ORIGINAL PAPER

Nagoya J. Med. Sci. **74**. 93 ~ 104, 2012

A PERMISSION SYSTEM FOR CARBAPENEM USE REDUCED INCIDENCE OF DRUG-RESISTANT BACTERIA AND COST OF ANTIMICROBIALS AT A GENERAL HOSPITAL IN JAPAN

YOSHIAKI IKEDA[1,3], TAKAYOSHI MAMIYA[3,4], HIDEKI NISHIYAMA[2], SHIHO NARUSAWA[3], TAKENAO KOSEKI[3], AKIHIRO MOURI[3] and TOSHITAKA NABESHIMA[3,4]

[1]*Department of Pharmacy, Japanese Red Cross Nagoya Daiichi Hospital, Nagoya, Japan*
[2]*Department of Clinical Laboratory, Japanese Red Cross Nagoya Daiichi Hospital, Nagoya, Japan*
[3]*Department of Chemical Pharmacology, Graduate School of Pharmaceutical Sciences, Meijo University, Nagoya, Japan*
[4]*Japanese Drug Organization for Appropriate Use and Research, Nagoya, Japan*

ABSTRACT

Some drug management systems have been established in Japanese hospitals to reduce medical costs and regulate drug usage. Among the many available prescription drugs, antimicrobials should be given special attention because their inappropriate use often leads to sudden outbreaks of resistant bacteria. As drug specialists, pharmacists should monitor the use of all drugs, particularly antimicrobials. Carbapenems are a class of broad-spectrum antimicrobials that are widely used to treat infections worldwide. However, their inappropriate use has led to an increase in the incidence of drug-resistant bacteria and consequently, medical costs, at hospitals. To reduce inappropriate use and drug resistance, we have established a permission system to control the use of carbapenems at the Japanese Red Cross Nagoya Daiichi Hospital. In this study, we retrospectively evaluated the applicability of the new permission system compared to that of the notification system and the non control system for 14 months each. The two management systems were able to maintain total antibiotic use density and control the outbreak of drug-resistant bacteria (*P. aeruginosa, E. coli,* and *K. pneumoniae*). The number of carbapenem prescriptions was decreased dramatically when this permission system was enforced. Compared to the non control system, the cost of antimicrobials was reduced by $757,470 for the 14-month study period using the permission system. These results suggest that our system to control the use of antimicrobials can efficiently suppress the incidence of drug-resistant bacteria and medical costs at hospitals.

Key Words: Carbapenem, Antimicrobial, Permission system, ATC/DDD system, Drug-resistant bacteria

INTRODUCTION

Most drugs are developed with the objective of treating patients. As antimicrobials exert their effects not on patients directly but on pathogenic microorganisms, it is necessary to ensure that the therapy will benefit the patients. Antimicrobials are classified into at least 10 types by chemical structure (penicillins, cephems, oxacephems, carbapenems, aminoglycosides, lincos-

Corresponding Author: Toshitaka Nabeshima, PhD
Department of Chemical Pharmacology, Graduate School of Pharmaceutical Sciences, Meijo University, 150 Yagotoyama, Tempaku-ku, Nagoya 468-8503, Japan
Tel: +81-52-839-2735, Fax: +81-52-839-2738, E-mail: tnabeshi@meijo-u.ac.jp

amides, tetracyclines, quinolones, glycopeptides, and others) and each has a specific spectrum. Of these, carbapenems are one of the most potent, broad-spectrum antimicrobials that have low adverse effects and prove effective against infections.[1,2] Because of this, they are often used to treat infections caused by enterobacteria that produce extended-spectrum β-lactamases. However, the emergence of enzymes capable of inactivating carbapenems would limit the options for treatment. To suppress the incidence of drug-resistant bacteria, the appropriate use of antimicrobials that are stronger than conventional ones is required. In the USA, some management systems for proper antimicrobial use have been proposed,[3-8] but they have yet to be enforced. In Europe, it has been reported that a relationship exists between the amount of antimicrobials used and the incidence of drug-resistant bacteria.[9-12] However, there is no system in place to reduce both the use of antimicrobials and the incidence of drug-resistant bacteria. In 2007, the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America developed antimicrobial stewardship programs that include the appropriate selection, dosing, routing, and duration of antimicrobial therapy determined by medical doctors, pharmacists, medical technologists, infection control practitioners, and hospital administrators. The programs focus on ensuring the proper use of antimicrobials to assure the best patient outcomes, lessen the risk of adverse effects, promote cost-effectiveness, and reduce or stabilize resistance levels. Until recently, their focus has been on the first three goals (patient outcome, toxicity, and cost). It is likely that now, the objective of mitigating antimicrobial resistance will be paramount.[13]

Similar to the Centers for Disease Control and Prevention (CDC) in the USA,[14] the Japanese Ministry of Health, Labour and Welfare has recommended that medical facilities reduce antibiotic prescriptions to suppress the emergence of drug-resistant bacteria. Based on that recommendation, we at the Japanese Red Cross Nagoya Daiichi Hospital have organized an Infection Control Team (ICT) to provide information on infections and encourage the appropriate use of antimicrobials.

We have also developed two drug management systems; a notification system and a permission system, to control the prescription of carbapenems and suppress the emergence of drug-resistant bacteria. The former system requires medical doctors to inform the pharmacy whenever they prescribe carbapenems. The latter system requires medical doctors to secure permission from the department head or the ICT before prescribing carbapenems. The approval is effective for only two weeks. Despite many reports on notification and permission systems in Japan, no study has compared the use of those two systems for more than 12 months at the same hospital.

