

## Individual Patient-by-Patient Surveillance of the Antimicrobial Usage among Inpatients in Kanazawa University Hospital

Kazumasa Naruhashi<sup>†1</sup>, Mariko Asahi<sup>†2</sup>, Yasuko Higuchi<sup>†1</sup>, Ryo Matsushita<sup>†1</sup>,  
Sakae Shimizu<sup>†1</sup>, Kazuko Kimura<sup>†1</sup>, Nagao Suzuki<sup>†1</sup>, Koichi Yokogawa<sup>†2</sup>,  
Shin-ichi Fujita<sup>†3</sup> and Ken-ichi Miyamoto<sup>\*†2</sup>

Division of Pharmacy and Health Sciences, Graduate School of Natural Science  
and Technology, Kanazawa University<sup>†1</sup>

Department of Hospital Pharmacy<sup>†2</sup> and Central Clinical Laboratory<sup>†3</sup>,  
Kanazawa University Hospital

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To explore appropriate antimicrobial usage in Kanazawa University Hospital, the surveillance of antimicrobial use on an individual patient basis was conducted and analyses of outstanding cases were made in detail. All data of inpatients between August 1<sup>st</sup> and November 30<sup>th</sup> 1999, who were prescribed at least one of the 11 antimicrobial injections that are frequently used at our hospital were collected by utilizing a computer database support system of the hospital. The overall usage seemed appropriate in terms of the period of use based on an antimicrobial analysis. However, an analysis on an individual-patient basis suggested some inappropriate usage/misuse in certain cases. Imipenem was prescribed from the ophthalmology ward in more than 50% of all cases. This was found to be used as a postoperative prophylactic antibiotic. Since no antibiotic was prescribed to these patients thereafter, this usage cannot be defined as inappropriate although alternative antibiotics may be considered. Vancomycin was prescribed to some methicillin-resistant *Staphylococcus aureus*-negative patients. We also found some extensively prolonged usage of antimicrobials. All of these were considered to be inappropriate in regard to usage specified for insurance. After investigations of medical charts and consultations with attending physicians, these antimicrobials had been empirically prescribed. In one case, imipenem was prescribed to an imipenem-insensitive patient. A different effective antimicrobial drug should have been prescribed. In conclusion, we were able to uncover some inappropriate usage of antimicrobials in a patient-by-patient investigation. Our findings suggest that further surveillance and on-time suggestions to prescribers should result in a more appropriate administration of antimicrobials.

**Keywords** — Nosocomial infection, antimicrobial, appropriate usage, MRSA

### Introduction

The discovery of potent antimicrobials in the 1940s contributed to the treatment of infectious diseases. Unfortunately, however, this advantage is now threatened by the

emergence of antimicrobial-resistant pathogens<sup>1)</sup>, including methicillin-resistant *Staphylococcus aureus* (MRSA)<sup>2)</sup> and vancomycin resistant enterococci<sup>3,4)</sup>. The emergence of these resistant pathogens in Japan was due to, in part, the inappropriate use of antimicrobials in hospitals in the 80s and the

<sup>†1</sup> 石川県金沢市宝町13-1 ; Takara-machi, Kanazawa 920-0934 Japan

<sup>†2,3</sup> 石川県金沢市宝町13-1 ; Takara-machi, Kanazawa 920-8641 Japan

early 90s. Hospitals became the largest reservoir of resistance. To make the matter worse, malpractice by the medical staff led to nosocomial infection within the hospital<sup>5)</sup>. Since then, the awareness of the danger made us pharmacists, explore the appropriate usage of antimicrobials. In the hospital setting, increased use of antimicrobials is often associated with increased frequency of resistance, and reduced consumption of the antimicrobial is suggested to estimate diminution of the frequency of resistance to specific drugs<sup>6)</sup>. Therefore, as an initial approach to this exploration, the reports documented the statistics of the amounts of prescribed antibiotics in relatively large hospitals both in Japan<sup>7,8)</sup> and other countries<sup>9)</sup>. This figure indirectly demonstrated the appropriate usage of antimicrobials. This approach has advantages in hospitals with large numbers of inpatient beds, since it is difficult to follow every single prescription. Now, the number of the MRSA compromised patients in hospitals is decreasing in Kanazawa University Hospital<sup>10)</sup> and the trend is the same all over Japan. Therefore, it is time to take the next step toward further appropriate usage of antimicrobials. The use of antimicrobials in excessive amounts can cause not only the emergence of further resistant pathogens but also deterioration in quality of life of patients. As mentioned above, the statistics were able to demonstrate the overall appropriate usage of antimicrobials. However, it cannot estimate the real appropriateness in individual patient basis. In this study, we surveyed the use of frequently used antimicrobial injections in individual patient level in Kanazawa University Hospital and documented two case reports. Then, we will discuss how to promote further appropriate usage of antimicrobials in the future.

