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Antibiotic-associated adverse drug events at a Japanese academic hospital



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ABSTRACT

Introduction: To promote antimicrobial stewardship activity, an understanding of the incidence of antibiotic-associated adverse drug events (ADEs) is essential. In this study, we aimed to describe the occurrence of antibiotic-associated ADEs at our hospital.

Methods: We retrospectively searched the ADE registration system in Osaka University Hospital between 2010 and 2017. Registrations of ADEs were dependent on the patients' drug history and clinical course after hospitalization. We classified the data according to types of ADEs (gastrointestinal, hepatobiliary, renal, cardiac, respiratory, hematologic, neurologic, dermatologic, and musculoskeletal) and antibiotic class.

Results: During the study period, we found 707 cases of antibiotic-associated ADEs, accounting for 22.3% of all the cases. Beta-lactam antibiotics constitute more than half of the cases (51.3%). The most common ADE was dermatologic abnormalities (53.4%), followed by liver dysfunction (9.7%) and gastrointestinal symptoms (8.9%). Among all antibiotics, oral third-generation cephalosporins were frequently reported as offending drugs (107 cases), accounting for 29.5% of beta-lactam ADEs and 46.3% of cephem ADEs.

Conclusion: Antibiotic-associated ADEs covered approximately 20% of all the ADEs at our hospital. We believe that the data would be helpful in ensuring patient safety by promoting antimicrobial stewardship in hospitals.

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Development of and benefits from antibiotic treatment have been the Great things for modern medicine. In current acute-care settings, approximately half of hospitalized patients receive antibiotics during their hospitalization [1]. However, the global emergence of antimicrobial-resistant pathogens is an imminent crisis to combat [2]. Therefore, there is an urgent need to enhance antimicrobial stewardship programs (ASP) to maintain the effectiveness of antibiotics in the future. The understanding of antibiotic-associated adverse drug events (ADEs) would be beneficial to enhance and

promote ASP in hospitals. Nevertheless, there are only a limited number of studies on this issue [3–6]. Differences of approved drugs can influence the occurrence of ADEs in each medical situation; thus, a review of local data is essential. To underscore the importance of ASP activities from the viewpoint of preventing ADEs, we report the impact and characteristics of antibiotic-associated ADEs using the drug registration system at our hospital.

This descriptive study was performed at the Osaka University Hospital (Japan), a 1086-bed tertiary care facility. From 2010 to 2017 (8 years), we reviewed the ADE registration system at our hospital and extracted data related to antibiotic administration. There was no strict criteria or definition to register ADEs in the system, and registrations of ADEs were entrusted to each medical healthcare worker based on patients' drug history and clinical course after

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hospitalization. We summarized the numbers (proportions) of antibiotic-associated ADEs based on antibiotic classifications and manifestations. We included only systemic administration of antibiotics, and the use of topical or inhaled antibiotics was excluded from the analysis. To estimate the years in which the temporal trend of the proportion of antibiotic-associated ADEs showed a significant change, we applied the Joinpoint regression model using the joinpoint Regression Program, version 4.5.0.1 [7]. A p value ≤ 0.05 was considered statistically significant. The need for informed consent was waived by the Institutional Review Board of Osaka University School of Medicine because the data were anonymized and obtained retrospectively for antimicrobial stewardship activity.

During the 8-year study period, the total number of hospitalized patient-days per year remained in the same range (approximately 334,000–346,000). The total number of ADE registrations was 3,171, of which antibiotic-associated ADEs accounted for 707 (22.3%) cases, with annual proportions ranging from 19.0% to 28.3% (Fig. 1). An increase in the reported number of ADEs after 2016 was due to a hospital workshop regarding the preceding underreports of ADEs, which was held by Department of Drug Information Management. Overall, the average annual percentage change in the proportion of antibiotic-associated ADEs was -0.7% (95% confidence interval, -6.4 to 5.3), suggesting no significant trend change for the proportion of antibiotic-associated ADEs throughout the study period.

The classifications of offending antibiotics are shown in Fig. 2A. Beta-lactam antibiotics (51.3%), followed by fluoroquinolones (17.5%) and macrolides (8.6%), accounted for approximately three-fourth of the cases. Among beta-lactam antibiotics, cepheids (63.6%) were the most frequent agents. Antibiotic-associated ADEs resulted in a wide range of manifestations (Fig. 2B). The most commonly observed ADEs were dermatologic manifestations (53.4%), followed by liver dysfunction (9.7%) and gastrointestinal symptoms (8.9%).

