Effectiveness of Reporting System for Carbapenem Antibiotics in Restricting Their Use

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We designed a reporting system for the use of carbapenem antibiotics at Fuchu Hospital in order to restrict their use. We also examined the effect of the system on the number of vials of antibiotics used from December 2002 to November 2004 and compared the total amount of antibiotics used before and after introducing the system.

In our hospital, a large amount of panipenem is used, while the use of imipenem is limited. The antimicrobial use density (AUD) of panipenem decreased significantly from 9.85 to 7.59 due to the introduction of the reporting system ($p < 0.01$) while that of imipenem decreased from 0.06 to 0.04. Therefore, the introduction of the system significantly influenced the use of panipenem but not that of imipenem. Following its introduction, the rate of occurrence of panipenem-resistant *Pseudomonas aeruginosa* decreased from 41.38% to 24.00% ($p < 0.001$) while that of imipenem-resistant *P. aeruginosa* decreased from 18.23% to 10.91% ($p < 0.01$). We therefore conclude that the reporting system brought about an apparent reduction in the occurrence of carbapenem-resistant *P. aeruginosa*.

Key words carbapenem antibiotics, *Pseudomonas aeruginosa*, restricted use, antimicrobial use density, defined daily doses

Introduction

A series of broad-spectrum antibiotics have been introduced in clinical practice. However, the extensive use of antibiotics increases the risk of colonization and emergence of antibiotic-resistant strains such as methicillin-resistant *Staphylococcus aureus* (MRSA) that may cause clinical complications^{1,2}. Resistance to antipseudomonal antibiotics has increasingly become a problem in recent years following the emergence of a relatively high frequency of antimicrobial resistance during therapy^{3,4}. Further, the extensive use of carbapenem antibiotics was reported to be one of the risk factors for the occurrence of multiple drug-resistant *Pseudomonas aeruginosa* (MDRP) infections⁵. In order to prevent the outbreak of such infections, an infection control team (ICT) comprising pharmacists, physicians, nurses, and medical technologists was formed in Fuchu Hospital in 1996. This team has surveyed the clinical use of all antibiotics, particularly the use of carbapenem antibiotics, by using a report system. Recently, the World Health Organization (WHO) has recommended the number of defined daily doses

(DDD) as a unit of measure for comparing antimicrobial use⁶. Antimicrobial use density (AUD) can be calculated using the DDD number; this calculation is described in Methods. The AUD adjusts for the influence of the number of patients and number of days in the hospital. We calculated the AUD for the main antibiotics used by using the appropriate DDD number in the equation mentioned below (Methods, Calculation of the antimicrobial use density). The effect of restricting carbapenem use by the introduction of the report system was verified by using the calculated AUD. We evaluated whether the introduction of the report system was able to reduce the occurrence of carbapenem-resistant *P. aeruginosa*. In this study, the pharmacy worked in conjunction with the ICT. The pharmacy determined the appropriate use of the antibiotics with the ICT.

The pharmacy proposed the introduction of the report system at the infection control committee, and the report form was developed. The pharmacists proposed the method of operation of the report system. The operation method involved submitting the form to the pharmacy, ensuring the submission of the form to the pharmacy, and conveying the contents of the form to the ICT. If the doctor did not submit the

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form, the pharmacist did not give him the antibiotics. The pharmacist then called the doctor and explained the necessity of submitting the form to him. Not submitting the form constituted a violation of the report system ; preventing this violation is key to the success of this system. We attempted to eliminate this violation.

The purpose of this study is to decrease the inappropriate use of carbapenem antibiotics by the introduction of the report system. In addition, we speculate that the decreased resistance of *P. aeruginosa* to carbapenem is related to the decreased use of this antibiotic.

Methods

1. Experimental Procedure

Fuchu Hospital provides medical treatment for acute-phase patients ; it has 380 beds. The hospital has a variety of treatment departments (cardiology, pulmonology, hepatology, hematology, general medicine, surgery, neurosurgery, cardiac surgery, orthopedic surgery, urology, obstetrics and gynecology, radiology, ophthalmology, otolaryngology, and dermatology). This study aimed to examine the antibiotics used to treat patients in Fuchu Hospital. The antibiotics examined during this study are listed in Table 1. All the antibiotics in the list are medicines used in our hospital.

When using carbapenem antibiotics, such as panipenem and imipenem, the physician in charge is required to fill the form depicted in Fig. 1. Unless this form is submitted to the Department of Pharmacy, the physician in charge cannot use carbapenem antibiotics. By analyzing these forms, the ICT can examine the usage of all carbapenem antibiotics. This report system has been introduced since December 2003. In

Table 1 . List of the Antibiotics Examined in this Study.