## Methods

### 1. Patients and antimicrobials

Eleven antimicrobials of injectable dosage forms, which are frequently prescribed in Kanazawa University Hospital, were selected. Two of the 11 antimicrobials were adopted in two different dosage forms in our hospital. The antimicrobials investigated in this study were as follows; vancomycin hydrochloride (VCM) 0.5 g, teicoplanin (TEIC) 0.2 g, arbekacin sulfate (ABK) 0.1 g, piperacillin sodium (PIPC) 1 g/2 g, cefazolin sodium hydrate (CEZ) 1 g/2 g, cefotiam dihydrochloride (CTM) 1 g, flomoxef sodium (FMOX) 1 g, imipenem/cilastatin sodium (IPM/CS) 0.5 g, meropenem trihydrate (MEPM) 0.5 g, panipenem/betamipron (PAPM/BP) 0.5 g, fosfomycin sodium (FOM) 2 g.

The study includes patients hospitalized in Kanazawa University Hospital in Japan, between August 1<sup>st</sup> and November 30<sup>th</sup> 1999.

### 2. The surveillance

All inpatients that were prescribed one or more of the 11 antimicrobials were sampled from the computer database

support system of the hospital. The prescription data were inspected by using prescription ordering system of the hospital. (The computer support system and the prescription ordering system are independent.) The prescription data were integrated manually and the period of consecutive antimicrobial use in individual patient and the usage of antimicrobials in each ward were surveyed. One consecutive usage of antimicrobial was counted as one case. In case of VCM, the relationship between the period of consecutive use and MRSA detection, the data of which were sample from the prescription ordering system, were analyzed.

The precautions cases were then investigated in detail from medical charts in the ward and the pharmacist consulted with the attending physicians.

## Results

### 1. Background of Kanazawa University Hospital

Kanazawa University Hospital has a capacity of 792 beds. The number of average inpatients every day is 722.4. The average duration of administration is 34.8 days/inpatient. (The data in 1999)

### 2. The period of consecutive antimicrobial use

Fig. 1 shows the period of consecutive use of individual antimicrobials. Two thousand four hundred and seventy cases in 1444 patients were prescribed at least one antimicrobial between August 1<sup>st</sup> and November 30<sup>th</sup> 1999. The number of cases in which two or more antimicrobials were prescribed between August 1<sup>st</sup> and November 30<sup>th</sup> 1999 was 1209 in 354 patients (average: 3.4 antimicrobials/patient). The separate analysis of consecutive usage of each antimicrobial indicated less than 7 days in 72% and 14 days in 94.5% (Fig. 2, separate counting). However, we conducted combined analysis to investigate the antimicrobial usage on the individual-patient basis. The number of the cases of consecutive use of two or more antimicrobials was 291 (Fig. 2, combined counting). The period of the length of combined counting analysis tended to be longer than that of separate counting analysis. Among them, the alteration of the antimicrobials was found to be from narrow-spectrum (e.g. CEZ) to broad-spectrum (e.g. carbapenems) in most cases (data not shown).

From these surveys, some cases of inappropriate antimicrobial usage were uncovered. (1) Some patients were prescribed IPM/CS as the first choice although the antimicrobial is broad-spectrum. (2) Some patients were prescribed VCM or IPM/CS more than 28 days consecutively. We proceeded with the investigation focusing on these problems.

### 3. IPM/CS usage as the first choice in each ward (Fig. 3)

Among the patients who were prescribed more than one antimicrobial, IPM/CS was prescribed as the first choice to

