Trends in Antipseudomonal Agent Use Based on the 2006 to 2015 Sales Data in Japan

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Pseudomonas aeruginosa resistance is a major issue worldwide. Drug resistance is related to inappropriate antibiotic use. Because antipseudomonal agents have a wide spectrum, they must be used appropriately. The purpose of this study was to clarify the trends in antipseudomonal agent use in Japan based on sales data from 2006 to 2015. The total antipseudomonal agent use was increased significantly (r = 0.10, P_{trend} = 0.00040). The proportion of fluoroquinolones use was the highest throughout the year, accounting for 88.6–91.4%. The use of piperacillin/tazobactam significantly increased. The increased use of these drugs may be due to the launch of higher doses and additional indications. On the other hand, for antipseudomonal agents, parenteral carbapenems use was 2.7–3.7%, but it has remained unchanged over the years. In Japan, permit and notification systems have been introduced to prevent the inappropriate use of parenteral carbapenems in medical institutions. It was speculated that these efforts suppressed the inappropriate use of parenteral carbapenems. This study clarified the trend of antipseudomonal agent use in Japan from 2006 to 2015. It is important to continue monitoring antipseudomonal agents use to conduct appropriate antimicrobial resistance measures.

Key words antipseudomonal agent; Pseudomonas aeruginosa; antibiotic use; antimicrobial resistance; surveillance

INTRODUCTION

Drug-resistant bacteria are a major global health problem. The WHO announced the global trend of antimicrobial resistance (AMR) for the first time in 2014.1 The WHO also adopted a global action plan on AMR in 2015.2 In Japan, a national action plan was formulated to promote AMR countermeasures in 2016.3 The inappropriate use of antibiotics is one of the causes of drug-resistant bacteria. Thus, continuous surveys on antibiotic use, based on the internationally unified antimicrobial use index, is required as a strategy in the national action plan on AMR.3

Pseudomonas aeruginosa is a ubiquitous bacterium that causes opportunistic infections. P. aeruginosa easily propagates in medical devices such as catheters and is one of the causes of serious nosocomial infections, including ventilator-associated pneumonia and sepsis.4 The inherent resistance mechanism of P. aeruginosa includes low outer membrane permeability, expression of efflux pumps that drive antibiotics out of the cells, and the production of antibiotic-inactivating enzymes.5 The resistance of P. aeruginosa was selected due to the improper use of antibiotics. Therefore, the national action plan for AMR especially aimed at reducing the resistance rate of P. aeruginosa to carbapenems to less than 10% by 2020.6 However, these goals have not been achieved.6 There is an urgent need to reduce the resistance rate of P. aeruginosa to carbapenems.

Broad-spectrum antibiotics, such as carbapenems, monobactams, broad-spectrum penicillins, third- and fourth-generation cephalosporins, aminoglycosides, and quinolones, have antipseudomonal action. Our previous study reported that broad-spectrum antibiotics are associated with resistance to P. aeruginosa.7 Therefore, it is necessary to pay attention to inappropriate use. However, the previous study did not cover all medical institutions in Japan and was limited to intravenous antibiotics.8 Therefore, it is necessary to evaluate the trend of broad-spectrum antibiotic use (including oral and intravenous antibiotics) in Japan.

We previously evaluated the trends of antibiotic use in each anatomical therapeutic chemical (ATC) classification system in Japan.9 However, because antipseudomonal agents cross multiple ATC classification systems, it is necessary to evaluate not only them but also each drug. Therefore, the purpose of this study was to evaluate the trends of antipseudomonal agent use in Japan, based on sales data from 2006 to 2015 to clarify the findings before the national action plan was formulated.

MATERIALS AND METHODS

Data Collection Information on the use of antipseudomonal agents from as far back as possible needed to be evaluated in order to clarify the findings before the national action plan was formulated. Given that the oldest available sales data were from 2006, we obtained sales data from 2006 to 2015 for 10 years within the funding. Sales data on antipseudomonal agents included in J01CA, J01CR, J01DD, J01DE, J01DF, J01DH, J01GB, and J01MA of the ATC classification (fourth level) by the WHO were consumed by the IQVIA Services Japan K.K. (Tokyo, Japan). By generation, fluoroquinolones are classified as first-generation fluoroquinolones (norfloxacin), second-genera-
tion fluoroquinolones (ofloxacin, ciprofloxacin, enoxacin, lomefloxacin, fleroxacin, sparfloxacin, levofloxacin (LVFX), and tosufloxacin), and third-generation fluoroquinolones (moxifloxacin, gatifloxacin, prulifloxacin, garenoxacin (GRNX), sitafloxacin (STFX), and pazufloxacin). Although GRNX is not indicated for *P. aeruginosa*, it is a broad-spectrum antibiotic and was included in the analysis. Aminoglycosides included tobramycin as an inhalant.