Here, we evaluated the feasibility of the permission system in comparison with the notification system and the non control system for 14 months each. In addition, we checked the use of various antimicrobials, the appearance of drug resistance to three bacteria [*Pseudomonas aeruginosa* (*P. aeruginosa*), *Escherichia coli* (*E. coli*), and *Klebsiella pneumoniae* (*K. pneumoniae*)], and the medical costs incurred during the period.

METHODS

We divided 42 months into three 14-month periods, as follows:

(i) Non control system (April, 2005 to May, 2006): Medical doctors can prescribe any antimicrobials including carbapenems without any notification or permission.

(ii) Notification system (June, 2006 to July, 2007): Medical doctors must inform the pharmacy whenever they prescribe carbapenems.

(iii) Permission system (August, 2007 to September, 2008): Medical doctors must secure permission from the department head or the ICT before prescribing carbapenems.

When the medical doctors prescribe antimicrobials, they must follow the instructions in each system. As no major influenza epidemic occurred during those periods, the amount of antimicrobials prescribed was not affected by it.

We surveyed antimicrobial use at Japanese Red Cross Nagoya Daiichi Hospital from the prescriptions made during those periods and calculated the cost of antimicrobials based on a price list of medicines in Japan (2008). All prescriptions were kept in the pharmacy together with

Table 1 Abbreviations and defined daily dose (DDD) of antimicrobials used in this study

Efficacy group		General name	Abbreviation	DDD
Carbapenem		biapenem	BIPM	1.2*
		panipenem / batamipron [1)]	PAPM / BP	2
		imipenem / cilastatin	IPM / CS	2
		doripenem [2)]	DRPM	1.5*
		meropenem	MEPM	2
Penicillin		piperacillin	PIPC	14
		ampicillin / cloxacillin	ABPC / MCIPC	2
		ampicillin / sulbactam	ABPC / SBT	2
Cephem	1st generation	cefazolin	CEZ	3
	2nd generation	cefmetazole	CMZ	4
		cefotiam [3)]	CTM	4
	3rd generation	cefotaxime	CTX	4
		ceftriaxone [4)]	CTRX	2
		sulbactam / cefoperazone	SBT / CPZ	4
	4th generation	cefozopran	CZOP	4*
		cefpirome	CPR	4
		cefepime	CFPM	2
Oxacephem		flomoxef	FMOX	4*
Aminoglycoside		amikacin	AMK	1
		tobramycin	TOB	0.24
Lincosamide		clindamycin	CLDM	1.8
Tetracycline		minocycline	MINO	0.2
Quinolone		pazufloxacin [5)]	PZFX	1
		ciprofloxacin	CPFX	0.5
Medicine for anti-MRSA		teicoplanin	TEIC	0.4
		vancomycin	VCM	2
		arbekacin	ABK	0.2
		linezolid [6)]	LZD	1.2
fosfomycin			FOM	8

1) 2008.7 withdrawn, 2) 2007.6 adoption, 3) 2007.7 withdrawn, 4) 2008.4 adoption, 5) 2007.9 withdrawn, 6) 2006.8 adoption.
*: maximum dose recommended by pharmaceutical companies as the daily standard dosage. DDD: defined daily dose.

the original diagnosis cards for the patients. The antimicrobials used and the defined daily dose (DDD) are listed in Table 1. Drugs marked by an asterisk (*) are defined by the maximum dose that pharmaceutical companies recommend as the daily standard dosage. All except three of the antimicrobials listed could be used throughout this study. Panipenem/batamipron, cefotiam, and pazufloxacin were withdrawn, and doripenem, ceftriaxone, and linezolid were adopted, as shown in Table 1. We determined antimicrobial use density (AUD) using the Anatomical Therapeutic Chemical Classification System with Defined Daily Dose (ATC/DDD system).[15] This system can evaluate AUD among hospitals, regions, and countries and is recommended by WHO as an international standard.[16] AUD (DDD/100 bed days) = amount of antimicrobial (g)/DDD/total hospitalization days of inpatient (bed days) × 100.

Antibacterial activity: We checked drug resistance to the three most problematic bacteria worldwide (*P. aeruginosa, E. coli,* and *K. pneumoniae*). Antimicrobial susceptibility tests of all isolates were performed by the Broth Microdilution (BMD) method as described in the Clinical and Laboratory Standards Institute (CLSI) document M100-S16 (2006).[17] Then, we classified the isolated bacteria into three groups: "susceptible," "resistant," and "intermediate" (Tables 3–5). This classification was based on the standard MIC breakpoints set by CLSI. We judged "drug-resistant bacteria" and estimated isolation (%) as the incidence of drug-resistant bacteria when we found that the MIC values indicated "resistant" and "intermediate."

Data analysis: All results are expressed as means ± SD for each group. AUD and the incidence of drug-resistant bacteria were analyzed with the Mann-Whitney U-test and the χ^2 test, respectively. $P<0.05$ was taken to indicate statistical significance. This retrospective study was approved by the Institutional Review Board of our hospital.

RESULTS

AUD under notification and permission systems

Under the non control system, carbapenem AUD was 3.84, whereas under the notification and permission systems, it was 2.62 and 0.75, respectively (Fig. 1A). Total AUDs were 20.39, 21.03, and 21.14 under the non control, notification, and permission systems, respectively (Fig. 1B), and no significant difference was observed among them. Carbapenem accounted for approximately 18.8% of the total antimicrobials prescribed under the non control system, and this value was reduced to 3.5% under the permission system. The detailed results are shown in Table 2. The decrease in AUD of carbapenem under the permission system paralleled those of tetracycline, anti-MRSAs, and fosfomycin. Meanwhile, increases in AUDs of cephem, aminoglycoside, lincosamide, and quinolone were observed, whereas the AUDs of penicillin and oxacephem showed no change (Table 2).

