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Evaluation of antimicrobial stewardship (AS) for appropriate use of antimicrobial agents

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We implemented an antimicrobial stewardship (AS) program whereby pharmacists sought appropriate use of antimicrobial agents in January 2012. At that time, we targeted anti-methicillin-resistant *Staphylococcus aureus* (MRSA) agents and carbapenems; however, in January 2014, we added tazobactam/piperacillin (TAZ/PIPC). We evaluated outcomes using multilateral analyses. The average one-day dosage of carbapenems increased; however, the duration of administration and number of recipient patients decreased significantly ($P < 0.01$). Moreover, the percentage of patients receiving meropenem (MEPM), for whom the time above minimal inhibitory concentration (MIC) was 40% or higher increased ($P < 0.01$). In contrast, patient utilization of TAZ/PIPC increased significantly after targeting of carbapenems as specific antibacterial agents. However, after TAZ/PIPC was targeted as a specific antibacterial agent, the number of TAZ/PIPC administrations decreased significantly ($P < 0.01$). The duration of hospitalization and mortality rate in patients receiving specific antibacterial agents significantly decreased after implementation of the AS program ($P < 0.01$). In conclusion, pharmacist's interventions to provide AS and patient follow-up reduced improper use and promoted proper administration of antibacterial agents. Furthermore, AS was effective in improving patient prognoses and suppressing drug-resistant strains, as well as promoting effective treatment.

1. Introduction

Infection prevention measures were included in the 2012 medical fee revisions. This addition includes promotion of the proper use of antimicrobial agents for interventions and use of a feedback and specification system. The guidelines also announced (Dellit et al. 2007) promotion of the proper use of antimicrobial agents based on the antimicrobial stewardship (AS) program jointly initiated at the Infectious Diseases Society of America and the United States Medical Epidemiology Society in 2007. Optimizing the use of antimicrobial agents to avoid inappropriate antimicrobial use can achieve a maximum therapeutic effect for patients, thereby improving prognoses, suppressing side effects, reducing the number of resistant bacteria, and reducing costs. The guidelines recommend a "specification system and approval system" and "aggressive intervention and feedback" as a central strategy for AS, combined with some additional strategies. In addition, they recommend that core participants in AS be infectious disease specialists and pharmacists who have received training in the treatment of infectious diseases."

In Japan, only large hospitals have infectious disease specialists and infectious diseases departments; such hospitals include university hospitals. Ogaki Municipal Hospital (the hospital of the present study) is an acute phase community hospital with 903 beds. However, it does not have a full-time infectious disease specialist. Therefore, pharmacists play a crucial role in optimizing antimicrobial use. In January 2012, we began an AS program initiated by pharmacists with follow-up in patients to promote the appropriate use of antimicrobial agents. AS is currently being introduced in Japan and has been utilized in various applications (Niwa et al. 2012; Matsumoto et al. 2014). However, a uniform protocol has not been established; therefore, methods vary among the different hospitals. We used a step-by-step approach for proper use of antibiotics. We report a multilateral analysis for the outcomes of these efforts.

2. Investigations and results

2.1. Three-year trends in the number of each type of intervention

Figure 1 shows the number of pharmacist interventions, proposals, and interventions conducted during hospital rounds in each year of the 3-year period (2012–2014). The number of pharmacist's interventions increased every year, with the 3rd year showing a 370% increase over the first year. Although the number of interventions conducted during hospital rounds in the 2nd year increased 240% over the 1st year of interventions, while there was nearly no increase in the 3rd year. Whereas the percentage of pharmacist's

