Objective  The importance of antimicrobial stewardship is increasingly highlighted in this age of antimicrobial resistance. A better comprehension of adverse drug events (ADEs) can promote the appropriate use of antibiotics. We aimed to quantify the incidence of ADEs associated with broad-spectrum systemic antibiotics in a hospital setting.

Methods  We conducted a six-month prospective, observational study at Osaka University Hospital to describe the incidence of ADEs in patients hospitalized in general wards undergoing treatment with broad-spectrum antibiotics (carbapenems, piperacillin/tazobactam [PIPC/TAZ], and anti-methicillin-resistant Staphylococcus aureus agents). The occurrence of ADE was defined as any cardiac, gastrointestinal, hepatobiliary, renal, neurologic, hematologic, dermatologic, or musculoskeletal manifestation after 48 hours or more of systemic antibiotic therapy.

Results  The 3 most frequently prescribed antibiotics were PIPC/TAZ (242 cases), meropenem (181 cases), and vancomycin (92 cases). Of 689 patients, 118 (17.1%) experienced ADEs, including gastrointestinal (6.4%), hepatobiliary (4.2%), dermatologic (2.5%), and renal (2.3%) manifestations. Patients treated with PIPC/TAZ, meropenem, doripenem, vancomycin, daptomycin, and teicoplanin developed ADEs at rates of 20.7%, 16.0%, 15.4%, 19.6%, 11.8%, and 10.9%, respectively.

Conclusion  Our study provides a quantitative value for the incidence of ADEs associated with broad-spectrum antibiotics in clinical practice. To optimize patient safety, clinicians need to be aware of the risks associated with antibiotic administration.

Key words: choosing wisely, adverse drug event, antibiotic stewardship, antimicrobial resistance

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is essential, but studies regarding the prevalence of antibiotic-associated ADEs in actual clinical practice have been insufficient. Previous studies were based on administrative databases alone and limited to a single infectious syndrome (4) or antibiotic class (5, 6). A comprehensive analysis of the ADE incidence among hospitalized patients was performed only recently in a study that was limited to a single facility (2).

In the present study, we aimed to evaluate the incidence of antibiotic-associated ADEs using actual clinical data from our hospital, focusing on patients receiving broad-spectrum antibiotics.

### Materials and Methods

This observational study was conducted at Osaka University Hospital, a 1,086-bed tertiary care facility in Japan. The need for informed consent was waived since the data were anonymized for antimicrobial stewardship activities.

The clinical data from patients administered broad-spectrum antibiotics between January and June of 2018 (six months) were collected from digital records. We defined broad-spectrum antibiotics as carbapenems (meropenem, imipenem, doripenem, biapenem), piperacillin/tazobactam (PIPC/TAZ), and anti-MRSA drugs (vancomycin, teicoplanin, daptomycin, linezolid, and arbekacin). The use of topical or inhaled antibiotics was excluded. A daily case conference was held on the validity of using broad-spectrum antibiotics at the Division of Infection Control and Prevention. An infectious disease physician and a pharmacist adjudicated all potential associations between data abnormalities and the antibiotics in the context of their medical history and clinical course.

Criteria for the definition of antibiotic-associated ADEs (cardiac, gastrointestinal, hepatobiliary, renal, neurologic, hematologic, dermatologic, anaphylactic, musculoskeletal manifestations, and Clostridium difficile infection) were defined based on the previous literature (Table 1) (2). Patient data regarding these events were observed until cessation of the antibiotic treatment. To avoid overestimating the incidence of ADEs in patients who were administered multiple antibiotics, each ADE was categorized under a single antibiotic based on its likelihood of causing the specific ADE, as has been done in the recent publication (2). For example, thrombocytopenia in a patient receiving a combination of linezolid and meropenem was regarded as a linezolid-associated ADE. For the analysis, we included only cases treated in the general ward and excluded those treated in the intensive-care units in order to avoid the possibility of multiple factors leading to ADEs. Aside from an anaphylactic event, all manifestations that developed in patients undergoing ≥48 hours of antibiotic treatment were included.

### Results

During the study period, totally, antibiotics were administered to the patients as follows: PIPC/TAZ to 355, meropenem to 318, doripenem to 58, imipenem to 2, vancomycin to 215, teicoplanin to 61, daptomycin to 63, linezolid to 29, and arbekacin to 2. Of them, 689 (6.7%) out of 10,214 patients admitted to general ward of the hospital received broad-spectrum antibiotics (Table 2). The median age of the population was 61 years (interquartile range [IQR], 40-72 years), and the men-to-women ratio was 1.6 (421 to 268).