Economic benefits of antimicrobials under permission system

The costs of antimicrobials under the non control, notification, and permission systems were 3.49, 3.42, and 2.73 million dollars, respectively (based on the exchange rate of $1=¥83 for March 15, 2011), for each 14-month period (Fig. 2). The antimicrobial cost for the permission system was $ 757,470 less than that for the non control system, indicating a 21.7% reduction in antimicrobial cost.

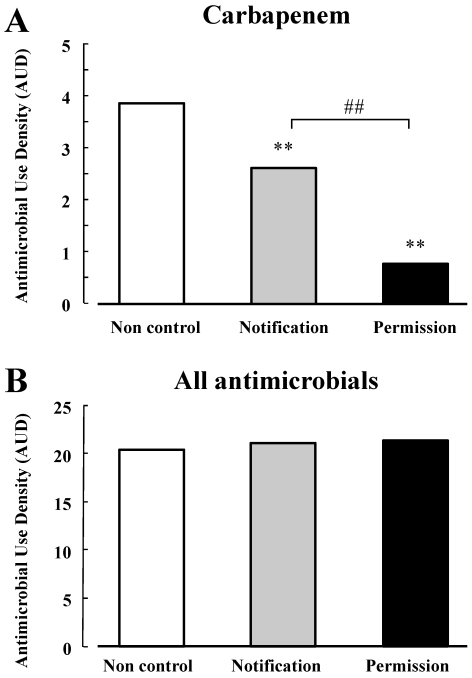

Fig. 1 Effects of enforcing notification and permission systems for (A) carbapenem and (B) all antimicrobials, expressed as antimicrobial use density (AUD), for 14 months. $^{**}P<0.01$ vs. Non control system, $^{\#\#}P<0.01$ vs. Notification system.

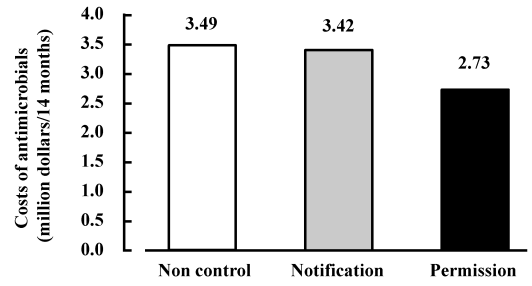

Fig. 2 Effects of enforcing notification and permission systems for carbapenem use on the cost of antimicrobials for 14 months each.

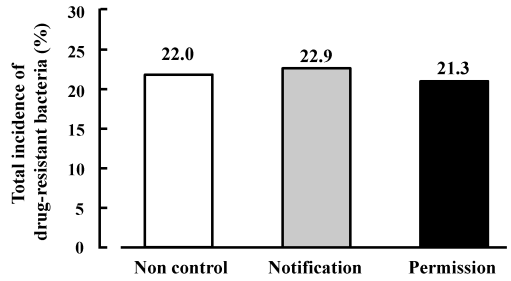

Fig. 3 Effects of enforcing notification and permission systems for carbapenem use on the total incidence of drug-resistant bacteria (%) for 14 months each.

Decrease in incidence of drug-resistant bacteria under permission system.

The total incidence of drug-resistant bacteria was 22.0, 22.9, and 21.3 under the non control, notification, and permission systems, respectively (Fig. 3). The incidence of carbapenem-resistant *P. aeruginosa* was significantly reduced under the permission system, whereas that of carbapenem-resistant *E. coli* and *K. pneumoniae* showed no changes (Tables 3–5).

In contrast, the incidence of cephem-resistant *P. aeruginosa*, *E. coli,* and *K. pneumoniae* was significantly increased under both notification and permission systems. The notification system did not result in any decrease in the incidence of drug-resistant bacteria except for minocycline against *E. coli*.

Under the permission system, compared to non control system, the incidence of resistant *P. aeruginosa* was increased by cephem, decreased by carbapenem, and not affected by other antimicrobials; that of resistant *E. coli* was increased by cephem and oxacephem, decreased by minocycline and fosfomycine, and not affected by other antimicrobials; and that of resistant *K. pneumoniae* was increased by cephem, and not affected by other antimicrobials in all the antimicrobials we tested. The patients infected with cephem-resistant *P. aeruginosa*, were cured by treatment of carbapenem, quinolone and/or aminoglycoside. The detailed results are shown in Tables 3–5.

Table 2 Antimicrobial use density (AUD) during enforcement of non control, notification, and permission systems, respectively