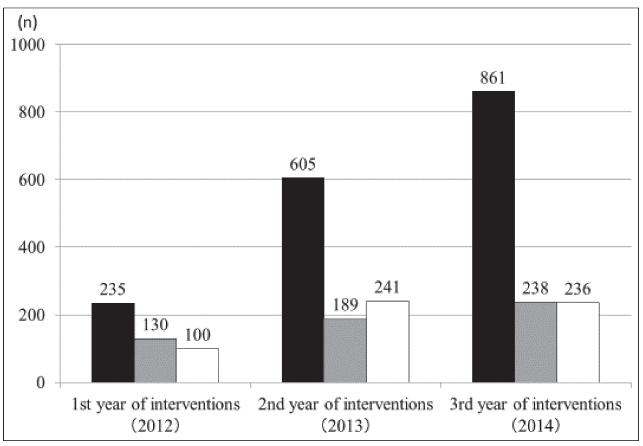

Fig. 1: Three-year (2012–2014) trends in the number of each type of intervention.
■ Number of pharmacist interventions
■ Number of interventions conducted during hospital rounds
□ Number of pharmacist proposals

interventions that developed into interventions during rounds in the 1st year was 42.6% (100/235), that number decreased to 27.4% (236/861) during the 3rd year. In addition, there was nearly no change in the number of pharmacist's proposals to physicians from the 2nd year to the 3rd year of interventions. As shown in Fig. 2, excluding therapeutic drug monitoring (TDM), the proportion of proposals suggesting "ending administration of the antimicrobial agent" increased every year. The proposal acceptance rate in the 1st year of interventions was a favorable 86.8% and increased further to 91.6% by the 3rd year.

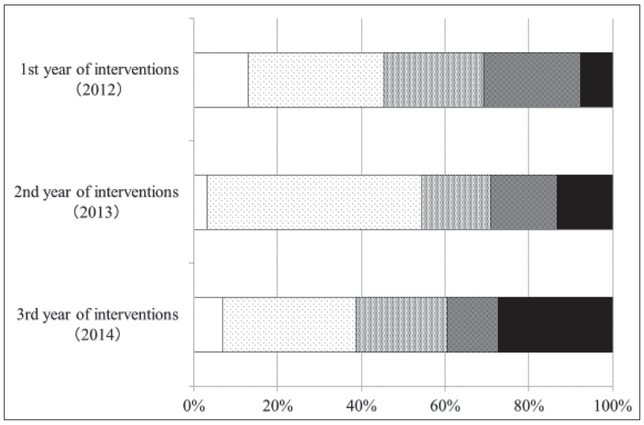

Fig. 2: Proportion of interventions and content of pharmacist proposals in the 3–year period following introduction of interventions.
- Administration
- Dosage
- Changes in antimicrobial agents based on culture results (including de-escalation)
- Changes in antimicrobial agents based on consideration of side effects or organ migration
- End of administration of the antimicrobial agent

2.2. *Trends in the use of carbapenems and tazobactam/piperacillin (TAZ/PIPC) during the three periods*

Whereas antimicrobial use density (AUD) and daily usage of carbapenems increased significantly from pre-intervention to post-intervention I, daily usage in post-intervention II remained mostly unchanged. AUD, days administered, and administration count during post-intervention II decreased significantly (Fig. 3). However, AUD and administration count for TAZ/PIPC increased significantly from pre-intervention to post-intervention I, whereas the administration count decreased significantly in post-intervention II. Daily usage and days administered were unchanged for all 3 periods (Fig. 4).

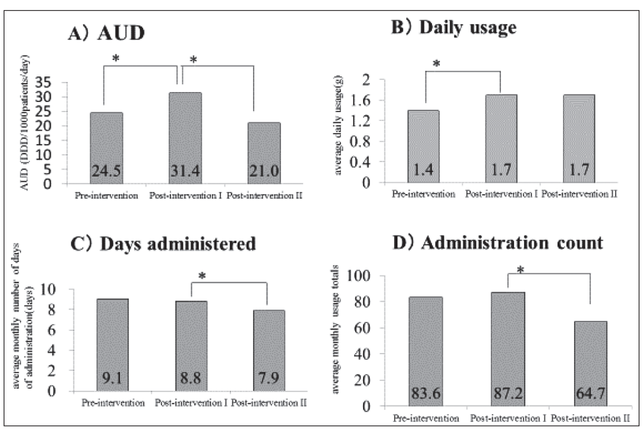

Fig. 3: Trends in the use of carbapenems during the 3 periods.
A: Antimicrobial use density (AUD). B: Daily usage. C: Days administered. D: Administration count
* $P < 0.01$ compared to pre-intervention period (using an unpaired *t*-test)

