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The Impact of Antimicrobial Stewardship by Infection Control Team in a Japanese Teaching Hospital

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The objective of this study is to investigate an effect on the antimicrobial appropriate use of the antimicrobial stewardship. We investigated the consumption of injectable antimicrobials from 2001 to 2007 and the administration period of specific antimicrobials (carbapenems, fourth-generation cephalosporins, anti-methicillin-resistant *Staphylococcus aureus* (MRSA) agents) in the individual patient. Since September 2004, the infection control team at Osaka University Hospital has been promoting appropriate use of antimicrobials through consultation, education, and weekly surveillance of specific antimicrobial usage. We obtained the amount of all antimicrobial injections as titer from the medical information database of the electronic medical chart system retrospectively. Antimicrobial use densities (AUD) were evaluated by measuring the number of doses administered/1000 patient-days. Although the number of in-patient admissions and operations increased 1.53- and 1.39-fold, respectively, in the seven years from 2001 to 2007, the expenditure on specific antimicrobials decreased markedly with AUD of specific antimicrobials decreasing from 39.6 to 29.2. The percentage of inpatients receiving specific antimicrobials decreased from 19.8% to 9.8%, and the ratio of the number of inpatients administered a specific antimicrobial within seven days to the number of inpatients administered each specific antimicrobial increased to over 60%. This led to reduction in the total expenditure of antimicrobials by about ¥100 million annually. The incidence of hospital-associated MRSA (HA-MRSA) infection decreased from 0.93% (2003) to 0.68% (2007). We can reduce the expenditure of antimicrobials without increasing incidence of the HA-MRSA by antimicrobial stewardship, and we think that appropriate use of antimicrobials is achieved progressively.

Key words——infection control team; antimicrobial stewardship; appropriate use; antimicrobial use density; Japan

INTRODUCTION

The cost of antimicrobial agents is estimated to constitute about one-third of the pharmacy budget in general hospitals.[1,2] It is reported that 25–50% of inpatients receive antimicrobial agents[3] and 30–50% of all courses of antimicrobial therapy are thought to be unnecessary.[4,5] In addition to the toxicity of the administered drug, excessive and long-term administration of antimicrobials causes significant adverse effects, such as emergence of resistant microorganisms, increase in morbidity, and associated infections.[6,7] It also results in an increase in healthcare costs.[8–10] In particular, the emergence of multidrug-resistant organisms (MDROs) such as methicillin-resistant *Staphylococcus aureus* (MRSA) and multidrug-resistant *Pseudomonas aeruginosa* (MDRP) is a serious global concern.[11–14] Therefore, more attention should be paid to the use of frequently prescribed antimicrobials (*i.e.*, glycopeptides, oxazolidinone, carbapenems, and fourth-generation cephalosporins), and a device or system for preventing this increase in MDROs is required. Until date, in Japan, there was no generalized system that systematically supported and regulated the use of antimicrobial agents, and prescriptions were dispensed at the discretion of each physician.[15] Therefore, these physicians tended to prescribe broad spectrum antimicrobials frequently and for long durations.

A multidisciplinary team comprising physicians, nurses, pharmacists, and clinical laboratory technologists working together to take care of patients has recently become a mainstream clinical practice in Japan; this team also works with the infection control team (ICT). The importance of infection control and prevention has increased and become an indispensable factor.[16] The diagnosis procedure combination (DPC) system has been implemented for limiting healthcare costs.[17] Infection control and patient safety contribute to reduction in antimicrobial consumption and containment of healthcare costs. Patient safety practices such as continuous work improve-

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ment and causal analysis can strengthen the infection control and prevention program.[18] Suppression of the development of resistant microorganisms is also anticipated, and hence, the program for appropriate use of broad spectrum antimicrobials has been implemented in many hospitals. Introduction of a pre-authorization and notification system, knowledge of appropriate use of antimicrobials, and pharmacokinetic analyses based on monitoring of therapeutic drugs recommended by the Japan Council for Quality Health Care (JCQHC) are also being practiced in many hospitals.

Several university hospitals introduced a pre-authorization and notification system and reported an effect on appropriate use of antimicrobials.[19–22] We build antimicrobial usage monitoring system without introducing a pre-authorization and notification system of specific antimicrobials in the Osaka University Hospital and grasp administered patients and the duration of administration. The objective of this study is to investigate an effect on the antimicrobial appropriate use of the antimicrobial stewardship such as consultation and education to the primary physician by the infectious disease physician and the surveillance that used antimicrobial usage monitoring system. We also investigated the administration period of specific antimicrobial agents in the individual inpatient.