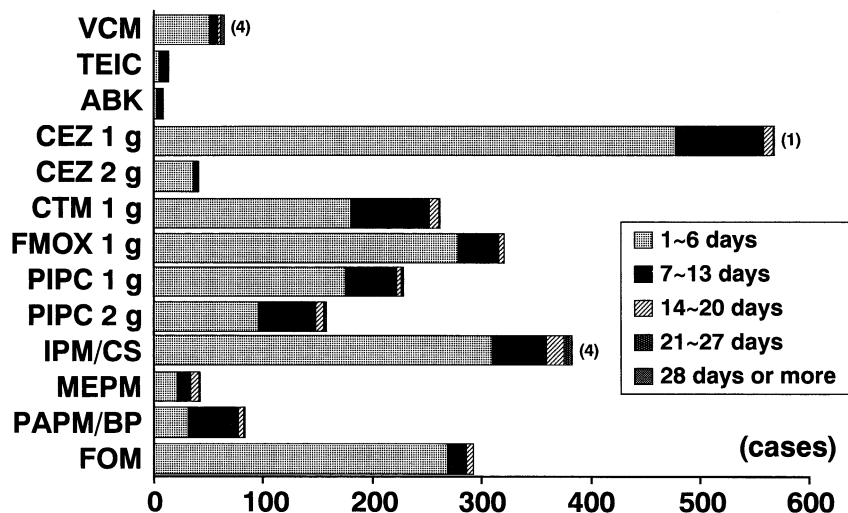


Fig. 1. The Period of Consecutive Use of Individual Antimicrobials in Kanazawa University Hospital. The number of cases of various duration is shown between August 1<sup>st</sup> and November 30<sup>th</sup>, 1999. The total number indicates the cases in which inpatients were prescribed one or more antimicrobials. The number in parentheses indicates the cases of 28 consecutive days or more.

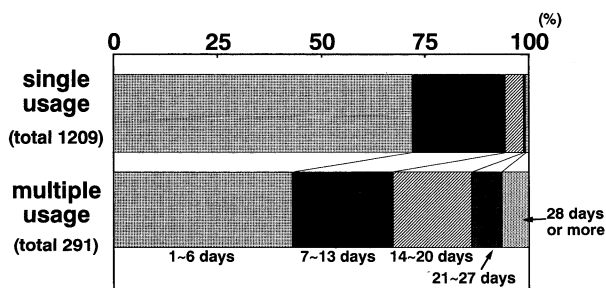


Fig. 2. The Period of Consecutive Use of Antimicrobials in Inpatients Who were Prescribed More than One Antimicrobial in Kanazawa University Hospital. Three hundred and fifty four patients were prescribed more than one antimicrobial between August 1<sup>st</sup> and November 30<sup>th</sup>, 1999. The number of "individual counting" was counted from the data of each antimicrobial separately. The number of cases of "combined counting" was counted from the integrated data of all antimicrobials investigated in this study. For example, patient A was prescribed PIPC (2 g), IPM/CS and MEPM from October 23<sup>rd</sup> to November 1<sup>st</sup> (10 days), from November 11<sup>th</sup> to November 19<sup>th</sup> (9 days) and from November 20<sup>th</sup> to November 29<sup>th</sup> (10 days), respectively. This patient was counted three cases of 7 ~ 13 days as "separate counting", while one case of 14 ~ 20 days as "combined counting" since the last two antimicrobials were prescribed consecutively.

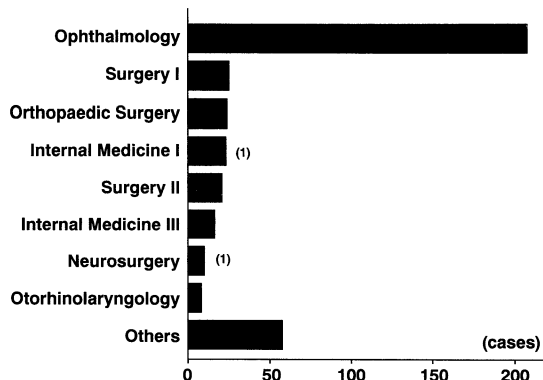


Fig. 3. The Usage of IPM/CS in Individual Wards in Kanazawa University Hospital. The surveillance was between August 1<sup>st</sup> and November 30<sup>th</sup>, 1999. The number in parentheses indicates the number of MRSA positive patients.

383 patients. The number of the patients in each ward is shown in Fig. 3. More than 50% of the cases were in the ophthalmology ward. Long-term usage (28 days or more) was found in the orthopedic ward (two cases), the first internal medicine ward (one), and the neurosurgery ward (one: refer to case report 1). The patients of the two latter cases were MRSA-positive and concomitantly *Pseudomonas* and *staphylococcus* positive and complicated a combination drug therapy was indicated.

4. The relationship between the period of consecutive VCM use and MRSA detection (Fig. 4)

MRSA-positive patients were 82.4% among patients of consecutive use of 1-6 days, while only 25% among patients of consecutive use of 28 days or more (refer to case report 2).