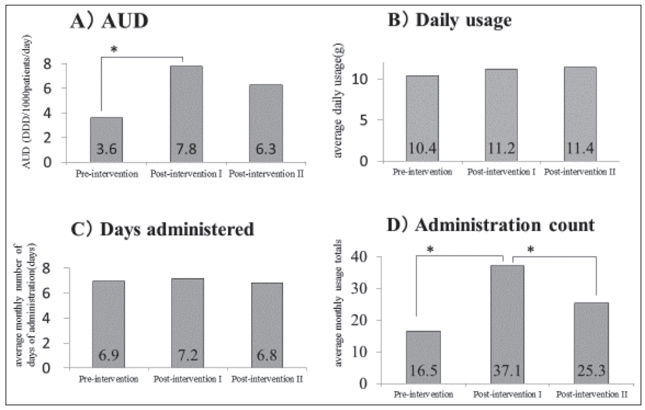

Fig. 4: Trends in the use of tazobactam/piperacillin (TAZ/PIPC) during the 3 periods.
A: Antimicrobial use density (AUD). B: Daily usage. C: Days administered. D: Administration count.
* $P < 0.01$ compared to pre-intervention period (using an unpaired *t*-test)

The proportion of meropenem (MEPM) % time above MIC (%TAM) exceeding 40% increased significantly from the 1st year to the 2nd year of interventions ($P < 0.01$). The increase continued in the 3rd year (Fig. 5).

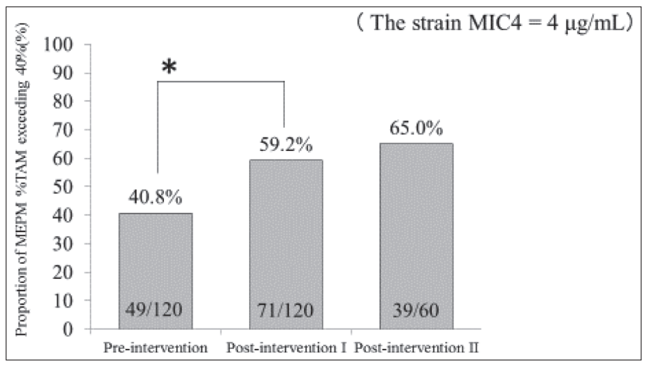

Fig. 5: 3-year (2012–2014) proportion of meropenem (MEPM) and % time above minimal inhibitory concentration (%TAM) exceeding 40%.
Numbers in in the graph show: number of patients with MEPM %TAM exceeding 40%/ survey number.
* $P < 0.01$ compared to pre-intervention period (using a χ^2 test)

2.3. *Hospital stay and mortality*

The average length of hospital stay and mortality rate in each of the 3 periods, including pre-intervention, post-intervention I, and post-intervention II, are shown in Table. The mortality rate and average length of hospital stay decreased significantly from the pre-intervention period in all cases ($P < 0.01$).

Table 1 The average lenght of hospital stay and mortality rate in patients using specific antibacterial agents

	Number of patients	Mortality	Mortality rate (%)	Average length of hospital stay (days)
Pre-intervention	2,022	570	28.2	74.7
Post-intervention I	2,657	533	* 20.1	* 64.6
Post-intervention II	961	191	* 19.9	* 52.9

* $P < 0.01$ vs period before intervention, log-rank test

2.4. Questionnaire survey results

The recovery rate from the questionnaire survey was 60.0% (72/120). Among the 72 physicians who responded, 100% assigned a score of 4 or 5 to "I think that it's useful for the pharmacist to intervene," 88.4% assigned a score of 4 or 5 to "I changed my approach to the use of antimicrobials (dosage, administration, and selection, including de-escalation) based on the pharmacist's recommendations," 58.0% assigned a score of 4 or 5 to "I think that the types of antimicrobials in interventions should be increased," and 89.9% assigned a score of 4 or 5 to "I strongly want to see pharmacist's interventions in the future."