METHODS

Hospital Setting Osaka University Hospital (24 wards, 30 diagnosis and treatment departments) is an advanced treatment hospital with 1076 beds. We are using an electronic record and an ordering system in our hospital. In 2007, the mean number of inpatients was 918, and the average length of hospital stay was 19.9 days. In this hospital, after physicians applied for the adoption of medical supplies, comparison of the drugs with the same indications and consideration of safety are performed by a pharmacy and therapeutic committee, and the adoption or rejection of the medical supplies is decided.

No other restrictive control measures on antimicrobial use have been implemented. Physicians can prescribe any antimicrobial in the formulary without restriction. In September 2004, the ICT has played an important role in promotion of appropriate use of broad spectrum antimicrobials and anti-MRSA agents at Osaka University Hospital (Osaka, Japan). Three infectious disease physicians in the ICT started supporting consultation along with their prescriptions and suggested measures for effective selection and use of antimicrobials. The ICT offered advice in response to requests for help. Since June 2005, we have hospital guidelines for antimicrobial use with no restriction policy.

Measurement of Antimicrobial Expenditure We obtained the amount of all antimicrobial injections in ''titer'' from the medical information database of the electronic health record system. These amounts were based on prescribed doses. We retrospectively reviewed data from January 2001 to December 2007. Injectable antimicrobial consumption was measured in grams and the number of vials/ampoules. We appointed carbapenems (imipenem/cilastatin, panipenem/betamipron, meropenem, biapenem and doripenem), fourth-generation cephalosporins (cefozopran, cefepime and cefpirome) and anti-MRSA agents (arbekacin, teicoplanin, linezolid and vancomycin) as specific antimicrobials in our hospital. The amount of an antimicrobial agent was expressed as defined daily dose (DDD) and antimicrobial use density (AUD). DDD is defined by the World Health Organization as the assumed mean maintenance adult daily dose of an antimicrobial agent for one day of treatment (anatomical therapeutic chemical classification/DDD index 2010). AUD was calculated to normalize the amount of antimicrobial consumption in an individual hospital. AUD was expressed as DDD per 1000 patient-days for individual antimicrobial agents

(Expression 1 : AUD=antimicrobial consumption /DDD×1000/patient-days).

We calculated patient-days by subtracting the day of admission from the day of discharge. So day cases score zero patient-days. Moreover, we calculated the administration period of specific antimicrobial agents in individual inpatients and investigated its change over seven years.

Monitoring Usage of Specific Antimicrobials We obtained prescription data of specific antimicrobials from pharmaceutical support system of a pharmacy. These data contained both administered and unadministered prescriptions. We gave these data to the ICT. Infectious disease physicians required a fair amount of time before consulting the primary physician to know the exact duration of antimicrobial administration in an individual inpatient. Therefore, in April 2007, we created an antimicrobial usage moni-

toring system using Microsoft® Access 2000 (Microsoft Corporation. 1999) for determining the time of consultation with the primary physician. Using this system, we procured a list of inpatients prescribed specific antimicrobials in the preceding week and those continuously using specific antimicrobials for ≥14 days. We provided these lists to the ICT on a weekly basis.

Isolation of MRSA We investigated the number of MRSA patients and the incidence of hospital-associated MRSA (HA-MRSA) infection from 2003 to 2007. In order to take measures against nosocomial infection more effectively, we have classified MRSA cases as either associated in or imported to the hospital. Genetic analysis is necessary to distinguish MRSA precisely, but this analysis is not convenient means for screening, costs money and is an inspection for an ascertainment. In our hospital, imported MRSA cases were defined by the following criteria: (1) patients with MRSA isolated from any site within 48 hours after admission, (2) patients with a history of MRSA culture positive in other hospital, outpatient care and previous hospitalization.[10] The incidence of HA-MRSA infection was calculated as the percentage of HA-MRSA patients in the hospitalization number of patients.

RESULTS

Patient Characteristics and Number of Operations Table 1 shows the characteristics of the study population. In the seven years from 2001 to 2007, the number of inpatient admissions and operations increased 1.53- and 1.39-fold. The number of inpatients ≤12 years of age constituted approximately 10% of the entire population. The mean length of hospital stay decreased by 11.5 days, and our hospital maintained the annual hospital bed occupancy rate of around 86 %.

