1 Clinical outcomes of intervention for carbapenems and anti-methicillin-resistant
2 *Staphylococcus aureus* antibiotics by an antimicrobial stewardship team
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Conflict of Interest

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Abstract

Background: There are no reports on the effects of interventions, such as discontinuation and change/de-escalation of carbapenems and anti-methicillin-resistant *Staphylococcus aureus* (MRSA) antibiotics by an antimicrobial stewardship team focusing on detailed patient outcomes. This study aimed to evaluate these effects.

Methods: This retrospective cohort study was conducted at a tertiary care hospital from December 2018 to November 2019.

Results: Favorable clinical responses were obtained in 165/184 cases (89.7%) in the intervention-accepted group, higher than those in the not accepted group (14/19 cases, 73.7%; P=0.056). All-cause 30-day mortality was lower in the accepted group than in the not accepted group (1.1% and 10.5%, respectively; P=0.045). The microbiological outcomes were similar between the two groups. Duration of carbapenem and anti-MRSA antibiotic use in the accepted group was significantly lower than that in the not accepted group (median [interquartile range]: 8 days [5-13] versus 14 days [8-15], respectively, P=0.026 for carbapenem; 10 days [5.3-15] versus 15.5 days [13.8-45.3], respectively, P=0.014 for anti-MRSA antibiotic).

Conclusion: This is the first study to investigate the effects of interventions such as discontinuation and change/de-escalation of antibiotics on detailed outcomes. Our intervention could reduce the duration of carbapenem and anti-MRSA antibiotic use without worsening clinical and microbiological outcomes.

Keywords: Antimicrobial stewardship team; Carbapenem; Methicillin-resistant *Staphylococcus aureus*; Outcome; Antibiotic use

Highlights

Carbapenem and anti-MRSA antibiotic intervention showed 89.7% favorable outcome.

Carbapenem and anti-MRSA antibiotic intervention could reduce the antibiotic uses.

Discontinuation and de-escalation of antibiotics did not worsen clinical outcomes.

Introduction

Increasing antibiotic consumption has become a critical global issue.[1-3] The unnecessary and inappropriate use of antibiotics has led to the emergence of resistant bacteria, thereby creating difficulty in treating infections.[1-3] Antibiotic resistance extends

hospital stay and increases medical costs.[3] In addition, unnecessary antibiotic use also increases medical expenditure.[2]

To solve these problems, implementation of antimicrobial stewardship programs (ASP) has been recommended.[4-7] The Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) guidelines have recommended “formulary restriction and pre-authorization” and “prospective audit and feedback (PAF)” as strategies of ASP.[4,5] Several studies have reported that implementation of ASP promotes appropriate antibiotic use,[8-10] prevents or delays emergence of resistant bacteremia,[11-15] and reduces hospital stay[12,16,17] and medical expenditure.[18-20]

Some studies have demonstrated the efficacy and safety of ASP by evaluating the relationship between antibiotic use and clinical outcomes. For example, ASP, including recommendations for antibiotic discontinuation and change, reduced both antibiotic use and length of hospital stay.[7] In addition, intervention for meropenem[21] or broad-spectrum antibiotics[22] decreased the use of antibiotics without increasing mortality. However, most studies on ASP have evaluated outcomes by 30-day mortality or length of hospital stay and have not investigated individual detailed clinical and microbiological outcomes.[7,16,22]

To our knowledge, there are no reports on the effects of interventions, such as

discontinuation and change/de-escalation of carbapenems and anti-methicillin-resistant *Staphylococcus aureus* (MRSA) antibiotics, focusing on individual clinical response and microbiological outcomes. The present study aimed to evaluate the effects of intervention for these antibiotics on the detailed clinical and microbiological outcomes and duration of antibiotic use.