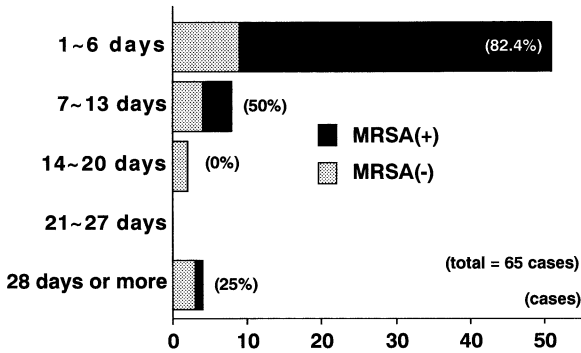


Fig. 4. The Period of Consecutive Use of VCM and MRSA Detection in Kanazawa University Hospital.

The surveillance was between August 1<sup>st</sup> and November 30<sup>th</sup>, 1999. The number in parentheses indicates the percentages of MRSA-positive patients.

5. Case reports

Case 1 (Fig. 5)

Twenty-four-year-old male with syringomyelia and Chiari malformation was hospitalized in the neurosurgery ward.

IMP/CS had been prescribed as a postoperative prophylactic antibiotic. However, it was found that the *Pseudomonas*, which was detected from this patient, was insensitive to IMP. In this patient, MRSA was detected from sputum and the throat, but the patient had no symptoms related to MRSA infection, therefore, no specific therapy (VCM) was practiced. Although gentamycin (GM) is not in the list of this surveillance, after this individual investigation, it was found that GM had been prescribed for a long-time period and the risk of adverse effects was suspected. It was found that GM was not administered intravenously to this patient, but was used topically when the cerebrospinal fluid was exchanged. Therefore, further investigation on adverse effects related to renal function was not conducted.

Case 2 (Fig. 6)

Thirty-three-year-old male with cancer in the sacral region was hospitalized in the orthopedic ward. Five months prior to administration in our hospital, MRSA was detected in the right buttock, resulting in the intermittent use of VCM. In spite that the *Staphylococcus aureus* was methicillin-sensitive when he was administered, thereafter, VCM was administered in a long-term period. On day 5 after admission, the peak concentration of VCM was as high as 44.8 μg/mL, which is over the therapeutic range of VCM (15~40 μg/mL). The pharmacist in the Therapeutic Drug Monitoring (TDM) Section suggested to the attending physician that the dose of VCM should be reduced, resulting in the daily dose being 1.25 mg/day. Nevertheless, MRSA was not detected, and VCM administration was out of indication. After consultation with the attending physician, the use of VCM was

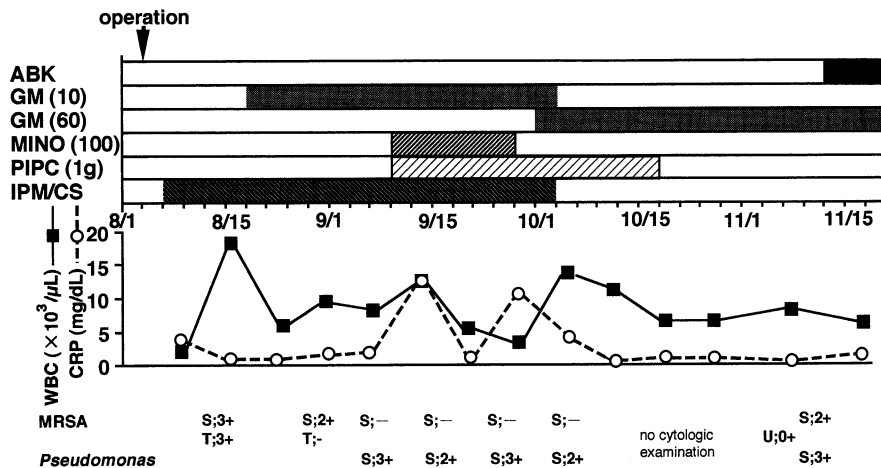


Fig. 5. Drug History, Laboratory Test Values, and the Results of Cytologic Examination in the Patient of Case 1.

CRP, C-reactive protein; WBC, white blood cells. The reference values: CRP, <0.3 mg/dL; WBC, 3.3~8.8×10<sup>3</sup>/μL. S, sputum; T, throat; U, urine. - and + indicate the detection of negative and positive, respectively, of the corresponding pathogen. The number followed by + indicates the intensity of the infection. It is notable that the *Pseudomonas* detected from this patient was insensitive to IPM.