Of these 689 patients, 118 (17.1%) experienced some type of ADE. Common manifestations included gastrointestinal (6.4%), hepatobiliary (4.2%), dermatologic (2.5%), and renal (2.3%) involvements. The most frequently prescribed antibiotics were PIPC/TAZ (242 cases), followed by meropenem (181 cases) and vancomycin (92 cases). Of these,
ADEs occurred most frequently with PIPC/TAZ, manifesting gastrointestinal (10.7%), renal (4.1%), hepatobiliary (2.9%), and dermatologic (2.5%) abnormalities. There was an anaphylactic case associated with PIPC/TAZ administration. Patients given meropenem developed ADEs in 29 of 181 instances.

| Broad-spectrum antibiotics | No. of patients receiving the agents | No. (%) of patients with ADEs | Duration, [median days] | Cardiac [N] | Gastrointestinal [N] | Hepatobiliary [N] | Renal [N] | Neurologic [N] | Hematologic [N] | Dermatologic [N] | Anaphylactic [N] | Muscular [N] | CDI [N] |
|----------------------------|------------------------------------|-------------------------------|-------------------------|-------------|----------------------|-------------------|-----------|----------------|-------------------|-------------------|-----------------|------------|---------|
| Piperacillin/Tazobactam     | 242                                | 50 (20.7)                     | 26 (10.7) [6]           | 7 (2.9) [9] | 10 (4.1) [7.5]       | 0                 | 4 (1.7)   | 6 (2.5) [5]   | 1                 | 0                 | 0               | 0          | 0       |
| Carabapenems                | 235                                | 37 (15.7)                     | 0                       | 16 (6.8) [10.5] | 15 (6.4) [9] | 0                 | 0         | 1 (0.4)       | 5 (2.1) [11]   | 0                 | 0               | 0          | 0       |
| Meropenem                   | 181                                | 29 (16.0)                     | 0                       | 12 (6.6) [9.5] | 13 (7.2) [9] | 0                 | 0         | 1 (0.6)       | 3 (1.7)          | 0                 | 0               | 1 (0.6)    | 0       |
| Doripenem                   | 52                                 | 8 (15.4)                      | 0                       | 4 (7.7)      | 2 (3.8)       | 0                 | 0         | 0             | 2 (3.8)          | 0                 | 0               | 0          | 0       |
| Imipenem                    | 2                                  | 0 (n.p.)                      | 0                       | 0            | 0             | 0                 | 0         | 0             | 0                 | 0                 | 0               | 0          | 0       |
| Anti-MRSA drugs             |                                    |                               |                          |              |              |                   |           |               |                   |                   |                 |            |         |
| Vancomycin†                 | 92                                 | 18 (19.6)                     | 0                       | 1 (1.1)      | 4 (4.3)       | 6 (6.5) [15.5]    | 0         | 5 (5.4)       | 2 (2.2)          | 0                 | 0               | 0          | 0       |
| Teicoplanin                 | 55                                 | 6 (10.9)                      | 0                       | 1 (1.8)      | 1 (1.8)       | 0                 | 0         | 0             | 2 (3.6)          | 0                 | 0               | 0          | 0       |
| Daptomycin                  | 51                                 | 6 (11.8)                      | 0                       | 0            | 2 (3.9)       | 0                 | 0         | 1 (2.0)       | 2 (3.9)          | 0                 | 2 (3.9)         | 0          | 0       |
| Linezolid                   | 14                                 | 1 (7.1)                       | 0                       | 0            | 0             | 0                 | 0         | 1 (7.1)       | 0                 | 0                 | 0               | 0          | 0       |
| Total                       | 689                                | 118 (17.1)                    | 0                       | 44 (6.4)     | 29 (4.2)      | 16 (2.3)          | 0         | 12 (1.7)      | 17 (2.5)         | 1 (0.1)           | 2 (0.3)         | 1 (0.1)    | 0       |