**Evaluation of Antipseudomonal Agent Use** The 2020 version of the ATC/defined daily dose (DDD) Index\(^{10}\) was ap-

### Table 1. ATC Codes and DDD of Antipseudomonal Agents

| Category                  | Route | Antipseudomonal agents | ATC  | DDD (g) |
|---------------------------|-------|------------------------|------|---------|
| First-fluoroquinolones    | O     | Norfloxacin            | J01MA06 | 0.8     |
|                           |       |                        |      |         |
| Second-fluoroquinolones   | O     | Ofloxacin              | J01MA01 | 0.4     |
|                           |       | Ciprofloxacin          | J01MA02 | 1       |
|                           |       | Enoxacin               | J01MA04 | 0.8     |
|                           |       | Lomefloxacin           | J01MA07 | 0.4     |
|                           |       | Fleroxacin             | J01MA08 | 0.4     |
|                           |       | Sparfloxacin           | J01MA09 | 0.2     |
|                           |       | Levofloxacin           | J01MA12 | 0.5     |
|                           |       | Tosufloxacin           | J01MA22 | 0.45    |
|                           | P     | Ciprofloxacin          | J01MA02 | 0.8     |
|                           |       | Levofloxacin           | J01MA12 | 0.5     |
|                           |       |                        |      |         |
| Third-fluoroquinolones    | O     | Moxifloxacin           | J01MA14 | 0.4     |
|                           |       | Gatifloxacin           | J01MA16 | 0.4     |
|                           |       | Prulifloxacin          | J01MA17 | 0.6     |
|                           |       | Garenoxacin            | J01MA19 | 0.4     |
|                           |       | Sitafloxacin           | J01MA21 | 0.1     |
|                           | P     | Pazufloxacin           | J01MA18 | 1       |
|                           |       |                        |      |         |
| Carbapenems               | P     | Meropenem              | J01DH02 | 3       |
|                           |       | Doripenem              | J01DH04 | 1.5     |
|                           |       | Biapenem               | J01DH05 | 1.2     |
|                           |       | Imipenem/Cilastatin    | J01DH51 | 2       |
|                           |       | Panipenem/Betamipron   | J01DH55 | 2       |
|                           | P     |                        |      |         |
| Monobactums               | P     | Aztreonam              | J01DF01 | 4       |
|                           |       | Carumonam              | J01DF02 | 2       |
|                           |       |                        |      |         |
| Aminoglycosides           | P     | Tobramycin             | J01GB01 | 0.24    |
|                           |       | Gentamicin             | J01GB03 | 0.24    |
|                           |       | Kanamycin              | J01GB04 | 1       |
|                           |       | Amikacin               | J01GB06 | 1       |
|                           |       | Netilmicin             | J01GB07 | 0.35    |
|                           |       | Sisomicin              | J01GB08 | 0.24    |
|                           |       | Dibekacin              | J01GB09 | 0.14    |
|                           |       | Ribostamycin           | J01GB10 | 1       |
|                           |       | Isepamicin             | J01GB11 | 0.4     |
|                           |       | Arbekacin              | J01GB12 | 0.2     |
|                           |       | Bekanamycin            | J01GB13 | 0.6     |
|                           |       | Astromicin             | J01GBXA*1 | 0.4*2 |
|                           |       | Micronomicin           | J01GBXB*1 | 0.24*2 |
|                           |       |                        |      |         |
| Inhal                      |       | Tobramycin             | J01GB01 | 0.3     |
|                           |       |                        |      |         |
| Third-cephalosporins       | P     | Ceftazidime            | J01DD02 | 4       |
|                           |       |                        |      |         |
| Fouth-cephalosporins       | P     | Cefepime               | J01DE01 | 4       |
|                           |       | Cefpirome              | J01DE02 | 4       |
|                           |       | Cefozopran             | J01DE03 | 4       |
|                           | P     | Pipercillin/Tazobactam | J01CR05 | *3      |
| Penicillins with extended spectrum | P      | Pipercillin            | J01CA12 | 14      |