Penicillin	Ampicillin (ABPC)	1 g
	Ampicillin/Cloxacillin	0.1 g
	Piperacillin (PIP)	1 g
	Ampicillin/Sulbactam (ABPC/SBT)	1.5 g
First-generation cephem	Cefazolin (CEZ)	1 g
Second-generation cepheids	Cefmetazole (CMZ)	1 g
	Cefotiam (CTM)	1 g
	Flomoxef (FMOX)	1 g
Third-generation cepheids	Cefoperazone (CPZ)	1 g
	Ceftazidime (CAZ)	1 g
Fourth-generation cepheids	Cefozopran (CZOP)	1 g
	Cefpirome (CPR)	1 g
Monobactam	Aztreonam (AZT)	1 g
Amino glycoside	Isepamicin (ISP)	0.2 g
	Gentamicin (GM)	0.04 g
	Dibekacin (DKB)	0.1 g
	Amikacin (AMK)	0.2 g
	Streptomycin (SM)	1 g
Carbapenem	Panipenem/Betamipron (PAPM/BP)	0.5 g
	Imipenem/Cilastatin (IPM/CS) *	0.5 g
Fosfomycin	Fosfomycin (FOM)	1 g
Tetracycline	Minocycline (MINO)	0.1 g
Lincomycin	Clindamycin (CLDM)	0.6 g
Macrolide	Erythromycin (EM)	0.5 g
New quinolone	Ciprofloxacin (CPFX)	0.3 g
Medicine for anti-MRSA	Arbekacin (ABK)	0.1 g
	Vancomycin (VCM)	0.5 g

* Temporary usage

this study, the total number of vials of carbapenem antibiotics used, such as panipenem and imipenem, from December 2002 to November 2003 and from December 2003 to November 2004 was calculated, and the effect of intervention in their use was evaluated as AUD. In addition, the use of other antibiotics was examined in an identical manner.

2. Calculation of the antimicrobial use density (AUD)

The AUD for each main antibiotic was calculated on the basis of its DDD number that is defined by the WHO by using the following equation^{7,8)}.

AUD =
$$\frac{\text{Total amount of antibiotics used in the period before and after the system was adopted}}{\text{DDD(g)} \times \text{patients days in the period before and after the system was adopted}} \times 1000 \text{ (patient days)}$$

The AUD for the main antibiotics that was calculated on the basis of the corresponding DDD number are summarized in Table 2.

3. Evaluating susceptibility to the antibiotics

The susceptibility to the antibiotics was classified as sensitive (S), resistant (R), and intermediate (I) based on the guidelines proposed by the National Committee for Clinical Laboratory Standards. Each examination was performed by

Patient Number
Name
Date of birth
Sex
Age
Ward
Prescription day

Director
Physician in charge

Report on the use of carbapenems

Beginning of use

Check the reason for the use of carbapenems

☐ sepsis

☐ other antibiotics are ineffective

☐ Others ()

Underlying disease ()

Name of infectious disease ()

Clinical symptoms

Body temperature °C

CRP mg/dl

History of antibiotic use

1. g/day / ~ /

2. g/day / ~ /

3. g/day / ~ /

1. g/day / ~ /

Report day: Name of the physician in charge

() ()

Discontinuance of use

Date of discontinuance of carbapenem use

Report day: Name of the physician in charge

() ()

Please submit the upper part of the form entitled "Beginning of use" to the pharmacy after it has been completed and signed by the Director and the physician. After confirming the receipt of the report, carbapenem antibiotics will be provided to each ward based on the report. Please insert the form between the first page of the patient's clinical record as soon as it is delivered to the ward. Please submit the lower part of the form entitled "Discontinuance of use" to the pharmacy when carbapenem is no longer effective, when medication with another antibiotic has been started, or when the status of the infectious disease has improved.

Fig. 1 . Form Used to Report the Use of Carbapenems.

using the disk method, and the automatic detector from Becton Dickinson was operated by the medical technologist at our hospital. The rates for the occurrence of resistant *P. aeruginosa* before and after the introduction of the report system were compared by using the susceptibility test for carbapenem antibiotics.

Results and Discussion

Fig. 2 shows the effect of the carbapenem report system on the total amount of all antibiotics (open circle) and the total amount of carbapenem antibiotics (closed square) used in terms of the total number of vials used during each half year from December 2002 to June 2003, July 2003 to No-

vember 2003, December 2003 to June 2004, and July 2004 to November 2004. With regard to the total amount of antibiotics used, no significant effect was observed following the introduction of the report system. However, as shown in Fig. 2, the system caused a decrease in the use of carbapenem antibiotics. The AUD for panipenem was calculated by using the total amount of panipenem used each year before and after the introduction of the report system in the abovementioned equation (Methods, Calculation of the antimicrobial use density). The introduction of the report system significantly reduced the AUD for panipenem from 9.85 to 7.59 ($p < 0.01$, Chi-square test) while that for imipenem decreased from 0.06 to 0.04, i.e., no significant difference in its use was observed following the introduction of the report

Table 2 . Comparison of the Overall Amount of Antibiotics and the Antimicrobial Use Density (AUD) Used at Fuchu Hospital before and after the Implementation of the System.