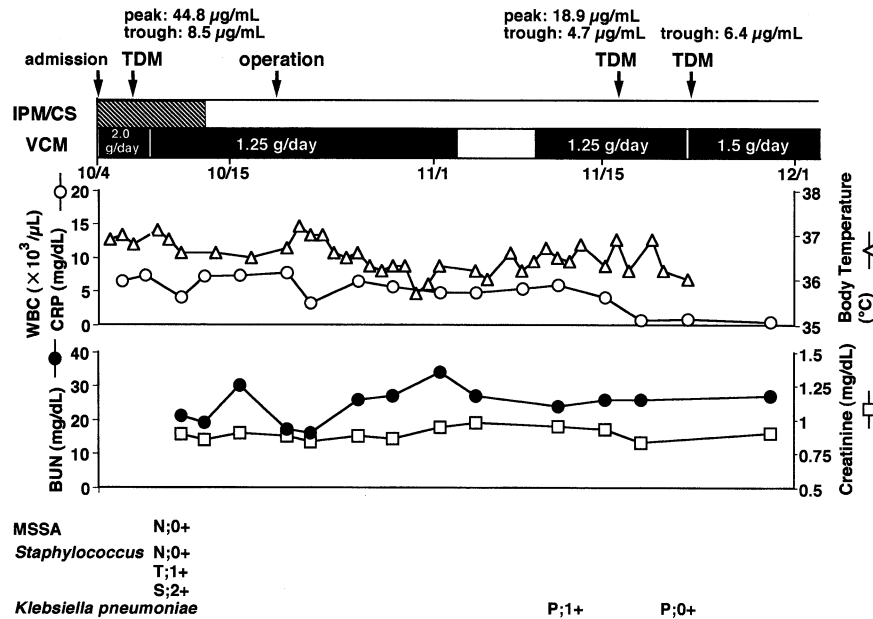


Fig. 6. Drug History, Laboratory Test Values, and the Results of Cytologic Examination in the Patient of Case 2.

CRP, C-reactive protein; WBC, white blood cells; BUN, blood urea nitrogen; MSSA methicillin-sensitive *Staphylococcus aureus*. The reference values: CRP, <0.3 mg/dL; WBC, 3.3~8.8×10<sup>3</sup>/µL; BUN, 7~22mg/dL; Creatinine, 0.6~1.2 mg/dL (male). S, sputum; T, throat; N, nasal; P, pus. - and + indicate the detection of negative and positive, respectively, of the corresponding pathogen. The number followed by + indicates the intensity of the infection (0 + does not mean negative).

once discontinued. Soon after the discontinuation, the value of C-reactive protein (CRP), which is the marker of inflammation, rose up to 3.4 mg/dL and resumed the VCM prescription. After the second consultation with the physician, it was found that this was the empiric use in the case of infection in the deep part of the sacrum.

### Discussion

The rapid dissemination of antimicrobial-resistant pathogens, especially MRSA in hospitals in Japan became a very big issue in the 80s and the early 90s. This was the result, in part, of the excessive inappropriate use of antibiotics due to the lack of knowledge of appropriate antibiotic therapy and the negligence in the proper prevention of cross infections<sup>2,5</sup>. Then, the recognition of antibiotic usage was altered among medical specialists including physicians, pharmacists and nurses. As an attempt to pursue appropriate usage of antibiotics, statistics of total amounts of antibiotics prescribed have been reported from large hospitals<sup>7,8</sup>. To discuss the relationship between the statistics and the emergence of resistant pathogens especially MRSA, it has been indirectly demonstrated that the antibiotic use has gradually become corrected. This method is the simplest by utilizing computer systems, however, there still remains room for fur-

ther appropriateness. From the statistics of the amounts, no information on the individual usage is available and no judgment can be made whether the antibiotic therapy is made properly to each patient. Therefore, we conducted the surveillance of individual usage of antibiotics. We first examined the length of the antibiotic therapy in each patient. In terms of the period of the antibiotic usage, it seemed that the overall antibiotic therapy was proper in Kanazawa University Hospital (Fig. 1). This was considered the result of the efforts by medical specialists during the last decade.