Injectable Antimicrobial Consumption Annual change in the quantity of antimicrobial injections is shown in Fig. 1. The total antimicrobial consumption decreased until 2005, but increased thereafter. The total antimicrobial consumption was 103.6 kg in 2007. Among these, cephalosporins constituted ≥40

Table 1. Characteristics of the Study Population

Characteristics	2001	2002	2003	2004	2005	2006	2007
The number of inpatient admissions							
Total	10,812	11,538	10,778	13,385	14,301	15,386	16,523
≤12 years old	1,075	1,143	1,002	1,380	1,438	1,573	1,677
Age (mean years±S.D.)	48.0±22.7	48.5±22.7	49.7±22.5	49.2±23.0	50.1±23.1	50.3±23.2	51.0±23.4
Gender							
Male	5,368	5,746	5,235	6,390	6,847	7,262	8,005
Female	5,444	5,837	5,543	6,995	7,454	8,124	8,518
Principal diagnosis (ICD-10) (%)							
Neoplasms (C00-D48)	38.5	39.5	40.7	39.9	41.7	42.9	40.3
Diseases of the circulatory system (I00-I99)	9.7	9.1	8.6	8.7	8.4	8.8	9.8
Diseases of the respiratory system (J00-J99)	2.3	2.4	2.0	2.2	2.4	2.9	2.7
Diseases of the digestive system (K00-K93)	4.5	4.4	4.2	4.3	4.3	4.3	4.3
Diseases of the genitourinary system (N00-N99)	3.5	3.5	3.4	3.7	3.9	3.6	4.2
Injury, poisoning and certain other consequences of the external causes (S00-T98)	2.0	2.5	2.4	2.1	2.0	2.0	2.3
Diseases of the musculoskeletal system and connective tissue (M00-M99)	5.3	4.6	5.0	5.3	4.4	3.4	4.0
Diseases of the eye and adnexa (H00-H59)	4.1	4.1	4.2	4.8	5.1	5.5	5.6
Diseases of the ear and mastoid process (H60-H95)	1.6	1.4	1.3	1.4	0.9	0.5	0.4
Other	28.5	28.5	28.2	27.6	26.9	26.1	26.4
Length of the hospital stay (days)	31.4	29.6	28.4	24.9	23.1	21.4	19.9
Annual bed occupancy rate (%)	86.0	87.2	77.8	84.6	85.6	85.6	85.3
Number of operations	5,926	6,208	6,486	6,906	7,229	7,822	8,237
Inpatient days	326,148	330,324	293,655	317,904	319,458	317,512	305,149
Total mortality	302	330	289	319	292	288	306

% of the usage of each class of antibiotics. From 2001 to 2007, consumption of carbapenem antibiotics showed a slight decrease, and its annual usage was 8.5%, 10.4%, 9.9%, 11.0%, 10.7%, 9.4%, and 7.1%. Consumption of penicillin antibiotics increased since 2004. In 2007, penicillin antibiotics accounted for approximately 25.2% of the total antimicrobial consumption. Consumption of first-generation cephalosporins was 20.0 kg, and approximately 44.6% of consumed cephalosporin antibiotics were of the first-generation type. Until 2004, the drug cost (pharmaceutical prices×amount used) of specific antimicrobials increased from ¥124 million (2001) to ¥138 million (2004), but decreased to ¥85 million (2007) thereafter. The drug cost of all antimicrobials fell from ¥379 million to ¥262 million (Table 2). We saved about ¥100 million a year. Table 3 shows AUD of the main antimicrobial classes. AUD of specific antimicrobials decreased since 2005. In contrast, AUD of penicillins and first-generation cephalosporins increased.

Changes in the Administration Period of Antimicrobial Agents The ratio of the number of inpatients administered a specific antimicrobial to the number of inpatients is shown in Table 4. We classified the administration period into two groups: A (≤7 days) or B (>7 days). The ratio of each group to the number of inpatients administered each specific antimicrobial is also shown in Table 4.

In the seven years from 2001 to 2007, the number of inpatients receiving carbapenems, fourth-generation cephalosporins, and anti-MRSA agents decreased from 1214 to 871, 780 to 340, and 569 to 483, respectively. The ratio of inpatients administered a specific antimicrobial within seven days to the number of inpatients administered each specific antimicrobial was 56.6%→63.5%, 66.9%→65.6%, and 48.8%→61.1%, respectively. The administration periods of carbapenems and anti-MRSA agents became shorter.