3. Discussion

In the United States, it has been reported (Cosgrove et al. 2007) that inappropriate antibiotic use occurs in 50 to 72% of the total number of antibiotic prescriptions. Many reports (Drew 2009; Bantar et al. 2003) also state that AS programs reduce inappropriate use of antibiotics, thus contributing to the improvement of antimicrobial susceptibility. AS is important for interventions, as it is based on knowledge of infectious diseases and microbiology, hospital antibiograms, as well as the organ migration and pharmacokinetic/pharmacodynamic (PK/PD) characteristics of each antimicrobial agent. As a result of interventions by pharmacists, we evaluated three factors affecting antimicrobial agent use: the number of patients in which the agent was used, daily usage, and trends in the number of days in which the agent was used.

We suggest that the increase in carbapenem AUD from pre-intervention to post-intervention I contributes to the significant increase observed in daily usage. Empirical treatments are employed in many cases in which specific antibacterial agents are used, and there are many instances wherein MIC is unknown, with no actual detection of the pathogenic bacterium. Thus, we cannot expect maximal bactericidal action without administration plans that enable demonstration of maximum therapeutic effects, i.e., administration and dosages that result in values at least equal to or greater than the target value for the PK/PD %TAM parameter for β-lactam antimicrobial agents. However, it cannot be said that all prescribing physicians were taking this into consideration, and proposals increasing administration frequency and dosage were unavoidable at the beginning of the interventions. We believe that this result is related to the significant increase in the percentage of patients receiving MEPM with a %TAM greater than 40%. In contrast, the daily usage established in post-intervention I was maintained in post-intervention II, whereas the number of administration days and number of administered patients significantly decreased. Low-dose and long-term usage (Tanaka et al. 2008; Miyazaki 2008; Hirakata et al. 2003; Falagas and Kopterides 2006) of carbapenems promote resistance to antimicrobials in *Pseudomonas aeruginosa* (Guillemot et al. 1998). Furthermore, insufficient %TAM is a risk factor for increased MIC in *P. aeruginosa* infections, and AS programs based on PK/PD models are also useful for suppressing bacterial resistance.

In contrast, the number of patients taking the non-specific antibacterial agent, TAZ/PIPC, was 220% higher during post-intervention I than that of the pre-intervention period. It has been reported thus far that fourth-generation cephalosporins and similar treatments are used in excess when not limited. TAZ/PIPC has a broad-spectrum effect similar to that of carbapenems, and thus clinical practice guidelines have been established for a variety of infectious diseases. TAZ/PIPC has been promoted as a therapeutic agent for febrile neutropenia, respiratory infections, and intra-abdominal infections. Therefore, its widespread use has likely resulted in its application to cases where administration was unnecessary. However, intervention with notification and positive monitoring has made it possible to decrease the number of patients using TAZ/PIPC by 70% without affecting the use of other antibiotics.