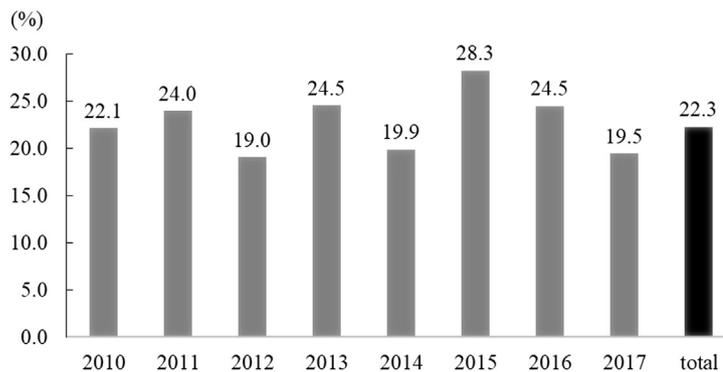
Regarding cepheid-associated ADEs (231 cases), third-generation cephalosporin, especially the oral forms (107 cases, 46.3%), constituted majority of the reported ADEs (Fig. 3A). Similar to the overall antibiotic-associated ADEs, dermatologic (52.3%), gastrointestinal (12.6%), and liver dysfunction (11.7%) were the frequent oral third-generation cephalosporin-associated ADEs (Fig. 3B).

Our review uncovered that antibiotics constituted approximately one-fourth of all the registered ADEs in our hospital. A recent study

reported that ADEs occurred in 20% (298/1488 inpatients) of antibiotic users, with a 3% increased risk of ADEs for every 10 additional days of administration [6]. The occurrence of antibiotic-associated ADEs is thus very common in clinical situations. In addition, severe ADEs may yield fatal outcomes in patients. Despite the low incidence rate (around 0.004%–0.015% of cases) [8], penicillin anaphylactic reactions possibly result in undesirable consequences. A recent study newly revealed that exposure to fluoroquinolone can cause an increased risk of aortic aneurysm or dissection [9]. Therefore, medical personnel should be mindful of antibiotic-associated ADEs in daily clinical practice. Hypercautious attitudes to ADEs, in contrast, may lead to overprescribing of inappropriate antibiotics. Once a patient is labeled as being allergic to an antibiotic agent, he or she should avoid the particular antimicrobial class, subsequently leading to increased administration of broad-spectrum antibiotics [10]. To achieve antimicrobial stewardship in clinical medicine, it is essential to maintain a balance between adequate caution and excessive concern to antibiotic-associated ADEs.

Dermatologic ADEs covered approximately half (53.4%) of the ADEs. However, this may not reflect the actual situation owing to the possibility of underreporting of other manifestations. According to a recent study on antibiotic-associated ADEs in inpatients, gastrointestinal (42%, excluding *Clostridium difficile* infection), renal (24%), and hematologic (15%) abnormalities were commonly observed [6], while skin disorders were not problematized. Since skin problems are conspicuous, even to the patients themselves, they tend to be easily recognized and registered. Our investigation was based on voluntary registrations by on-site medical staffs, and therefore dermatologic ADEs could have been overestimated. To reveal the actual occurrence of antibiotic-associated ADEs better, a well-established study focusing on other organ dysfunctions is warranted in future.

Among various possible offending drugs, beta-lactams accounted for nearly half of the cases. Of these, cepheids constituted 63.6% of the cases, and among a variety of cepheids, oral forms of third-generation cephalosporin constituted 46.3% (107/231 cases). Another study also reported that cephalosporin (28.4%), followed by penicillin (13.2%), was the most common antimicrobial class labeled to cause allergic reactions [10]. Beta-lactams are globally the most common antibiotics in clinical use since its introduction in the early 1940's. For example, beta-lactams constituted 58% of antibiotics administered at the community settings in the European



The numbers of ADEs reported in the registration

| | | | | | | | | | |
|------------------------------------|---------|---------|---------|---------|---------|---------|---------|---------|-----------|
| Total ADEs | 217 | 263 | 252 | 212 | 327 | 336 | 629 | 935 | 3171 |
| Antibiotic-associated ADEs | 48 | 63 | 48 | 52 | 65 | 95 | 154 | 182 | 707 |
| Hospitalized patient-days per year | 337,514 | 346,781 | 339,459 | 339,404 | 334,607 | 337,552 | 334,258 | 336,723 | 4,495,169 |

Fig. 1. Annual incidences and proportions of antibiotic-associated adverse drug events (ADEs).

The present research covered all in- and out-patients who were treated at our hospital for 8 years, possibly providing real-world data to estimate the impact of antibiotic-associated ADEs. The limitations of the study include its retrospective nature, absence of detailed review for health-care records, and lack of well-established criteria for registration.

In conclusion, using the ADE register system in our hospital, we uncovered that antibiotic-associated ADEs are approximately 20% of all ADEs. The most common ADEs were dermatologic disorders. However, other organ dysfunctions could have been under-reported. Notably, the cephem class, especially oral third-generation agents, was frequently reported as offending drugs. In the absence of an exact definition of ADEs in this study, under-reporting as well as overestimation of data is undeniable. Nevertheless, we believe that the presented data is of value to clinicians and infection control practitioners to promote antimicrobial stewardship in hospitals.

Contribution

Study concept; H. Hagiya. Data extraction; E. Matsui and R. Kokado. Drafting of the manuscript; H. Hagiya. Statistical analysis; T. Koyama. Proof reading and critical revision: D. Morii, H. Okuno, S. Hamaguchi, H. Yoshida, Y. Miwa, and K. Tomono.

Conflict of interests

The authors confirm that there are no conflicts of interests to declare.

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All authors meet the ICMJE authorship criteria.

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