The Number of MRSA Patient and the Incidence of HA-MRSA Infection Annual change in the number of MRSA patients and the incidence of HA-MRSA infection from 2003 to 2007 is shown in Table 5. The number of MRSA patients was about 300 persons per year in all investigation periods. From 2003 to 2007, the ratio of the number of HA-MRSA patients to the number of MRSA patients was 64%,

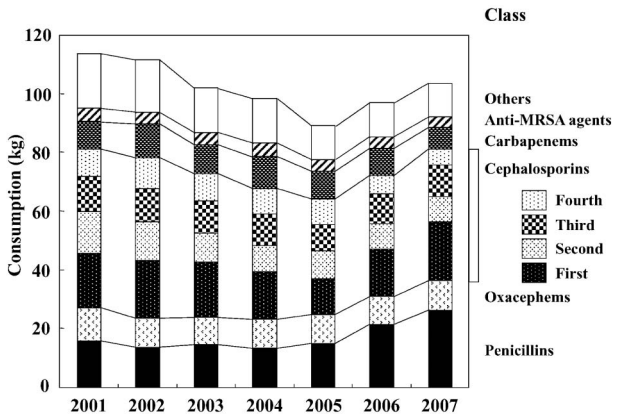

Fig. 1. Annual Change in Consumption of Antimicrobial Injections

Table 3. The Antimicrobial Use Density of Main Antimicrobial Classes

Antimicrobial injections	2001	2002	2003	2004	2005	2006	2007
Carbapenems	14.7	17.7	17.6	17.5	15.4	14.8	12.8
Fourth-generation cephalosporins	8.2	9.4	9.6	9.2	9.1	7.1	7.1
Anti-MRSA agents	9.3	9.0	11.6	13.0	10.9	10.5	9.3
Penicillins	10.6	9.7	10.9	9.5	10.8	18.0	22.3
First-generation cephalosporins	18.7	20.0	21.5	16.9	12.7	17.2	21.9

Table 2. Annual Expenditures Related to Specific Antimicrobial Injections

	2001	2002	2003	2004	2005	2006	2007
The number of used antimicrobial injections	42,538	47,231	45,030	47,019	42,846	38,190	33,242
Carbapenems	20,739	25,066	22,765	24,093	21,798	20,355	17,783
Fourth-generation cephalosporins	10,854	12,065	10,959	9,975	9,806	7,068	5,975
Anti-MRSA agents	10,945	10,100	11,306	12,951	11,242	10,767	9,484
Specific antimicrobial expenditures (1,000 JPY)	124,090	129,316	129,233	137,680	134,869	117,253	85,073
Compared with preceding year (1,000 JPY)	—	5,226	−82	8,447	−2,811	−17,615	−32,180
Total antimicrobial expenditures (1,000 JPY)	290,596	301,490	371,374	359,169	379,454	296,143	262,528
Compared with preceding year (1,000 JPY)	—	10,894	69,883	−12,204	20,284	−83,310	−33,615

Table 4. Annual Change of the Number of Patients Administered a Specific Antimicrobial Injection

Class/Administration period (days)	The number of patients (Ratio*)						
	2001	2002	2003	2004	2005	2006	2007
Carbapenems/	1114 (9.6)	1214 (9.8)	1179 (10.2)	1163 (8.2)	1129 (7.5)	1099 (6.8)	871 (5.1)
≤7 days (%)	56.6	56.6	56.1	57.0	57.0	62.9	63.5
≥8 days (%)	43.4	43.4	43.9	43.0	43.0	37.1	36.5
Fourth-generation cephalosporins/	726 (6.3)	780 (6.3)	661 (5.7)	585 (4.1)	561 (3.7)	405 (2.5)	340 (2.0)
≤7 days (%)	66.9	71.9	66.7	67.7	63.3	65.9	65.6
≥8 days (%)	33.1	29.1	33.3	32.3	36.7	34.1	34.4
Anti-MRSA agents/	459 (4.0)	461 (3.7)	569 (4.9)	568 (3.5)	535 (2.8)	495 (2.7)	483 (2.5)
≤7 days (%)	48.8	50.5	50.8	45.2	54.6	55.6	61.1
≥8 days (%)	51.2	49.5	49.2	54.8	45.4	44.4	38.9

*Numbers in parentheses indicate the ratio of the number of patients administered a specific antimicrobials to the number of inpatients.