Antimicrobials		Abbreviation	Antimicrobial Use Density (AUD)		
			Non control system	Notification system	Permission system
Carbapenem		BIPM	0.54±0.12	0.36±0.21	0.03±0.03
		PAPM / BP	0.24±0.20	0.17±0.09	0.06±0.06
		IPM / CS	0.45±0.15	0.26±0.07	0.06±0.03
		DRPM	–	0.01±0.02	0.02±0.03
		MEPM	2.61±0.23	1.82±0.47	0.58±0.16
		total	3.84±0.36	2.62±0.69$^{\downarrow\downarrow}$	0.75±0.19$^{\downarrow\downarrow,\downarrow\downarrow}$
Penicillin		PIPC	0.11±0.03	0.27±0.10	0.29±0.10
		ABPC / MCIPC	0.10±0.06	0.13±0.08	0.09±0.07
		ABPC / SBT	3.30±0.61	3.19±0.47	3.45±0.60
		total	3.51±0.65	3.59±0.53	3.83±0.56
Cephem	1st generation	CEZ	0.81±0.26	0.94±0.22	1.56±0.18$^{\uparrow\uparrow,\uparrow\uparrow}$
	2nd generation	CMZ	1.25±0.22	1.23±0.24	1.84±0.14
		CTM	1.11±0.19	1.32±0.44	–
		total	2.36±0.32	2.55±0.34	1.84±0.14$^{\downarrow\downarrow,\downarrow\downarrow}$
	3rd generation	CTX	0.24±0.12	0.28±0.11	0.25±0.10
		CTRX	–	–	0.32±0.44
		SBT / CPZ	0.12±0.02	0.10±0.03	0.14±0.05
		total	0.36±0.11	0.38±0.11	0.70±0.45$^{\uparrow,\uparrow}$
	4th generation	CZOP	0.56±0.09	0.53±0.20	0.62±0.19
		CPR	0.30±0.10	0.30±0.09	0.09±0.03
		CFPM	2.79±0.59	4.23±0.62	5.94±0.56
		total	3.65±0.57	5.06±0.68$^{\uparrow\uparrow}$	6.65±0.72$^{\uparrow\uparrow,\uparrow\uparrow}$
	total		7.18±0.48	8.93±0.66$^{\uparrow\uparrow}$	10.75±0.68$^{\uparrow\uparrow,\uparrow\uparrow}$
Oxacephem		FMOX	2.07±0.15	1.96±0.21	2.06±0.31
Aminoglycoside		AMK	0.31±0.07	0.46±0.07	0.64±0.15
		TOB	0.02±0.01	0.04±0.03	0.04±0.03
		total	0.33±0.06	0.50±0.09$^{\uparrow\uparrow}$	0.68±0.15$^{\uparrow\uparrow,\uparrow\uparrow}$
Lincosamide		CLDM	0.63±0.12	0.55±0.13	0.96±0.25$^{\uparrow\uparrow,\uparrow\uparrow}$
Tetracycline		MINO	1.17±0.24	0.86±0.25$^{\downarrow\downarrow}$	0.51±0.24$^{\downarrow\downarrow,\downarrow\downarrow}$
Quinolone		PZFX	0.12±0.06	0.08±0.09	0.01±0.03
		CPFX	0.51±0.19	0.70±0.30	0.79±0.16
		total	0.63±0.23	0.78±0.36	0.80±0.14$^{\uparrow}$
anti-MRSAs		TEIC	0.27±0.12	0.36±0.18	0.17±0.12
		VCM	0.56±0.11	0.66±0.23	0.41±0.17
		ABK	0.07±0.06	0.11±0.15	0.06±0.06
		LZD	–	0.03±0.05	0.12±0.12
		total	0.90±0.16	1.16±0.33	0.76±0.29$^{\downarrow\downarrow,\downarrow\downarrow}$
FOM			0.13±0.04	0.11±0.03	0.04±0.02$^{\downarrow\downarrow,\downarrow\downarrow}$
total			20.39±1.19	21.03±0.85	21.14±1.12

↑: P<0.05, ↑↑ or ↓↓: P<0.01 vs. Non control system, ↑: P<0.05, ↑↑ or ↓↓: P<0.01 vs. Notification system. DRPM, CTRX and LZD were adopted, and CTM was withdrawn during this study.

Table 3 Incidence of drug-resistant *P. aeruginosa* (%)

Antimicrobials		Abbreviation	MIC[1)] S	I	R	Incidence of Drug-resistant *P. aeruginosa* (%) Non control system	Notification system	Permission system
Carbapenem		IPM / CS	≦4		>8	32.4 (156/481)	35.4 (192/543)	20.0 (111/554)
		MEPM	≦4		>8	21.1 (101/478)	27.3 (148/543)	16.2 (90/554)
		total				26.8 (257/959)	31.3$^{\uparrow}$ (340/1086)	18.1$^{\downarrow\downarrow,\downarrow\downarrow}$ (201/1108)
Penicillin		PIPC	≦16		>64	8.9 (43/481)	12.3 (67/543)	9.7 (54/555)
Cephem	3rd generation	CTX	≦8		>32	89.0 (428/481)	88.2 (479/543)	87.7 (487/555)
	4th generation	CZOP	≦8		>16	13.7 (66/481)	18.8 (102/543)	17.8 (99/555)
		CPR	≦8		>16	25.2 (121/481)	32.2 (175/543)	31.7 (176/555)
		CFPM	≦8		>16	20.8 (100/481)	24.3 (132/543)	24.3 (135/555)
		total				19.9 (287/1443)	25.1$^{\uparrow\uparrow}$ (409/1629)	24.6$^{\uparrow\uparrow}$ (410/1665)
	total					37.2 (715/1924)	40.9$^{\uparrow}$ (888/2172)	40.4$^{\uparrow}$ (897/2220)
Aminoglycoside		AMK	≦16		>32	8.1 (39/481)	12.5 (68/543)	9.4 (52/555)
		TOB	≦4		>8	11.2 (54/481)	17.3 (94/543)	13.7 (76/555)
		total				9.7 (93/962)	14.9$^{\uparrow\uparrow}$ (162/1086)	11.5$^{\downarrow}$ (128/1110)
Tetracycline		MINO	≦4		>8	91.5 (440/481)	89.7 (487/543)	89.7 (498/555)
Quinolone		CPFX	≦1		>2	20.3 (97/478)	23.9 (130/543)	18.0$^{\downarrow}$ (100/555)
FOM			≦4		>16	95.6 (460/481)	93.7 (509/543)	93.9 (521/555)
total						36.5 (2105/5766)	39.6$^{\uparrow\uparrow}$ (2583/6516)	36.0$^{\downarrow\downarrow}$ (2399/6658)

The antimicrobial susceptibility test measures the minimum inhibitory concentration (MIC) using the CLSI broth microdilution method pursuant to the Japan Society of Chemotherapy.
1): S=Susceptible I=Intermediate R=Resistant
↑: P<0.05, ↑↑ or ↓↓: P<0.01 vs. Non control system, ↓: P<0.05, ↓↓: P<0.01 vs. Notification system.

