 (2 DDD per 100 PD, P <0.01) compared with 2014 (3 DDD per 100 PD). Additionally, although the DOT of all antimicrobials was not significantly different between the three groups, fewer carbapenem DOT were recorded in 2015 and 2016 (4 DOT per 100 PD, P <0.01) compared with 2014 (6 DOT per 100 PD). In this study, 80% meropenem was the carbapenem that was mainly used for DDD and DOT.

The results of multivariate regression analysis of the factors associated with de-escalations, intravenous to oral conversions,

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TABLE 3: Antimicrobial consumption				
	2014	2015	2016	P*
DDD of all antimicrobials per month, DDD per 100 PD	15 (3)	23 (4)†	20 (2)†	<0.01
DDD of carbapenem per month, DDD per 100 PD	3 (0.6)	2 (0.4)†	2 (0.5)†	<0.01
DOT of all antimicrobial per month, DOT per 100 PD	23 (2)	22 (2)	22 (2)	0.45
DOT of carbapenems per month, DOT per 100 PD	6 (1)	4 (0.8)†	4 (0.9)†	<0.01

Values are reported as means with standard deviation in parentheses.
* One-way ANOVA followed by Tukey–Kramer post-hoc test or $\chi 2$-test.
† Significant compared with 2014.
DDD=defined daily dose; DOT=days of therapy; PD=patient-days

TABLE 4: Multivariate logistic regression analyses of factors associated with de-escalations			
	Odds ratio	OR (95% CI)	P
Interventions by AST or ward pharmacists -	1.00		
Interventions by AST or ward pharmacists +	2.63	1.34-4.93	< 0.01

Abbreviations: OR, odds ratio; CI, confidence interval.
AST=antimicrbial stewardship team

TABLE 5: Multivariate logistic regression analyses of factors associated with intravenous to oral conversions			
	Odds ratio	OR (95% CI)	P
Intervention by ward pharmacists -	1.00		
Intervention by ward pharmacists +	2.29	0.67-5.99	0.13

Abbreviations: OR, odds ratio; CI, confidence interval.

and duration of carbapenem therapy are shown in Tables 4–6. Interventions by both the AST and ward pharmacists showed a positive association with de-escalations (OR, 2.63; 95% CI, 1.34–4.93), and interventions by ward pharmacists tended toward a positive association with intravenous to oral conversions (OR, 2.29; 95% CI, 0.67–5.99). Interventions by the AST had a negative association with duration of carbapenem treatment (adjusted R^2 values of 0.006).

DISCUSSION

The total number of interventions significantly increased after the ASP with once-weekly follow-up by ward pharmacists commenced. In multivariate analysis, interventions by the AST and ward pharmacists were associated with de-escalations and decreased duration of carbapenem therapy. However, interventions by the AST and ward pharmacists affected only 20% of all carbapenem regimens. Furthermore, the number of de-escalations and intravenous to oral conversions did not increase after interventions by ward pharmacists started. Nevertheless, the number of patients, consumption of carbapenem, and duration of carbapenem therapy decreased after increasing the total number of interventions. These results suggest that our interventions strongly affected carbapenem therapy because they promoted re-consideration of the regimen by the physicians. Additionally, these effects are supported by a systematic review (1). Moreover, the duration of carbapenem therapy decreased by one day from 10 days in 2014 to 9 days in 2015 and 2016. In a systematic review, the duration of antibiotic treatment decreased by 1.95 days from 11.0 days by ASP, which is similar to our result (1). In addition, mortality rates within 30 and 60 days were not changed by the interventions. Therefore, ASP with once-weekly follow-up by a ward pharmacist might improve the performance of the ASP and optimize carbapenem therapy without changing patient outcomes.

The susceptibility of *P. aeruginosa* to imipenem and meropenem increased from 70% to 80%, additionally, the DDD and DOT of carbapenems decreased by one-third after the total interventions increased. Goldstein et al. reported that the susceptibility of *P. aeruginosa* to imipenem increased from 61% to 81% after decreasing the amount of imipenem usage, which resembles our

TABLE 6: Multivariate regression analysis of factors associated with the duration of carbapenems

	Duration of carbapenems	*P*
Interventions by AST	-0.07 (0.28)	< 0.01
Notification to AST	0.05 (0.17)	0.10
Adjusted R^2	0.006	

Values are shown as the partial regression coefficient (standard error).

results (1,8). Therefore, ASP with once-weekly follow-up by a ward pharmacist might improve the susceptibility of *P. aeruginosa* to carbapenems by reducing carbapenem consumption.

Voluntary notifications to the AST by physicians regarding the diagnosis and reason for prescribing carbapenems commenced in November 2014. The AST was notified of approximately 80% of carbapenem therapy cases after 2015. However, multivariable analysis revealed that these notifications tended toward a positive association only with the duration of carbapenem therapy. However, the AST gained an understanding of the focus of the infection and the physician's diagnosis via these notifications. Therefore, we considered that notifications from physicians to the AST might offer several advantages other than the direct effects of antimicrobial use.

The DDD and DOT of all antimicrobials were 15 to 20 per 100 PD in this study, which is similar to a previous Japanese study (7). However, in the United States and France, the average DDD and DOT among all antimicrobials were reported to be 60 to 70 per 100 PD (9,10), which is contrary to our results. On the other hand, the average DDD among all antimicrobials were reported to be 16 per 100 PD in French local hospitals (10) and resembled those of our study. Thus, the consumption of antimicrobials in our hospital was lower than that in large hospitals and resembled the rates in local general hospitals. Alternatively, The DDD of all antimicrobials in 2015 and 2016 were significantly increased compared with 2014. This reason for this is that, although the consumption of carbapenems decreased, that of ampicillin/sulbactam and ceftriaxone increased. Additionally, the DDD of ampicillin/sulbactam and ceftriaxone was close to that recommended by the WHO, contrary to the DDD of other antimicrobials in Japan.

A once-weekly ASP targeting only carbapenems is not a standard procedure. Ideally, the ASP should target all antimicrobials and be performed daily. However, it is often difficult for smaller hospitals to manage a daily ASP because of limited human resources (4). Thus, a once-weekly ASP and follow-up by a ward pharmacist would be easier for smaller hospitals to introduce and manage, but the ultimate goal should be daily ASP targeting all antimicrobials.

Our study has some limitations because of its retrospective design, lack of a control group, and small sample size. Moreover, a once-weekly ASP targeting only carbapenems is not a standard procedure.

ASP with once-weekly follow-up by ward pharmacists improved carbapenem therapy and susceptibility of *P. aeruginosa* to carbapenem in our 261-bed Japanese hospital. These interventions are simple and beneficial methods that could be introduced to smaller hospitals with limited human resources.

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