ATC, Anatomical Therapeutic Chemical; P, parenteral; O, oral; Inhal, inhalation; DDD, defined daily dose. *1: Astromicin and micronomicin were classified as J01GBXA and J01GBXB, which have the same drug efficacy and action site, because there is no ATC classification with the same drug efficacy, action site, and components. *2: Japan DDD (JDDD) of astromicin and micronomicin was defined as the maximum dose in the Japanese package insert was used because DDD is not listed in the ATC/DDD Index 2019. *3: J01CR05 includes tazosin\(^{¥}\) and zosyn\(^{¥}\). The combination ratio of pipercillin/tazobactam of zosyn\(^{¥}\) was 8:1 and that of tazosin\(^{¥}\) was 4:1. Because of the different mixing ratios, DDD used 17.5 for tazosin\(^{¥}\) and 15.75 for zosyn\(^{¥}\).
plied to all data. Table 1 shows the DDD of antipseudomonal agents. For drugs with no DDD in the ATC/DDD Index 2020, Japan DDD (JDDD),11) defined as the maximum dose in the Japanese package insert, was used. Population data were obtained from the Statistics Bureau of Japan.12) In addition, each drug was tabulated in dosage form (oral/parenteral). The sales data were reported as DDDs per 1000 inhabitants per day (DID),9) using the following equation:

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\text{DID (DDDs/1000 inhabitants/d)} = \frac{\text{Use in each year (g)}}{\text{DDD (g)} \times \text{population for each year (/1000 inhabitants)} \times 365 (d)}
\]

**Statistical Analysis** Evaluation of antibiotic use is generally performed using a time-series analysis. Time series analysis requires detailed information such as months and days as well as interventions, which are the starting points for change. However, this study used annual sales data and could not be used to set the starting point change. Thus, the trends of antipseudomonal agent use were evaluated using linear regression analyses.13–15) The analyses were performed using JMP® Pro 14 (SAS Institute Inc., Cary, NC, U.S.A.). A two-sided \( p \) value < 0.05, was considered statistically significant for all analyses. The requirement for informed consent was waived because anonymized sales data were used.

**RESULTS**

**Trends of Antipseudomonal Agent Use from 2006 to 2015** Figure 1 and Table 2 show the trends of antipseudomonal agent use from 2006 to 2015. The total antipseudomonal agents use was 2.4 DDDs/1000 inhabitants/day in 2006 and increased to 3.0 DDDs/1000 inhabitants/day in 2015, representing an increase of 0.6 DDDs/1000 inhabitants/day per year. The use of fluoroquinolones, carbapenems and monobactams, aminoglycosides, third- and fourth-cephalosporins, and penicillins also increased significantly from 2006 to 2015. The changes in the use of each class of antipseudomonal agents are shown in Table 2. The values show DID (DDDs/1000 inhabitants/d). CI, confidence interval.

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**Table 2. Trend of Antipseudomonal Agents Use from 2006 to 2015**

|          | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | Change | \( P \) for trend | 95% CI          |
|----------|------|------|------|------|------|------|------|------|------|------|--------|---------------|----------------|
| Fluoroquinolones | 2.1  | 2.1  | 2.1  | 2.3  | 2.5  | 2.7  | 2.9  | 2.9  | 2.7  | 2.7  | 0.10   | 0.00030       | 0.062 to 0.14  |
| Carbapenems and monobactams | 0.090 | 0.085 | 0.084 | 0.081 | 0.082 | 0.085 | 0.087 | 0.086 | 0.084 | 0.084 | -0.00017 | 0.57          | -0.00084 to 0.00050 |
| Aminoglycosides | 0.084 | 0.076 | 0.070 | 0.063 | 0.061 | 0.058 | 0.054 | 0.049 | 0.046 | 0.045 | -0.0043 | <0.0001       | -0.0049 to -0.0037 |
| Third- and fourth-cephalosporins | 0.076 | 0.073 | 0.071 | 0.064 | 0.063 | 0.058 | 0.053 | 0.049 | 0.045 | 0.044 | -0.0038 | <0.0001       | -0.0042 to -0.0035 |
| Penicillins | 0.024 | 0.025 | 0.028 | 0.044 | 0.054 | 0.060 | 0.068 | 0.077 | 0.080 | 0.086 | 0.0077 | <0.0001       | 0.0068 to 0.0087 |
| Total     | 2.4  | 2.4  | 2.4  | 2.5  | 2.8  | 3.0  | 3.2  | 3.1  | 3.0  | 3.0  | 0.10   | 0.00040       | 0.062 to 0.14  |