Table 4 Incidence of drug-resistant *E. coli* (%)

Antimicrobials		Abbreviation	MIC[1)] S	I	R	Incidence of Drug-resistant *E. coli* (%) Non control system	Notification system	Permission system
Carbapenem		IPM / CS	≦4		>8	0.4 (3/739)	0.5 (4/782)	0.4 (3/821)
		MEPM	≦4		>8	0.1 (1/732)	0.1 (1/782)	0.2 (2/821)
		total				0.3 (4/1471)	0.3 (5/1654)	0.3 (5/1642)
Penicillin		PIPC	≦16		>64	32.1 (237/739)	35.7 (279/782)	32.6 (268/821)
		ABPC / MCIPC	≦8		>16	37.1 (274/739)	39.6 (310/782)	37.6 (309/821)
		ABPC / SBT	≦8		>16	37.1 (274/739)	39.6 (310/782)	37.6 (309/821)
		total				35.4 (785/2217)	38.3$^{\uparrow}$ (899/2346)	36.0 (886/2463)
Cephem	1st generation	CEZ	≦8		>16	10.8 (80/739)	14.5$^{\uparrow}$ (113/782)	13.8 (113/821)
	2nd generation	CMZ	≦16		>32	0.5 (4/739)	1.8 (14/782)	2.4 (20/821)
		CTM	≦8		>16	3.5 (26/739)	7.9 (62/782)	7.4 (61/824)
		total				2.0 (30/1478)	4.9$^{\uparrow\uparrow}$ (76/1564)	4.9$^{\uparrow\uparrow}$ (81/1645)
	3rd generation	CTX	≦8		>32	3.3 (24/738)	6.1$^{\uparrow\uparrow}$ (48/782)	4.6 (38/821)
	4th generation	CZOP	≦8		>16	2.8 (21/739)	5.5 (43/782)	4.5 (37/821)
		CPR	≦8		>16	2.8 (21/739)	5.5 (43/782)	4.0 (33/821)
		CFPM	≦8		>16	3.0 (22/739)	5.8 (45/782)	4.3 (35/821)
		total				2.9 (64/2217)	5.6$^{\uparrow\uparrow}$ (131/2346)	4.3$^{\uparrow,\downarrow}$ (105/2463)
	total					3.8 (198/5172)	6.7$^{\uparrow\uparrow}$ (368/5474)	5.9$^{\uparrow\uparrow}$ (337/5750)
Oxacephem		FMOX	≦8		>32	0.8 (6/739)	2.2$^{\uparrow}$ (17/782)	2.9$^{\uparrow\uparrow}$ (24/821)
Aminoglycoside		AMK	≦16		>32	0.3 (2/739)	0.4 (3/782)	0.5 (4/821)
		TOB	≦4		>8	11.4 (84/739)	10.4 (81/782)	10.4 (85/821)
		total				5.8 (86/1478)	5.4 (84/1564)	5.4 (89/1642)
Tetracycline		MINO	≦4		>8	18.1 (134/739)	13.2$^{\downarrow\downarrow}$ (103/782)	10.2$^{\downarrow\downarrow}$ (84/821)
Quinolone		CPFX	≦1		>2	19.1 (140/732)	18.0 (141/782)	21.9 (180/821)
FOM			≦4		>16	8.5 (63/739)	8.6 (67/782)	5.2$^{\downarrow\downarrow,\downarrow\downarrow}$ (43/821)
total						10.7 (1416/13287)	12.0$^{\uparrow\uparrow}$ (1684/14076)	11.1$^{\downarrow}$ (1648/14781)

The antimicrobial susceptibility test measures the minimum inhibitory concentration (MIC) using the CLSI broth microdilution method pursuant to the Japan Society of Chemotherapy.
1): S=Susceptible I=Intermediate R=Resistant
↑: P<0.05, ↑↑ or ↓↓: P<0.01 vs. Non control system, ↓: P<0.05, ↓↓: P<0.01 vs. Notification system.

Table 5 Incidence of drug-resistant *K. pneumoniae* (%)