Patients and methods

Study Design and intervention

This retrospective cohort study was conducted at a 939-bed tertiary care medical center. The study protocol was approved by the ethics committee of the institution where the present study was conducted (Institutional Review Board number: 019-0120) and was performed in accordance with the Declaration of Helsinki. The requirement for informed consent was waived because of the retrospective observational nature of the study. This study was conducted using the opt-out method on our hospital website. Data of patients treated with carbapenems and/or anti-MRSA antibiotics between December 2018 and November 2019 were obtained for the present study from the medical charts.

Antimicrobial stewardship team (AST) pharmacists reviewed all cases where

carbapenem and/or anti-MRSA antibiotic were used, with a focus on their doses, duration of use, culture results, infection sites, therapeutic effects, and adverse effects. The reviews were performed from the start of treatment with the target antibiotics on weekdays. The reviewed carbapenems included meropenem, doripenem, and imipenem/cilastatin, which are intravenous carbapenems administered in our hospital. The reviewed anti-MRSA antibiotics included vancomycin, teicoplanin, linezolid, tedizolid, daptomycin, and arbekacin. Oral antibiotics linezolid and tedizolid were also reviewed. Data from patients admitted to the intensive care unit (ICU) were excluded from the review because our restriction and review systems were applied to patients in general wards.

Inappropriate use of antibiotics found on the pharmacist's review was discussed with AST members. The AST physician contacted prescribing physicians about the inappropriate use and made suggestions, such as discontinuation, change of antibiotic, de-escalation, change in dosage, addition of antibiotics, and/or addition of examination (blood, bacterial, and imaging tests). In addition to these suggestions, we checked the patients' status and/or provided information, such as side effects, to the physician. The status of patients identified in our review was checked by discussions with the prescribing physicians; there were no suggestions. These reviews and interventions, i. e.

PAF, were performed every weekday.

In our ASP, antibiotic discontinuation was recommended when the course of therapy, defined by guidelines, such as the Sanford guide to antimicrobial therapy,[23] was completed, and further antibiotic treatment was considered unnecessary due to sufficient improvement. De-escalation was recommended based on bacterial information, including minimum inhibitory concentrations, according to the following criteria: (1) severity was clinically improved, (2) other infection sites were excluded, and (3) febrile neutropenia was not continued.[24] Changes in antibiotics, such as change in anti-MRSA antibiotics, were recommended based on bacterial information or development of side effects, such as renal failure, thrombocytopenia, or increased levels of creatine kinase.

Data collection

The following data during the study period were extracted from the medical charts: age, sex, admission to the intensive care unit (ICU), surgery within 30 days, Sequential Organ Failure Assessment (SOFA) score, underlying disease, site of infection, concomitant drugs, whole blood cells (WBC), C-reactive protein (CRP), body temperature (BT), length of hospital stay, duration of antibiotic treatment, and bacterial information.

Definition of outcome

A favorable clinical response was defined as the resolution or partial resolution of the presenting symptoms and signs of infection. Clinical failure was defined as the persistence or worsening of symptoms and/or signs of infection. The clinical response was evaluated based on leukocytosis, inflammation, fever, and local signs. Microbiological persistence was defined as persistent detection of the same microorganisms and sources during antibiotic therapy. Microbiological recurrence was defined as the detection of the same microorganisms and sources within 30 days after discontinuation of antibiotic therapy. The outcomes were compared between the groups where the AST recommendation was accepted and that was not accepted.

Statistical analysis

In the statistical analyses of the characteristics and patient outcomes, categorical variables were compared using Fisher's exact test, and continuous variables were compared using the Mann-Whitney *U* test. Changes in WBC, CRP, and BT data were compared using Wilcoxon signed-rank test. Statistical significance was set at $P< 0.05$. The calculations were performed using JMP Pro version 14 (SAS Institute Inc., Japan) or

GraphPad Prism version 5 (GraphPad Software Inc., San Diego, CA, USA).

Results

Intervention

During the study period, the total number of patients treated with carbapenem was 673 (Table 1). Among these cases, we performed interventions for 144 cases (21.4%) and made recommendations for 98 cases, of which 89 (90.8%) were accepted. With regard to anti-MRSA antibiotics, the total number of patients was 710. We performed interventions in 195 cases (27.5%). Among them, we made recommendations for 146 cases and 136 cases (93.2 %) were accepted.