	Before the introduction of the system		After the introduction of the system		Increase and decrease
	total amount	AUD	total amount	AUD	
Penicillin	7169	7.35	7880	7.71	↑
The first generation cephem	13728	34.61	12415	31.31	↓
The second generation cephem	17239	32.6	17334	32.79	↑
The third generation cephem	6414	12.13	7412	14.02	↑
The fourth generation cephem	4111	7.77	5701	10.79	↑
Monobactam	429	0.81	411	0.78	-
Amino glycoside	1906	4.24	1439.5	3.20	-
Carbapenem	5234	9.91	4044	7.63	↓
Fosfomycin	3525	3.33	2083	1.97	↓
Tetracycline	829	3.14	1353	5.12	-
Lincomycin	3265	8.23	2444	6.16	↓
Macrolide	217	0.82	216	0.82	-
New quinolone	203	0.92	534	2.42	-
Medicine for anti-MRSA	3024	5.72	2888	5.51	↓

With regard to antibiotics of which more than 2000 vials used during the evaluation periods, we described the increase and decrease.

Fig 2 . Changes in the Overall Amounts of Antibiotics Used and the total Amounts of Carbapenem Antibiotics used from December 2002 to November 2004.

The open circle represents the overall amount of antibiotics. The closed square represents the total amount of carbapenem antibiotics. An arrow represents the month when for the report system was introduced.

system (Fig. 3).

Generally, carbapenem antibiotics are used to treat sepsis, severe infections, and refractory infections, and their use is recommended when other antibiotics are ineffective. However, physicians tend to prescribe carbapenem antibiotics even to those patients who do not fulfill the abovementioned criteria; this results in the emergence of carbapenem-resistant *P. aeruginosa* and also MDRP. Our report system compels physicians to specify the reason for the choice of carbapenem in the form and therefore restricts the excessive use of carbapenem antibiotics. (Fig. 3)

The total number of antibiotic vials used from December 2002 to November 2004 and the AUD before and after the introduction of the report system is summarized in Table 2. The report system caused a significant decrease in the use of carbapenem as well as in the use of first-generation cepheims, fosfomycin, lincomycin, and anti-MRSA drugs; however, it caused an increase in the use of fourth-generation cepheims, i.e., ceftazopran and ceftipime, and second- and third-generation cepheims. The introduction of the system significantly reduced the AUD for carbapenem, although the overall use of antibiotics remained unaltered. Interestingly, the AUD of both third- and fourth-generation cepheims increased from 12.13 to 14.02 and from 7.77 to 10.79, respectively. These increases may be attributed to the substitution of carbapenem antibiotics with these cepheims for treating *P. aeruginosa* infections.

Fig. 4 and 5 show the changes in the susceptibility of *P. aeruginosa* to panipenem and imipenem before and after the introduction of the report system. The appearance of panipenem-resistant *P. aeruginosa* decreased significantly from 41.38% to 24.00% after the introduction of the system ($p < 0.001$; Chi-square test), while the appearance of imipenem-resistant *P. aeruginosa* decreased from 18.23% to 10.91% ($p < 0.01$). Following the introduction of the report system, the reduced occurrence of panipenem-resistant *P. aeruginosa* was more apparent than that of imipenem-

Fig 3 . Comparison of the Antimicrobial Use Density for Carbapenem before and after the Introduction of the System.

Fig 4 . Change in Susceptibility of *Pseudomonas aeruginosa* to Panipenem after the Introduction of the System (inpatients).

The susceptibility to antibiotics is classified as sensitive(S), resistant(R), and intermediate(I) based on the guidelines proposed by the National Committee for Clinical Laboratory Standards.

Fig 5 . Change in Susceptibility of *Pseudomonas aeruginosa* to Imipenem after the Implementation of the System (inpatients).

The susceptibility to antibiotics is classified as sensitive(S), resistant(R), and intermediate(I) based on the guidelines proposed by the National Committee for Clinical Laboratory Standards.

resistant *P. aeruginosa*. The reduced occurrence was proportionate to the total amounts of both carbapenems used. In our hospital, more than 95% of the total carbapenem used is panipenem; hence, there was an obvious reduction in the occurrence of panipenem-resistant *P. aeruginosa* following the introduction of the report system. As described above, following the introduction of the system, the total amount of carbapenem antibiotics used decreased, while the total amounts of penicillins and second-, third-, and fourth-generation cephem antibiotics used increased.