Antimicrobials		Abbreviation	MIC[1)] S	I	R	Incidence of Drug-resistant *K. Pneumoniae* (%) Non control system	Notification system	Permission system
Carbapenem		IPM /CS	≦4		>8	0 (0/201)	0 (0/198)	0 (0/209)
		MEPM	≦4		>8	0 (0/201)	0 (0/198)	0.5 (1/209)
		total				0 (0/402)	0 (0/396)	0.2 (1/418)
Penicillin		PIPC	≦16		>64	30.8 (62/201)	31.8 (63/198)	32.1 (67/209)
		ABPC / MCIPC	≦8		>16	88.6 (178/201)	92.9 (184/198)	92.8 (194/209)
		ABPC / SBT	≦8		>16	88.6 (178/201)	92.9 (184/198)	92.8 (194/209)
		total				69.3 (418/603)	72.6 (431/594)	72.6 (455/627)
Cephem	1st generation	CEZ	≦8		>16	2.0 (4/201)	4.0 (8/198)	6.7↑ (14/209)
	2nd generation	CMZ	≦16		>32	0.5 (1/201)	1.0 (2/198)	6.2 (13/209)
		CTM	≦8		>16	1.0 (2/201)	3.0 (6/198)	3.3 (7/209)
		total				0.7 (3/402)	2.0 (8/396)	4.8↑↑,↑ (20/418)
	3rd generation	CTX	≦8		>32	0.5 (1/201)	2.0 (4/198)	1.9 (4/209)
	4th generation	CZOP	≦8		>16	1.0 (2/201)	2.0 (4/198)	0.5 (1/209)
		CPR	≦8		>16	0.5 (1/201)	2.0 (4/198)	1.0 (2/209)
		CFPM	≦8		>16	0.5 (1/201)	2.0 (4/198)	1.0 (2/209)
		total				0.7 (4/603)	2.0↑ (12/594)	0.8 (5/627)
	total					0.9 (12/1407)	2.3↑↑ (32/1386)	2.9↑↑ (43/1463)
Oxacephem		FMOX	≦8		>32	1.0 (2/201)	0 (0/198)	1.4 (3/209)
Aminoglycoside		AMK	≦16		>32	0 (0/201)	0 (0/198)	0 (0/209)
		TOB	≦4		>8	0.5 (1/201)	2.0 (4/198)	1.4 (3/209)
		total				0.2 (1/402)	1.0 (4/396)	0.7 (3/418)
Tetracycline		MINO	≦4		>8	12.4 (25/201)	9.6 (19/198)	12.9 (27/209)
Quinolone		CPFX	≦1		>2	1.5 (3/200)	3.5 (7/198)	2.9 (6/209)
FOM			≦4		>16	50.2 (101/201)	49.5 (98/198)	53.6 (112/209)
total						15.5 (562/3617)	16.6 (591/3564)	17.3↑ (650/3762)

The antimicrobial susceptibility test measures the minimum inhibitory concentration (MIC) using the CLSI broth microdilution method pursuant to the Japan Society of Chemotherapy.
1): S=Susceptible I=Intermediate R=Resistant
↑: $P<0.05$, ↑↑: $P<0.01$ vs. Non control system, ↑: $P<0.05$, vs. Notification system.

DISCUSSION

Japanese Red Cross Nagoya Daiichi Hospital consists of 34 diagnosis departments and 852 beds, is one of the typical large general hospitals in Japan. It has Departments of Hematology and Oncology where more than 60 hematopoietic stem cell transplantations are performed every year, and the Perinatal Medical Center that attends to immunodeficient patients. Therefore, our hospital uses more antimicrobials than other general hospitals.

Hospital management costs and nosocomial infection control are two of the most serious problems faced by hospitals of our scale. Thus, it is vital to increase hospital management efficiency in order to relieve hospital staff of undue physical and psychological stress brought about by those problems. This, in turn, is expected to lead to improved patient care. Medical costs, particularly for drugs, account for a large part of hospital expenditure. We have tried to decrease the number of prescriptions and switch to generics, but those moves were not sufficient to decrease hospital expenditure. As antimicrobials account for around 10% of total drug expenditure and cost 3.49 million dollars before this study, we have tried to control their use in an effort to reduce medical costs. In addition, because the sudden reduction or change of antimicrobials is linked to the outbreak of drug-resistant bacteria, we attempted to change the system and circumstances carefully step by step.

First, in order to encourage appropriate antimicrobial use, we launched a campaign. At our department, pharmacists started providing important information in the form of drug information

(DI) news on a monthly basis in 1996. Special lectures and seminars on all medicines, particularly antimicrobials, have been held for medical doctors and nurses once every three to four months since 2002. We also organized an Infection Control Team (ICT) that consists of two medical doctors, two pharmacists, one nurse, and one medical technologist to check and supervise the appropriate use of antimicrobials in 2004. However, in spite of such support extended to the medical staff, both AUD and drug costs did not see sufficient reduction. Therefore, in this study, we introduced and evaluated two control systems for antimicrobial use to decrease AUD, the incidence of drug-resistant bacteria, and medical costs at our hospital. In each system, a 14-month investigation period was set because at least four seasons were needed to compare the effects of the systems properly.

***AUD*:** Total AUDs were maintained throughout this study, suggesting that such AUD levels are needed to suppress and control the outbreak of drug-resistant bacteria. Some reports published in the period from 2006 to 2009 indicated that AUDs are 0.99–4.37 (mean ± SD; 2.1 ± 1.1) in Japan.[18-21] Generally, AUD is dependent on the department. The departments of hematology, surgery, and infectious diseases use more antimicrobials compared to other departments. At our hospital, the Departments of Hematology and Oncology and the Perinatal Medical Center are heavy users of carbapenems.

After the notification and permission systems were in place, our survey of diagnosis and prescription cards revealed that some broad-spectrum antimicrobials, such as carbapenems, were exchanged for 3rd- or 4th-generation cephems based on patient's clinical data, suggesting that medical doctors have become more careful in choosing the appropriate drug for treatment. As expected, both notification and permission systems significantly decreased carbapenem AUD. Tetracycline, anti-MRSAs, and fosfomycin use was also reduced. As *P. aeruginosa* resistant to those medicines has already appeared at a high frequency in the non control system (Table 3), we asked medical doctors not to use those antimicrobials except in the case of an emergency. Meanwhile, the use of other drugs, such as aminoglycosides, quinolone, cephem, and lincosamide, was increased. At our hospital, we recommended switching from carbapenem to quinolone alone or a combination of cephem and aminoglycoside for febrile neutropenia,[22] and to a combination of cephem and lincomycin for anaerobes in the case of oral or abdominal infection. The results suggested that restriction of carbapenem use led to the appropriate use of antimicrobials at our hospital.

***Economic effects*:** Compared to the non control system, the cost of antimicrobials was reduced by about $757,470 (21.7%) by the permission system but not by the notification system for the 14-month study period, suggesting that the permission system has definite economic benefits.