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**Fig. 1. Trend of Antipseudomonal Agents Use from 2006 to 2015**

**Fig. 2. Trend of Oral Fluoroquinolones Use from 2006 to 2015**
monal agent use increased significantly \((r = 0.10, P_{\text{for trend}} = 0.00040)\). The use of fluoroquinolones and penicillins has increased significantly. Carbapenems and monobactams use remained unchanged. In contrast, the use of third- and fourth-generation cephalosporins and aminoglycosides decreased significantly. The highest proportions throughout the year were those of fluoroquinolones, at 88.6–91.4%.

**Trend of Oral Fluoroquinolones Use from 2006 to 2015**

Oral fluoroquinolones accounted for more than 98% of the total fluoroquinolones use and increased significantly \((r = 0.10, P_{\text{for trend}} = 0.00030)\) (Fig. 2). For each antibiotic, LVFX (second generation; \(r = 0.049, P_{\text{for trend}} = 0.015\)), STFX (third generation; \(r = 0.031, P_{\text{for trend}} < 0.0001\)), and GRNX (third generation; \(r = 0.064, P_{\text{for trend}} = 0.00010\)) increased significantly.

**Trend of Parenteral Antipseudomonal Agent Use from 2006 to 2015**

Figure 3 shows the trend of parenteral antipseudomonal agent use from 2006 to 2015. Parenteral fluoroquinolones use increased significantly \((r = 0.0012, P_{\text{for trend}} = 0.0041)\) (Fig. 3a).

Parenteral carbapenems use was 2.7–3.7% of the total antipseudomonal agents, and remained unchanged over the years \((r = -0.00014, P_{\text{for trend}} = 0.65)\) (Fig. 3b). For each antibiotic, the trend for meropenem (MEPM) \((r = 0.0025, P_{\text{for trend}} < 0.0001}\) and doripenem (DRPM) \((r = 0.0014, P_{\text{for trend}} = 0.00020)\) increased significantly to 1.7 and 2.8 times, respectively, from 2006 to 2015. However, the trend for other parenteral carbapenems imipenem/cilastatin \((r = -0.0020, P_{\text{for trend}} < 0.0001}\), panipenem/betamipron \((r = -0.0014, P_{\text{for trend}} < 0.0001}\), and biapenem \((r = -0.00067, P_{\text{for trend}} < 0.0001}\) decreased significantly. Monobactams were rarely used between 2006 and 2015, and their use decreased significantly \((r = -0.000033, P_{\text{for trend}} < 0.0001}\) (data not shown).

The total use of third- and fourth-generation cephalosporins decreased significantly \((r = -0.0038, P_{\text{for trend}} < 0.0001}\) (Fig. 3c). For each antibiotic, the use of cefepime \((r = -0.00078, P_{\text{for trend}} < 0.0001}\), cefozopran \((r = -0.00091, P_{\text{for trend}} < 0.0001}\), cefpiramide \((r = -0.0013, P_{\text{for trend}} < 0.0001}\), and ceftazidime \((r = -0.00080, P_{\text{for trend}} < 0.0001}\) also decreased significantly.

The trend for piperacillin use decreased significantly \((r = -0.0012, P_{\text{for trend}} < 0.0001}\) (Fig. 3d). In contrast, the trend for PIPC/TAZ use increased significantly \((r = 0.0090, P_{\text{for trend}} < 0.0001}\).