However, this analysis does not always reflect the period of antimicrobial usage on the individual patient basis. For example, patient A was prescribed PIPC (2 g), IPM/CS and MEPM from October 23<sup>rd</sup> to November 1<sup>st</sup> (10 days), from November 11<sup>th</sup> to November 19<sup>th</sup> (9 days) and from November 20<sup>th</sup> to November 29<sup>th</sup> (10 days), respectively. When the data were analyzed on the antimicrobial basis (separate counting), patient A was counted three cases of 7~13 days, which are considered "appropriate" by our standard; less than 14 days. In patient A, however, IPM/CS and MEPM were prescribed without intermission and the period of consecutive use was actually 19 days, which should be considered pre-cautious. Therefore, we conducted "combined counting" analysis, which is more individual patient basis

than "separate counting" analysis (Fig. 2). The period of the length of combined counting analysis tended to be longer than that of separate counting analysis. After this individual-patient analysis, a few cases of the excessive long-term usage were exemplified. This result suggests the importance of this kind of patient-by-patient investigation.

Then, we proceeded the investigation of the problems. It was found that the number of patients who were prescribed IMP/CS was extremely high in the ophthalmology ward (Fig. 3). Further investigation of the consecutive usage found that more than 96.6% of the patients were prescribed IMP/CS as a postoperative prophylactic antibiotic, and the period was only one day in most cases. According to the physicians in the ward, the antibiotic was used as a postoperative prophylactic antibiotic. Although this usage is out of indication, there was no additional usage of any antibiotic thereafter in each patient, and no infection was reported. Therefore, this usage cannot be defined as inappropriate usage although there may be alternative antibiotics. In such cases, it is important to keep track of the any emergence of infection and collect data to prove the rationality and necessity. It is proposed that pharmacists can play the key role in this activity as medical specialists. The same concept is applied to the cases of VCM usage to MRSA-negative patients. These cases, which are out of indication, are controversial, however, by the consultation with the physicians who prescribed, they were found to be used as a prophylactic antibiotic during bone marrow transplantation and dialysis. These were cases that the clinical advantages took precedence over the indication. Monitoring the usage is very important especially in long-term usage to prevent adverse effects such as renal dysfunction. In addition, it is difficult to adjust the dose and to plan the schedule of VCM to avoid adverse effects, therefore, more caution is required. Pharmacists should urge the attending physicians to perform TDM and other laboratory tests.

We closely focused on the two cases of long-term usage of antibiotics; one of which is IMP/CS (Case 1) and the other is VCM (Case 2). In the former case, the choice was obviously wrong, since the *Pseudomonas* from the patient was insensitive to IMP. The antibiotic should have been altered as soon as possible after the susceptibility testing. In the latter case, choice of VCM seemed wrong and the period was too long to cover the cost by public insurance. Once the attending physician ceased VCM prescription, the level of CRP rose. Empiric VCM treatment was resumed in this patient. In this case, it is not always the best way to discontinue the VCM treatment. However, it is necessary to urge physicians to perform frequent TDM to prevent adverse effects and emergence of new resistant pathogens. Moreover, in cases of out of indication usage like this, we need to collect evidence from both literature and our own case reports so as to give physicians advice in the selection and dosage

of antimicrobials.

This surveillance was done on-going, however, the analysis was retrospective. Therefore, on-time recommendation was forwarded to attending physicians in only limited cases. This kind of surveillance should be practiced on-time by pharmacists who must make effort to distribute accurate and useful information to the prescribers. This surveillance was done with the cooperation of the Hospital Infection Control Team (HICT) in Kanazawa University Hospital. This organization is consisted of physicians, pharmacists, nurses and laboratory technicians. The activity ranges from prevention of infection in the hospital to surveillance of the emergence of MRSA and *Pseudomonas*, and so on. After this surveillance, we were able to show some cases of prolonged usage of antimicrobials, which reinforce the recognition of the requirement of proper usage among the physicians in Kanazawa University Hospital. Now, the system has been founded officially in Kanazawa University Hospital: HICT makes documents to warn the attending physicians that prescribe the same antimicrobial for 28 consecutive days or more.

There is no doubt that the computerization will play the important role in the near future, but it is more important to utilize the information and data from the computer. Pharmacists must acquire satisfactory knowledge on antimicrobials in proper selection, dosage and schedule. This must contribute to decreasing unnecessary potent-antimicrobial use, leading to lowering the emergence of new resistant-pathogens and improving quality of life of patients.

In summary, it was demonstrated that overall usage of antimicrobials in Kanazawa University Hospital was appropriate. However, some inappropriate usage was suspected from individual patient-by-patient investigation of antimicrobial usage. Some of the cases were found to be empiric treatments; the others would have needed interventions. Since the analysis was retrospective in this study, it is proposed that surveillance of this kind should be conducted continuously and pharmacists should give on-time suggestion to prescribers.

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