***Drug resistance*:** We have chosen three drug-resistant bacteria to evaluate the efficacy of the two control systems, because they are the most important indices to estimate the appropriate use of antimicrobials worldwide.[14,23-25] The permission system reduced the incidence of drug-resistant *P. aeruginosa*, but increased that of drug-resistant *K. pneumoniae* and drug-resistant *E. coli*. It is natural for the reduction of carbapenem use to be linked to the decrease in the incidence of carbapenem-resistant bacteria. Regarding carbapenems, the incidence of drug-resistant *P. aeruginosa* decreased, but not that of other bacteria. Overall, the two control systems regulated the incidence of 3 strains of bacteria resistant to antimicrobials.

***Secondary effects*:** As the effectiveness of the permission system was well appreciated by the hospital manager, five medical staffs were added to the existing ICT members of our hospital.

We have also presented our control systems at congress meetings. The Japanese Society for Hospital Pharmacists has created a special license for Infection Control Pharmacists to provide safe treatment for patients, and called it Board Certified Infection Control Pharmacy Specialist (BCICPS), which must be renewed every five year.[26] We will continue to find ways to improve the permission system. For example, we started the vancomycin permission system in January 2010 according to CDC guidelines.[27]

Many hospitals have tried to reduce AUD, the incidence of drug-resistant bacteria, and medical costs with their original systems for several months. They have reported effective systems to reduce AUD and control medical costs.[18-21] However, ours is the first study to assess two systems for more than 12 months at one hospital. In the USA, some hospitals have attempted to control antimicrobial use through a variety of mechanisms, although the medical environment is different from that in Japan. Some studies have shown not only cost benefits with these interventions, but also improvements in patient safety,[28] decreased antimicrobial resistance,[7] and decreased length of hospital stay[29] without compromising patient care. Conversely, there are studies that indicate no cost benefits associated with antimicrobial control strategies.[30,31] Those reports are highly informative, and we plan to incorporate parts of those systems into ours while taking the medical environment into due consideration.

There are some problems to be solved in this study: (i) Because this is a retrospective study, it is difficult to regulate the background of patients. Thus, to confirm the benefit of this permission system, prospective studies considering those backgrounds are needed. (ii) Different antimicrobials are still used by medical doctors for the same infection. Now we are providing more helpful information and having seminars about antimicrobials for medical staffs including medical doctors. (iii) We did not sufficiently check the doses and frequency of each antimicrobial prescribed in all patients. The next study must address ways to upgrade this system.

In conclusion, the permission system we established for carbapenem use at our hospital has helped us control the use of antimicrobials and suppress antimicrobial resistance and medical costs at our hospital.

Abbreviations: ATC: Anatomical Therapeutic Chemical Classification; AUD: antimicrobial use density; BCICPS: Board Certified Infection Control Pharmacy Specialist; CDC: Centers for Disease Control and Prevention in the USA; CLSI: Clinical and Laboratory Standards Institute; DDD: defined daily dose; DI: drug information; *E. coli: Escherichia coli*; ICT: Infection Control Team; *K. pneumoniae: Klebsiella pneumonia*; MIC: minimum inhibitory concentration; *P. aeruginosa: Pseudomonas aeruginosa.*

Conflict of interest statement: None declared.

ACKNOWLEDGMENTS

This study was supported by Grants-in-aid from the ‘Academic Frontier’ Project for Private Universities (2007–2011) from the Ministry of Education, Culture, Sports, Science and Technology of Japan (MEXT); by the Regional Joint Research Program supported by grants to Private Universities from MEXT, and by Research on Regulatory Science of Pharmaceuticals and Medical Devices from the Ministry of Health, Labour and Welfare (MHLW).