Interventions in which staff continue to observe changes over time and organize the information in individual cases require a considerable amount of time and effort. Under current conditions, it is difficult for pharmacists to secure sufficient time to implement AS programs; therefore, simplification of pharmacy practice is required. In addition, infection control support systems and other IT technologies are indispensable for continued sharing of information among a plurality of responsible pharmacists (Matsumoto et al. 2014). In an international study (Pulcini et al. 2015) of AS programs in 660 hospitals in 67 countries, approximately 60% of the total facilities performed AS. The reason for this low rate included a lack of personnel and systems, as only approximately 20% of facilities were using an AS system. Other factors include a lack of awareness among administrators and the prescribing physicians. It is therefore likely that the purpose of AS programs is still not sufficiently understood. Our hospital thus introduced such a system before its introduction to the rest of the country. In our hospital, patient data management was performed using commercially available database software before the dedicated system was introduced. Because this system was not linked to electronic medical charts, manual data input was required, which was time consuming. However, introduction of the system made it possible to rationalize the work, such as eliminating data input and simplifying the creation of material needed for rounds. Thus, the data creation time per patient was reduced. Further, by the third year of interventions, the number of pharmacist's interventions gradually increased to 370% of the first year figures. In contrast, there were no changes in the number of interventions in rounds and the number of proposals from the pharmacist to the physician. We suggest that development of the program up to the level of physician rounds is not required, and it is now possible for the pharmacist to evaluate interventions; thus, there is little need for proposals to physicians. Proposals are linked to administration and dosages of antimicrobial agents, including recommendations regarding when administration of antimicrobial agents should end, with changes to regulations at the end rather than at the start of administration. These proposals are thought to allow the pharmacist to be more deeply involved in infection treatments. Based on physician responses to "the intervention of the pharmacist is useful" and "I think that the concept of antibiotic use has changed based on the proposal of the pharmacist" in the questionnaire, it also appears that pharmacist AS activities are highly valued by physicians.

Development of antimicrobial agents is stagnant, and the diversification in recent years of resistant bacteria may lead to a crisis in the treatment of infectious diseases. Therefore, it is necessary to appropriately use existing antibiotics, and concepts such as AS programs are essential for the proper use of anti-microbial drugs. Fishman (2006) also described a method for boosting suppression of resistant bacteria and improving patient prognoses where it was important to combine various measures; however, it has been stated that AS programs are a core component of the total management for infectious diseases. It is now the fourth year since we implemented the AS program. The concept of AS involves significant reduction of mortality and days of hospitalization, which leads to improvement of maximum therapeutic effects and patient prognoses. The present results reflect this concept. The pharmacist engages in AS interventions, optimizes methods of administration, avoids inappropriate antibiotic use, and helps to suppress the development of resistant bacteria. These efforts improve patient prognoses and help in the administration of treatments. Although the significance of the pharmacist in AS is recognized, the current system is not adequate. Therefore, it is important for pharmacists to conduct active and sustained interventions with logical thinking and responsibility. Promotion of the proper use of antimicrobial agents requires pharmacists with expertise, as suggested by the evaluation results obtained from physicians in this study.

In conclusion, AS reduced the improper use of antibiotics and promoted effective administration of antibiotics in a hospital setting. Application of the AS program improved patient prognoses and suppressed infections caused by drug-resistant strains, which promoted successful treatment.

4. Experimental

4.1. Outline of AS at the study hospital

AS was initiated by pharmacists who targeted anti-methicillin-resistant *Staphylococcus aureus* (MRSA) agents and carbapenems in January 2012. The pharmacist in charge of AS performed the intervention starting the day after administration began in patients receiving the antimicrobial agent, two to three hours a day, five days a week, until the end of treatment. However, if administrations began on a Friday, the intervention began the following Monday; when administration began on the day before a holiday, the intervention began the day after the holiday ended. In January 2014, we implemented the hospital information system (electronic medical records) and the linked infection management support system for effective support of infection control (IMS system, BACT Web®: Eiken Chemical Co., Ltd.); this provided a central management of the information necessary for infection control.

The IMS system tracks hospital isolate data, antibiograms, and infection occurrence in wards. The data are mapped in a graphic format, enabling timely reference to information on usage of antibiotics. We have customized this system for AS operations to automatically create patient files from a list of patients using specific antibiotics and to manage the resulting data. With an intervention, we record the history and summary of progress described in the patient file. In addition, we confirm that culturing was performed; evaluate the need for antimicrobial agents, considering a focus on infectious disease; and ensure that appropriate antimicrobial agents have been selected. Furthermore, we confirm suitable dosage and administration protocols based on PK/PD by checking liver and kidney functions. If TDM is necessary, we conduct dose planning in all cases. Additionally, remarks including consultation confirmation and consultation with the attending physician are registered in the patient file, and this information is shared among the pharmacists. As the IMS system is linked to the electronic medical records, the time series in a vital or thermal graph, device insertion status, bacterial culture results, antibiotic use, and blood data can be viewed simultaneously from the patient file. After the second day of intervention, we used the above-described monitoring functions to check culture results and fluctuations in blood data and evaluated the selection and efficacy of antimicrobial agents, including protocols, dosage, and the presence or absence of side effects. When patients received antibiotics beyond the 7th day, we proposed terminating the treatment period after confirmation with the attending physician. Introduction of this system enabled the addition of TAZ/PIPC as a specific antibacterial agent and increased the breadth of the interventions.