Table 5. Annual Change in the Number of MRSA Patients and the Incidence of HA-MRSA Infection from 2003 to 2007

	2003	2004	2005	2006	2007
Imported MRSA	119	114	124	109	140
HA-MRSA	213	180	179	180	186
Incidence of HA-MRSA (%)	0.93	0.75	0.73	0.68	0.68

HA-MRSA: Hospital-associated MRSA.

61%, 59%, 62%, and 57%. This result shows that the number of HA-MRSA patients accounts for about 60 % of the number of MRSA patients. The incidence of HA-MRSA infection decreased from 0.92% in 2003 to 0.68% in 2007.

DISCUSSION

The number of infectious disease physicians in Japan is fewer than that in the USA. Therefore, the ICT has also played a role of the antimicrobial stewardship team in Japan. In Osaka University Hospital, the ICT consisting of infectious disease physicians, pharmacists, nurses, clinical laboratory technologists, and medical clerical employees formed the antimicrobial stewardship team. We organized education programs with regard to infection control for medical staff. We also started keeping electronic medical records and computer entries of physician orders, provided patient-specific culture and susceptibility data to optimize individual antimicrobial management, and performed weekly surveillance of specific antimicrobial usage. Our hospital has not introduced the pre-authorization and notification system of carbapenems, fourth-generation cephalosporins, and anti-MRSA agents, even though JCQHC recommended this.

Although the number of inpatients and operations increased 1.53- and 1.39-fold from 2001 to 2007, AUD of specific antimicrobials decreased by 26.3% (from 39.6 to 29.2). Since 2005, consumption of specific antimicrobials decreased gradually, and that of narrow spectrum antimicrobials such as penicillins and first-generation cephalosporins increased. These results show a possibility that antimicrobials used after empiric therapy has shifted from broad spectrum antimicrobials to narrow spectrum antimicrobials. Furthermore, it is highly possible that reduction in AUD was affected by the activities of the ICT in the antimicrobial stewardship program and consultation as well as education of primary physicians by infectious disease physicians. The decreasing tendency of AUD continues to exist. Although we cannot say for sure that the economical incentive of DPC has no influence on the current result, expenditures related to specific antimicrobial injections clearly decreased. As in previous reports,[23–25] the expenditure of total antimicrobial agents also decreased markedly, with annual savings of about ¥100 million. While DPC and accreditation by JCQHC advance, prevention of hospital-associated infection and appropriate use of antimicrobial agents are indispensable for hospital

management.

As a result of the survey on the administration period of specific antimicrobials, the ratio of the number of inpatients administered a specific antimicrobial to the number of inpatients decreased for each class of specific antimicrobials. In comparison with 2001, the ratio of the number of inpatients administered a specific antimicrobial within seven days to the number of inpatients administered each specific antimicrobial increased in 2007, except for fourth-generation cephalosporins. We think that this result is an accomplishment of the change from broad spectrum antimicrobial use to narrow spectrum antimicrobial use, which is effective for an individual causative microorganism (''de-escalation therapy'') on the basis of culture results. De-escalation therapy is an element of the antimicrobial stewardship program.[26,27]

The number of MRSA patients was almost constant through five years from 2003 to 2007. But if we consider the fact that the number of inpatients admission increased greatly, we can think that the number of MRSA patients decreased. Moreover, it became clear that imported MRSA patients occupy about 40 % of MRSA patients. By distinguishing between HA-MRSA case and imported MRSA case, we focus on HA-MRSA and can implement the identification of the infection route and the enhancement of the infection control. Our classification criteria have the problem that all the patient specimens that were not obtained within 48 hours after hospitalization become hospital-associated infection. We think that the simple classification criteria are better, because our distinction is screening to get to know the tendency of MRSA infection. With this classification result, we can approach infection control of HA-MRSA effectively and efficiently.

We built antimicrobial usage monitoring system without introducing a pre-authorization and notification system of specific antimicrobials in the Osaka University Hospital. We grasped administered patients and the administration period of specific antimicrobials in the individual patient by monitoring a status of antimicrobial use and prevented emergence of resistant microorganisms. We think that both effect of consultation/education to the primary physician and consciousness (Hawthorne effect) that use of the antimicrobial is always monitored by specific antimicrobial usage monitoring system led the decrease of the specific antimicrobial consumption and the reduction of drug costs. The decrease of the administration period of the specific antimicrobial and the decrease of the incidence of the HA-MRSA were found. Therefore, we think that the antimicrobial therapy of high dose/short duration based on Pharmacokinetics-Pharmacodynamics theory is performed progressively, and the appropriate use of antimicrobial is achieved.

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