REFERENCES

1) Zhanel GG, Wiebe R, Dilay L, Thomson K, Rubinstein E, Hoban DJ, Noreddin AM, Karlowsky JA. Comparative review of the carbapenems. *Drugs*, 2007; 67: 1027–1052.
2) Baughman RP. The use of carbapenems in the treatment of serious infections. *J Intensive Care Med*, 2009; 24: 230–241.
3) Craig WA, Uman SJ, Shaw WR, Ramgopal V, Eagan LL, Leopold ET. Hospital use of antimicrobial drugs. Survey at 19 hospitals and results of antimicrobial control program. *Ann Intern Med*, 1978; 89: 793–795.
4) Woodward RS, Medoff G, Smith MD, Gray JL 3rd. Antibiotic cost savings from formulary restrictions and physician monitoring in a medical-school-affiliated hospital. *Am J Med*, 1987; 83: 817–823.
5) Coleman RW, Rodondi LC, Kaubisch S, Granzella NB, O'Hanley PD. Cost-effectiveness of prospective and continuous parenteral antibiotic control: experience at the Palo Alto Veterans Affairs Medical Center from 1987 to 1989. *Am J Med*, 1991; 90: 439–444.
6) Maswoswe JJ, Okpara AU. Enforcing a policy for restricting antimicrobial drug use. *Am J Health Syst Pharm*, 1995; 52: 1433–1435.
7) White AC Jr, Atmar RL, Wilson J, Cate TR, Stager CE, Greenberg SB. Effects of requiring prior authorization for selected antimicrobials: expenditures, susceptibilities, and clinical outcomes. *Clin Infect Dis*, 1997; 25: 230–239.
8) Cannon JP, Silverman RM. A pharmacist-driven antimicrobial approval program at a Veterans Affairs hospital. *Am J Health Syst Pharm*, 2003; 60: 1358–1362.
9) Fridkin SK, Steward CD, Edwards JR, Pryor ER, McGowan JE Jr, Archibald LK, Gaynes RP, Tenover FC. Surveillance of antimicrobial use and antimicrobial resistance in United States hospitals: project ICARE phase 2. Project Intensive Care Antimicrobial Resistance Epidemiology (ICARE) hospitals. *Clin Infect Dis*, 1999; 29: 245–252.
10) Vander Stichele RH, Elseviers MM, Ferech M, Blot S, Goossens H. European surveillance of antimicrobial consumption (ESAC): data collection performance and methodological approach. *Br J Clin Pharmacol*, 2004; 58: 419–428.
11) Monnet DL. Toward multinational antimicrobial resistance surveillance systems in Europe. *Int J Antimicrob Agents*, 2000; 15: 91–101. Review.
12) Mutnick AH, Rhomberg PR, Sader HS, Jones RN. Antimicrobial usage and resistance trend relationships from the MYSTIC Programme in North America (1999–2001). *J Antimicrob Chemother*, 2004; 53: 290–296.
13) Dellit TH, Owens RC, McGowan JE Jr, Gerding DN, Weinstein RA, Burke JP, Huskins WC, Paterson DL, Fishman NO, Carpenter CF, Brennan PJ, Billeter M, Hooton TM. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin Infect Dis*, 2007; 44: 159–177.
14) Centers for Disease Control and Prevention. 2006. Management of multidrug-resistant organisms in healthcare settings.
http://www.cdc.gov/ncidod/dhqp/pdf/ar/mdroGuideline2006.pdf
15) Natsch S, Hekster YA, de Jong R, Heerdink ER, Herings RM, van der Meer JW. Application of the ATC/DDD methodology to monitor antibiotic drug use. *Eur J Clin Microbiol Infect Dis*, 1998; 17: 20–24.
16) WHO Collaborating Centre for Drug Statistics Methodology.
http://www.whocc.no/atcddd/
17) Clinical and Laboratory Standards Institute. 2006. Performance standards for antimicrobial susceptibility testing; 16th informational Supplement. CLSI document M100-S16. Clinical and Laboratory Standards Institute, Wayne, PA.
18) Muro T, Hideshima R, Nakamura K, Kamimura H. Effort to promote proper use of anti methicillin-resistant *Staphylococcus aureus* agents and carbapenems. *Jpn J Chemother*, 2006; 54: 511–519. (in Japanese)
19) Hara T, Kasai M, Yoda T, Arai S, Ishii K, Hayashi H. Appropriate use of antimicrobial agents in maternity center and children's hospital: Effects of antimicrobial use notification policy and intervention by infection control team. *Jpn J Environ Infect*, 2007; 22: 253–259. (in Japanese)
20) Tanaka D, Fukasawa S, Kiko Y, Kinoshita K, Sakaguchi M, Fujie T. Effects of use notification policy for various classes of antimicrobial agents on consumption of antimicrobial agents and antimicrobial resistance. *Jpn J Environ Infect*, 2008; 23: 361–365. (in Japanese)
21) Kimura T, Kai T, Nishiumi K, Takahashi H, Sasaki H. Effect of ICT intervention on the trend of antimicrobial use and drug resistant bacteria. *Jpn J Environ Infect*, 2009; 24: 405–410. (in Japanese)
22) Tamura K, Imajo K, Akiyama N, Suzuki K, Urabe A, Ohyashiki K, Tanimoto M, Masaoka T. and Japan

Febrile Neutropenia Study Group. Randomized trial of cefepime monotherapy or cefepime in combination with amikacin as empirical therapy for febrile neutropenia. *Clin Infect Dis*, 2004; 39: S15–24.
23) Ploy MC, Grélaud C, Martin C, de Lumley L, Denis F. First clinical isolate of vancomycin-intermediate *Staphylococcus aureus* in a French hospital. *Lancet*, 1998; 351: 1212.
24) Gaynes R, Edwards JR. Overview of nosocomial infections caused by gram-negative bacilli. *Clin Infect Dis*, 2005; 41: 848–854.
25) Hyle EP, Lipworth AD, Zaoutis TE, Nachamkin I, Fishman NO, Bilker WB, Mao X, Lautenbach E. Risk factors for increasing multidrug resistance among extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella species*. *Clin Infect Dis*, 2005; 40: 1317–1324.
26) http://www.jshp.or.jp/senmon/senmon2.html (in Japanese)
27) Centers for Disease Control and Prevention (CDC). Recommendations for preventing the spread of vancomycin resistance: recommendations of the Hospital Infection Control Practices Advisory Committee (HICPAC), MMWR 44, No.RR-12, 1995.
http://ftp.cdc.gov/pub/Publications/mmwr/rr/rr4412.pdf
28) Hirschman S, Meyers BR, Bradbury K, Mehl B, Gendelman S, Kimelblatt B. Use of antimicrobial agents in a university teaching hospital. Evolution of a comprehensive control program. *Arch Intern Med*, 1988; 148: 2001–2007. Review.
29) Gums JG, Yancey RW Jr, Hamilton CA, Kubilis PS. A randomized, prospective study measuring outcomes after antibiotic therapy intervention by a multidisciplinary consult team. *Pharmacotherapy*, 1999; 19: 1369–1377.
30) Rifenburg RP, Paladino JA, Hanson SC, Tuttle JA, Schentag JJ. Benchmark analysis of strategies hospitals use to control antimicrobial expenditures. *Am J Health Syst Pharm*, 1996; 53: 2054–2062.
31) Gould IM, Jappy B. Trends in hospital antimicrobial prescribing after 9 years of stewardship. *J Antimicrob Chemother*, 2000; 45: 913–917.