Consequently, the susceptibility of *P. aeruginosa* to both piperacillin and ceftazopran decreased, as shown in Fig. 6 and 7. There was a slight increase in the susceptibility of *P. aeruginosa* to ceftazopran, which was intermediate (I), ($p < 0.05$, Fig. 6), while the susceptibility of *P. aeruginosa* to piperacillin did not change significantly. The AUD for piperacillin increased from 7.35 to 7.71 and that for piperacillin, a type of penicillin, increased from 2.40 to 3.04. Because the amount usage of piperacillin in that of all antibiot-

Fig 6 . Change in Susceptibility of *Pseudomonas aeruginosa* to Piperacillin after the Implementation of the System (inpatients).

The susceptibility to antibiotics is classified as sensitive(S), resistant(R), and intermediate(I) based on the guidelines proposed by the National Committee for Clinical Laboratory Standards.

Fig 7 . Change in Susceptibility of *Pseudomonas aeruginosa* to Cefoperazone after the Implementation of the System (inpatients).

The susceptibility to antibiotics is classified as sensitive(S), resistant(R), and intermediate(I) based on the guidelines proposed by the National Committee for Clinical Laboratory Standards.

ics had become the result without too much a lot, there was no change in the susceptibility to this antibiotic. However, a decrease in susceptibility toward this antibiotic is predicted. The AUD for cefoperazone, a third-generation cephem, increased from 6.18 to 7.18 ; thus, there was a slight decrease in the susceptibility to cefoperazone. It should be noted that the susceptibility to cefoperazone decreases if its usage increases.

Table 3 shows the results regarding the detection of MDRP in our hospital before and after the introduction of the system. Prior to the introduction of the report system, over the past one year, MDRP was detected in 2.1% (five

cases) of 233 *P. aeruginosa*. However, the introduction of the system decreased the rate of MDRP to 0.66% during the same period ; however, this decrease was not significant.

There are some hospitals applying the report system⁹⁻¹²⁾. The submission rate was various. (40%⁹⁾, 77.5%¹⁰⁾, 91.4%¹¹⁾, from 80% to approximately 100%¹²⁾) In a past study, it was mentioned about the relation of the pharmacist to the report system as follows. If a doctor does not submit the report, a pharmacist contacts a nurse of the infection management room. A pharmacist manages the report. (It is not mentioned what a pharmacist does concretely.) If a doctor does not submit the report, a pharmacist contacts a chief physician or ICD.

There is a common point in a past study⁹⁻¹²⁾. It is that submission rate is not 100%. Though a report system is applied, the doctor can use the antibiotics even if the doctor does not submit a report. In this study, a pharmacist told the necessity of the report system to a doctor and the submission rate was 100%. It is necessary for the pharmacist to maintain communication with a doctor. The pharmacist contacted all doctors who did not submit a report, and they understood it. A difference with a past study and this study is that the pharmacist contacted all doctors who did not understand the report system and led them to follow a rule.

There is the study about the introduction of the report system in the broad spectrum antibiotics till now. In the past study, the total number of antibiotic vial was compared in the introduction of report system. In the neither study, AUD was used. If inpatients decrease in an investigation period, the total number of antibiotic vial decreases. If the period when the patient is hospitalized shortens, the total number decreases. It is necessary to add the number of inpatients and the hospitalization days so that we compare the use situation of the antibiotics appropriately. Therefore we used the AUD which was the value that revised the number of inpatients and the hospitalization days. Because we calculated AUD, we were able to compare quantity of the antibiotics more appropriately.

It has been reported that the development of bacterial resistance to antibiotics is correlated to the amount of antibiotic used, and optimization of antibiotic treatments is clearly required to prevent resistance^{13,14)}. Antibiotic control programs have played an important role in helping prevent the emergence of bacterial resistance^{15,16)}. In our hospital, the introduction of the report system for the use of both panipenem and imipenem has contributed enormously to the reduction in the total amount of carbapenem antibiotics used, has prevented the emergence of carbapenem-resistant

Table 3 . Detection of Multiple Drug-resistant *Pseudomonas aeruginosa* (MDRP) before and after the Implementation of the System.

	<i>P. aeruginosa</i>	MDRP	total	Ratio of MDRP[%]
Before the introduction	233	5	238	2.10
After the introduction	299	2	301	0.66

(N.S., Chi-square test)

P. aeruginosa, and has reduced the occurrence of MDRP.

We plan to establish appropriate guidelines for the use of third- and fourth-generation cephem antibiotics on the basis of the present study.

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