1 Table 1 Intervention for carbapenem and anti-MRSA antibiotic uses by AST.

2

Interventions	Carbapenem use (n=673)			Anti-MRSA antibiotic use (n=710)		
	Intervention		Accepted	Intervention		Accepted
	n	(%)	(%)	n	(%)	(%)
Recommendation						
Choice of antibiotic						
Discontinuation of antibiotic	39	(5.8)	92.3	50	(7)	92.0
Change/de-escalation of antibiotic	47	(7)	87.2	34	(4.8)	88.2
Addition of antibiotic	0	(0)	-	13	(1.8)	100
Dose adjustment						
Increase of dosage	6	(0.9)	100	9	(1.3)	77.8
Decrease of dosage	0	(0)	-	5	(0.7)	100
Others						
Recommendation of TDM	-	-	-	16	(2.3)	100
Addition of examination	5	(0.7)	100	17	(2.4)	100
Others	1	(0.2)	100	2	(0.3)	100
Checking patients' status	39	(5.8)	-	42	(5.9)	-
Providing information	7	(1)	-	7	(1)	-
Total	144	(21.4)	89/98 (90.8)	195	(27.5)	136/146 (93.2)

3

4 Abbreviations: AST, antimicrobial stewardship team; MRSA, methicillin-resistant

5 *Staphylococcus aureus*; TDM, therapeutic drug monitoring.

6

Population

Table 2 shows characteristics of the patients in which AST recommendation was done during the study period. In the analysis of the effect of our ASP, AST recommendations included the choice of antibiotic and dose adjustment and excluded elements, such as recommendation of TDM or examination, because the recommendation of TDM and examinations were considered to be indirectly associated with clinical outcome. Characteristics of patients between accepted and not accepted groups were almost similar except for the proportion of hematological malignancy, febrile neutropenia, and concomitant therapy.

1 Table 2 Characteristics of the patients in which AST recommendation[a] was done.

2

Characteristic	Accepted (n=184)	Not accepted (n=19)	P value
Age (year)	62 (43.5-71)	61 (55-65)	0.43
Sex (Men)	106 (57.6)	9 (47.4)	0.468
Admission to ICU within previous 30 days	43 (23.4)	1 (5.3)	0.081
Surgery within previous 30 days	57 (31)	3 (15.8)	0.197
SOFA score	2 (1-4)	4 (1-9)	0.064
Underlying condition			
Hypertension	40 (21.7)	7 (36.8)	0.156
Diabetes mellitus	25 (13.6)	3 (15.8)	0.731
Cardiovascular disease	48 (26.1)	2 (10.5)	0.169
Respiratory failure	17 (9.2)	2 (10.5)	0.694
COPD	2 (1.1)	1 (5.3)	0.257
Chronic renal insufficiency	15 (8.2)	2 (10.5)	0.664
Liver disease	19 (10.3)	3 (15.8)	0.441
Hepatic cirrhosis	7 (3.8)	0 (0)	1
Urogenital disorders	4 (2.2)	0 (0)	1
Cerebrovascular disease	24 (13)	2 (10.5)	1
HIV infection	1 (0.5)	0 (0)	1
Hematological malignancy	20 (10.9)	9 (47.4)	<0.001
Solid malignancy	77 (41.8)	5 (26.3)	0.226
Transplantation (solid)	8 (4.3)	0 (0)	1
Infection			
Intra-abdominal infection	59 (32.1)	4 (21.1)	0.438
Catheter-related blood stream infection	32 (17.4)	3 (15.8)	1
Urinary tract infection	21 (11.4)	3 (15.8)	0.477
Soft tissue infection	19 (10.3)	0 (0)	0.226
Febrile neutropenia	10 (5.4)	5 (26.3)	0.007
Osteomyelitis	13 (7.1)	0 (0)	0.616
Respiratory tract infection	9 (4.9)	3 (15.8)	0.089