**DISCUSSION**

In Japan, the trends of total antibiotic use and antibiotic use by ATC classification have been evaluated.\(^{16}\) There are concerns about increased broad-spectrum antibiotic use in previous reports.\(^{16}\) However, the trend of antipseudomonal agent use has not been clarified. This study clarified, for the first time, the trends of antipseudomonal agent use in Japan from 2006 to 2015. The total use of antipseudomonal agents significantly increased. The most commonly used antibiotics are oral fluoroquinolones. The proportion of parenteral carbapenems use for total antipseudomonal agent use was very low. In contrast, fluoroquinolones and penicillins use increased significantly, whereas the use of third- and fourth-generation cephalosporins and aminoglycosides decreased significantly. Carbapenems and monobactams use remained unchanged. In this study, the use of fluoroquinolones in 2015 was 2.74 DID, which was about five times higher than that in the U.K. (0.57 DID).\(^{21}\) Fluoroquinolones have a broad spectrum and also affect many bacteria other than *P. aeruginosa*. The resistance rate of *Escherichia coli* to fluoroquinolones in Japan was 29.3%,\(^{6}\) which is higher than that reported in the U.K. (15.6%).\(^{10}\) These results suggest that the use of fluoroquinolones in Japan may have affected the resistance rate. This is because LVFX has been reported to be cross-resistant to other quinolones\(^{39}\); thus, it is important to avoid unnecessary use of LVFX.

Among oral fluoroquinolones, the use of LVFX, GRNX, and STFX increased significantly. It is considered that one of the reasons for the increase in oral LVFX is that the high dose (500mg) was launched in 2009 according to the spread of pharmacokinetics/pharmacodynamics theory.\(^{29}\) In addition, it was estimated that urinary tract infections and pneumonia are increasing as the number of elderly people is increasing in Japan.\(^{21}\) LVFX, GRNX, and STFX are the first- and second-line drugs used in the treatment of pneumonia and urinary tract infections.\(^{22,23}\) Thus, it is considered that the use of LVFX, GRNX, and STFX has increased. It is necessary to continuously evaluate the trends of quinolone use, including LVFX, and promote appropriate use.

Most of the carbapenems used parenterally were MEPM and DRPM, and their use increased significantly. It was speculated that increasing indications, the revision of insurance coverage on the maximum daily dose, and the sale of products containing a high dosage, accounted for this increase. However, the use of other parenteral carbapenems has significantly decreased.

Parenteral carbapenems use was 2.7–3.7% of all antipseudomonal agents used, and it has remained unchanged over the years. In Japan, the permit and notification systems were introduced to monitor the inappropriate use of parenteral carbapenems in medical institutions.\(^{21}\) It was speculated that these efforts suppressed the inappropriate use of parenteral carbapenems. However, the selective pressure on parenteral carbapenems in patients should continue to be monitored.

On the other hand, the trend for PIPC/TAZ use increased significantly by approximately 43 times from 2006 to 2015. It is clear that the selective pressure on PIPC/TAZ increased in 2015 compared to 2006. PIPC/TAZ was approved in 2008 with the same mixture ratio (8:1) as in other countries, and acquired the indication for pneumonia. For these reasons, the trend for PIPC/TAZ use was considered to have increased significantly. Although the resistance rate of *P. aeruginosa* against PIPC/TAZ remains almost unchanged in Japan,\(^{5}\) it has been reported that the promotion of PIPC/TAZ use induced drug-resistant *P. aeruginosa* in Romania.\(^{29}\) Thus, it is necessary to pay attention to the increase in resistance of *P. aeruginosa* to PIPC/TAZ.

This study has some limitations. First, because antibiotic use in our study was based on the sales volume, the actual volume administered may not have been accurately reflected. Detailed information such as patient background, purpose of use, and number of patients to which they were administered were unknown. However, the use of surveys based on sales data is a common method in other countries.\(^{25}\) Second, the findings may not reflect the volume sold directly to medical institutions.\(^{16,15}\) However, the sales data used in this study accounted for approximately 98% of Japan’s total sales; therefore, it is considered to be highly comprehensive. Third, the most recent sales data were not included in this study. In the future, it will be necessary to conduct studies with more recent data.
Despite these limitations, this study clarified, for the first time, the trends of antipseudomonal agent use in Japan and provided useful information on how to promote appropriate use.

**CONCLUSION**

This study clarified, for the first time, the trends of antipseudomonal agent use in Japan. The most commonly used
antibiotics are oral fluoroquinolones. Although the proportion of parenteral carbapenems use was very low, the selective pressure on parenteral carbapenems in each patient needs to be monitored. It is important not only to monitor the total antibiotic use and antibiotic use by ATC classification, but also to continue monitoring the use of antipseudomonal agents to conduct appropriate AMR measures.

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Conflict of Interest Yuichi Muraki received an honorarium from Pfizer Japan, Inc. for lecturing. The other authors declare no conflicts of interest.

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