4.2. Evaluation of AS

4.2.1. Number of interventions and content of pharmacist proposals in the 3–year period following introduction of interventions

We investigated the number of interventions in each year of the 3-year period (2012–2014) following the introduction of interventions by the pharmacists, interventions conducted during hospital rounds (multiple interventions in the same cases were counted as multiple infectious disease treatments), and the number and content of pharmacist proposals. Proposal contents were classified into four types: administration and dosage, changes in antimicrobial agents based on culture results (including de-escalation), changes in antimicrobial agents based on consideration of side effects or organ migration, and end of administration of the antimicrobial agent.

4.2.2. Comparison of antimicrobial agent use

We investigated and compared average monthly AUD, average daily usage (daily usage), average monthly of the number of patients administered (administration count), and average monthly number of days of administration (days administered) for carbapenems and TAZ/PIPC during 3 periods as follows: 2 years prior to intervention (January 2010 to December 2011, pre-intervention); first 2 years of intervention (January 2012 to December 2013, post-intervention I); and the 3rd year of intervention, following the start of the TAZ/PIPC intervention (January to December 2014, post-intervention II).

4.2.3. Evaluation of proper MEPM use

We selected a sample of 60 cases/year from patients using MEPM in each of the 3 periods: pre-intervention, post-intervention I, and post-intervention II. We then calculated the MEPM PK/PD %TAM for strain MIC4 and compared the proportion of cases in which %TAM was 40% or higher (indicating the maximum bactericidal action) in each of the three periods. To calculate %TAM, we used the meropenem blood concentration simulation and %TAM calculation software, MeroTam ver. 4.0, from Dainippon Sumitomo Pharma (https://ds-pharma.jp/product/meropen/knowledge/merotam, 2014/06/30).

4.2.4. Length of hospital stay and mortality in patients using specific antibacterial agents

We calculated the average length of hospital stay and mortality rate in cases using specific antibacterial agents (anti-MRSA agents, carbapenems, and TAZ/PIPC) in each of the 3 periods: pre-intervention, post-intervention I, and post-intervention II.

4.2.5. Survey on pharmacist interventions with proper use of antimicrobials

In June 2015 (in the fourth year from the beginning of the interventions), we completed a questionnaire survey of physicians in the hospital regarding pharmacist interventions with proper use of antimicrobials. The four survey questions were as follows: "I think that it's useful for the pharmacist to intervene"; "I changed my approach to the use of antimicrobials (dosage, administration, and selection, including de-escalation) based on the pharmacist's recommendations"; "I think that types of antimicrobials in interventions should be increased"; and "I strongly want to see pharmacist interventions in the future." For answers, five levels of agreement/disagreement were available as follows: "1. Completely disagree"; "2. Somewhat disagree"; "3. Cannot say either way"; "4. Somewhat agree"; and "5. Strongly agree."

4.3. Statistical analysis

We used the statistical analysis software EZR (v.1.26) (Kanda 2013) to run $\chi 2$ tests for nominal variables, as well as F-tests and unpaired t-tests for continuous variables. We calculated the length of hospital stay per the Kaplan-Meier method and ran log-rank tests using average values, then compared the resulting data. Significant difference was defined as $P < 0.05$.

4.4. Ethical considerations

The present study was approved by the Institutional Review Board of Ogaki Municipal Hospital (Approval Number: 20151120-1).

Conflicts of interest: None declared.

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