Blood stream infection	7	(3.8)	0	(0)	1
Central nervous system infection	5	(2.7)	1	(5.3)	0.45
Others	6	(3.3)	0	(0)	1
Cardiovascular infections	3	(1.6)	0	(0)	1
Concomitant therapy					
Monotherapy	103	(56)	5	(26.3)	0.016
Bi-therapy	49	(26.6)	5	(26.3)	1
Three-therapy	26	(14.1)	7	(36.8)	0.019
Four-therapy	4	(2.2)	2	(10.5)	0.099
Five-therapy	1	(0.5)	0	(0)	1
Six-therapy	1	(0.5)	0	(0)	1
Days from start of carbapenem or anti-MRSA antibiotic to intervention	6	(2-11.8)	6	(4-9)	0.721

Data are presented as numbers (%) or medians (interquartile ranges).

[a] Recommendation includes choice of antibiotic and dose adjustment and excludes others such as recommendation of therapeutic drug monitoring (TDM) and addition of examination.

Abbreviations: AST, antimicrobial stewardship team; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; MRSA, methicillin-resistant *Staphylococcus aureus*.

Intervention based on target bacteria

Table 3 shows AST recommendations based on target bacteria. In intervention for carbapenem and anti-MRSA antibiotic uses, the most frequently conducted de-escalation was change to cefmetazole for *Escherichia coli* (including extended-spectrum β-lactamase producing type) (7 cases) and change to cefazolin for methicillin-sensitive *Staphylococcus aureus* (4 cases), respectively. In intervention for anti-MRSA biotic use, in addition to de-escalation, change to other anti-MRSA antibiotic or addition of anti-MRSA antibiotic for methicillin-resistant coagulase-negative Staphylococci or *Corynebacterium* species were performed frequently.

1 Table 3 AST recommendation (change/de-escalation and addition of antibiotics) based on target bacteria.

2

Bacteria	n	(%)	Accepted (n=184)										Not accepted (n=19)				
			Changed/de-escalation to (n)									Addition	Changed/de-escalation to (n)				
			AMPC	ABPC	CEZ	CMZ	CTRX	CAZ	CPZ/SBT	CFPM	Anti-MRSA antibiotics	(n)	CEZ	CMZ	CTRX	CFPM	Anti-MRSA antibiotics
Intervention for carbapenem use																	
MSSA	2	(6.5)			2												
MSCNS	1	(3.2)											1				
Serratia marcescens	1	(3.2)								1							
Bacteroides fragilis	1	(3.2)				1											
Enterococcus faecalis	1	(3.2)	1														
Enterococcus gallinarum	1	(3.2)									1						
Escherichia coli	10	(32.3)			4	4	1			1							
Escherichia coli (ESBL)	3	(9.7)				3											
Haemophilus influenzae (β-lactamaze (-))	1	(3.2)													1		
Klebsiella pneumoniae	2	(6.5)								1						1	
Klebsiella pneumoniae (ESBL)	2	(6.5)				1								1			
Peptostreptococcus species	1	(3.2)				1											
Pseudomonas aeruginosa	5	(16.1)						3	1	1							
Total	31	(100)	1		6	10	1	3	1	4	1		1	1	1	1	

Intervention for anti-MRSA antibiotic use									
MSSA	4	(8.7)		4					
MRSA	3	(6.5)			1	1			1
MSCNS	1	(2.2)		1					
MRCNS	20	(43.5)			15	5			
Corynebacterium species	11	(23.9)			5	6			
Enterococcus faecalis	1	(2.2)	1						
Enterococcus faecium	4	(8.7)			3	1			
Enterococcus gallinarum	1	(2.2)			1				
Klebsiella pneumoniae (ESBL)	1	(2.2)					1		
Total	46	(100)	1	5	25	13	1		1

Abbreviations: AST, antimicrobial stewardship team; AMPC, amoxicillin; ABPC, ampicillin; CEZ, cefazolin; CMZ, cefmetazole; CTRX, ceftriaxone; CAZ, ceftazidime; CPZ/SBT, cefoperazone/sulbactam; CFPM, cefepime; MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; MSCNS: methicillin-susceptible coagulase-negative Staphylococci; MRCNS, methicillin-resistant coagulase-negative Staphylococci; ESBL, extended-spectrum β-lactamase.