†intravenous administration only. CDI: Clostridium difficile infection, IQR: interquartile range, MRSA: methicillin-resistant Staphylococcus aureus. Median days to developing ADEs were displayed for those with more than 5 cases of ADEs. n.p., not applicable.
(16.0%) classified as hepatobiliary (7.2%), gastrointestinal (6.6%), and dermatologic (1.7%) disorders. Patients given doripenem also developed ADEs with a similar pattern. Regarding anti-MRSA agents, vancomycin-induced ADEs occurred most frequently (19.6%), followed by daptomycin (11.8%) and teicoplanin (10.9%). The 3 most common ADEs associated with vancomycin treatment were renal (6.5%), hematoic (5.4%), and hepatobiliary (4.3%) abnormalities. The hematologic disorder in all five patients treated with vancomycin was leukocytopenia. Teicoplanin-associated ADEs were less common than vancomycin-associated ADEs (10.9% vs. 19.6%). Daptomycin caused myositis in two patients and linezolid-induced thrombocytopenia in one patient. There were no patients with cardiac or neurological manifestations. One patient administered meropenem developed Clostridium difficile infection.

Discussion

This study was performed under the umbrella of in-hospital infection control activities in order to underscore the importance of antimicrobial stewardship. Our study revealed that 17.1% of patients hospitalized in the general ward (118 of 689 cases) developed ADEs that were associated with the administration of broad-spectrum antibiotics. This result mirrors the finding of a recent report (2), which showed that 20% of admitted patients treated with antibiotic therapy developed an antibiotic-associated ADE. Our study also highlights the high incidence of antibiotic-associated ADEs, suggesting a clinical need to reduce unnecessary treatment with broad-spectrum antibiotics.

Each of the preceding studies addressing antibiotic-associated ADEs had several limitations. According to a previous study based on an administrative database, only 0.45% to 0.6% of patients hospitalized with pneumonia developed antibiotic-associated ADEs (4). However, the results were derived from registration data and therefore had undeniable under-reporting of existing ADEs. Furthermore, the authors focused only on patients with respiratory infections, so their results cannot be fully generalized. Another study based on a medical record review demonstrated that 27% of fluoroquinolone use was linked to ADEs, such as gastrointestinal disorders (14%), colonization of multi-drug resistant organisms (8%) and C. difficile infections (4%) (6). The study period was a mere six weeks, and the authors focused only on fluoroquinolone use, limiting the versatility of the data.

In general, hospitalized patients are more vulnerable to ADEs than outpatients for several reasons. First, inpatients usually undergo intravenous antibiotic therapy at higher doses than oral regimens, possibly leading to a high incidence of ADEs (7). Second, the combined use of multiple medications is more frequent in inpatients than outpatients, potentially resulting in interactive drug reactions (8). Third, inpatients are generally older with multiple underlying diseases and decreased drug excretion (9). However, we should be mindful of antibiotic-associated ADEs in the outpatient cohort as well. According to a previous study assessing the frequency of drug-related adverse events in emergency department visits, antibiotic prescriptions accounted for 19.3% of cases (10). Thus, it is important to recognize that antibiotics introduce a potential risk of ADEs with high frequency in any medical situation.

Our study has the advantage of being relevant to the scientific community. In contrast to previous studies, we performed the present study in a prospective manner by focusing on the occurrence of broad-spectrum antibiotic-associated ADEs as part of the Antimicrobial Stewardship Program. However, several limitations should also be mentioned. First, the single-center nature of the miscellaneous patient population should be considered when generalizing the results to other medical settings. Second, reviewing medical charts may have led to an underestimation of ADEs, although we believe this approach is more appropriate and reliable than using an administrative database, which includes the possibility of miscoding. Conversely, the number of antibiotic-associated ADEs may have been overestimated because cases of ADEs caused by non-antibiotic drugs were also considered. Third, the case numbers were relatively few, and a more accurate estimate would be obtained from a larger-scale study. Fourth, other clinically common ADEs, including drug fever and eosinophilia, were not included in the study criteria. Finally, data on the treatment duration were lacking.

Collectively, the overall incidence rate of broad-spectrum antibiotic-associated ADEs was 17.1% for patients hospitalized in the general ward. Due to their varied manifestations, antibiotic-associated ADEs are often under-recognized by clinicians. However, the occurrence of antibiotic-associated ADEs cannot be ignored for inpatients, as they pose a high clinical burden for this patient group. To optimize patient safety, infection control practitioners and clinicians should pay close attention to ADEs as part of their antimicrobial stewardship activities.

The authors state that they have no Conflict of Interest (COI).

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