Changes in WBC, CRP, and BT

In the accepted group, WBC, CRP, and BT were significantly decreased one week after the intervention ($P<0.001$, respectively) (Table 4). In the not accepted group, although CRP and BT were numerically decreased one week after intervention, there were no significant differences.

Table 4 Changes in WBC, CRP, and BT of the patients in which AST recommendation[a] was done.

	At the time of intervention		1 week after intervention		P value
Accepted (n=184)					
WBC (/μL)	7150	(4400-10100)	5800	(4200-8250)	<0.001
CRP (mg/dL)	2.5	(1.1-7.9)	1.1	(0.4-3)	<0.001
BT (°C)	37.1	(36.7-37.5)	36.8	(36.6-37.1)	<0.001
Not accepted (n=19)					
WBC (/μL)	4800	(2275-7975)	6000	(3350-7150)	0.954
CRP (mg/dL)	2.2	(0.9-5.3)	0.8	(0.3-3.5)	0.202
BT (°C)	37.5	(37-37.8)	37.1	(36.8-37.6)	0.338

Data are presented as medians (interquartile ranges).

[a] Recommendation includes choice of antibiotic and dose adjustment and excludes others such as recommendation of therapeutic drug monitoring (TDM) and addition of examination.

Abbreviations: AST, antimicrobial stewardship team; WBC, whole blood cells; CRP, C-reactive protein; BT, body temperature.

Outcomes

Favorable clinical responses were obtained in 165 out of 184 cases (89.7%) in the accepted group, which was higher than those in the not accepted group (14/19 cases, 73.7%; P=0.056) (Table 5). In addition, all-cause 30-day mortality was lower in the accepted group than in the not accepted group (1.1% and 10.5%, respectively; P=0.045). However, there was no significant difference in the infection-related 30-day mortality between the accepted and not accepted groups (0.5% and 0%, respectively; P=1). The microbiological outcomes were similar between the two groups. The median length of hospital stay in the accepted and not accepted groups was 64 days (interquartile range [IQR] 44-134) and 88 days (IQR 48-171), respectively; P=0.538. Duration of carbapenem and anti-MRSA antibiotic use in the accepted group was significantly lower than that in the not accepted group (median [IQR], 8 days [5-13] versus 14 days [8-15], respectively; P=0.026 for carbapenem and 10 days [5.3-15] versus 15.5 days [13.8-45.3], respectively; P=0.014 for anti-MRSA antibiotic).

Table 5 Outcomes of the patients in which AST recommendation[a] was done.

Outcome	Accepted (n=184)		Not accepted (n=19)		P value
Clinical and microbiological outcome					
Favorable clinical response	165/184	(89.7)	14/19	(73.7)	0.056
All-cause 30-day mortality	2/184	(1.1)	2/19	(10.5)	0.045
Infection-related 30-day mortality	1/184	(0.5)	0/19	(0)	1
Microbiological persistence	13/58	(22.4)	1/4	(25)	1
Microbiological recurrence	10/72	(13.9)	1/7	(14.3)	1
Length of hospital stay (day)	64	(44-134)	88	(48-171)	0.538
Duration of carbapenem use (day)	8	(5-13)	14	(8-15)	0.026
Duration of anti-MRSA antibiotic use (day)	10	(5.3-15)	15.5	(13.8-45.3)	0.014

Data are presented as numbers (%) or medians (interquartile ranges).

[a] Recommendation includes choice of antibiotic and dose adjustment and excludes others such as recommendation of therapeutic drug monitoring (TDM) and addition of examination.

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

Discussion

To date, several studies regarding ASP, including recommendations for antibiotic discontinuation, change/de-escalation, addition, and dose adjustment, have been reported.[7,16,22,25] However, most of them have focused on antibiotic usage and have not investigated individual detailed clinical and microbiological outcomes other than 30-day mortality or length of hospital stay. To our knowledge, this is the first study to investigate the effects of interventions, such as discontinuation and change/de-escalation of carbapenems and anti-MRSA antibiotics, on detailed clinical and microbiological outcomes. Our results showed that our ASP could reduce the duration of carbapenem and anti-MRSA antibiotic use without worsening clinical and microbiological outcomes.

In our interventions, frequent recommendations were discontinuation and change of antibiotics (most frequent change for carbapenems was de-escalation), rather than performing TDM, also in interventions for anti-MRSA antibiotics (Table 1). This trend was consistent with other studies in which major recommendations were related to the choice of antibiotics.[7,22] A previous study investigated the safety and efficacy of de-escalating antibiotics[26]; *E. coli* was the most frequent pathogen, and second-generation cephalosporins (cefotiam, cefmetazole, and flomoxef) were mostly selected as definitive therapy, a trend consistent with our results (Table 3).

Several studies investigating the efficacy of ASP for broad-spectrum antibiotics, including carbapenems, have reported that there was no significant difference in all-cause and infection-related 30-day mortality between intervention and non-intervention groups, although it decreased numerically by intervention.[12,16,17,21,22] In contrast to these previous studies, the all-cause 30-day mortality was significantly reduced by intervention in our study (Table 5). A total of 4 patients died in two groups in the present study. In the accepted group, a patient died of an underlying disease (solid malignancy) and another patient died due to infection and an underlying disease (hematological malignancy). In the not accepted group, 2 patients died due to an underlying disease (hematological or solid malignancy). In the present study, severity of patients was numerically higher in the not accepted group than in the accepted group (SOFA score 4 and 2, respectively; P=0.064; Table 2). This might have been the cause of the higher all-cause mortality in the not accepted group. In addition, there were few deaths in our study, which could have introduced bias. When we analyzed mortality as infection-related, no difference was found between the accepted and not accepted groups, consistent with the results of the previous studies.[12,16,17,21,22]

In the present study, higher favorable clinical responses were obtained by our intervention, although the difference was not significant. In our study, the proportion of

hematological malignancy was higher in the intervention-not accepted group (Table 2), which could be a confounding factor. However, even when hematological malignancy was excluded from our population, similar trends were observed; that is, lower all-cause mortality and higher favorable clinical responses were obtained by the intervention (data not shown). Most studies regarding ASP, including recommendations such as antibiotic discontinuation and change/de-escalation, have not investigated detailed clinical and microbiological outcomes.[12,16,17,21,22] These previous studies evaluated only mortality or length of hospital stay as outcomes. However, our present study also evaluated the clinical response, microbiological persistence and recurrence, and changes in WBC, CRP, and BT. In our ASP, the interventions did not worsen the clinical and microbiological outcomes. Furthermore, when interventions were divided categorically, discontinuation and change (most were de-escalation in the case of carbapenems) also did not worsen the outcomes (data not shown); other categories could not be compared because all were accepted.

This study has several limitations. This was a retrospective single-center study that included patients with different characteristics, especially with respect to hematological malignancy, febrile neutropenia, and concomitant therapy. Thus, we cannot exclude the possibility that the outcomes did not deteriorate by discontinuation or de-escalation due

to the different backgrounds of the patients. Additionally, the sample size was small, and confounding factors could not be removed by multivariate analysis. These limitations should be considered when interpreting our results.

In conclusion, to our knowledge, this is the first study to investigate the effects of interventions such as discontinuation and change/de-escalation of carbapenems and anti-MRSA antibiotics on detailed clinical and microbiological outcomes. Our results showed that our ASP could reduce the duration of carbapenem and anti-MRSA antibiotic use without worsening clinical and microbiological outcomes. These results suggest that the review and intervention for these antibiotics by AST is as effective as ASP.

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