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MAJOR ARTICLE

Pharmacovigilance Study on Eosinophilic Pneumonia Induced by Anti-MRSA Agents: Analysis Based on the FDA Adverse Event Reporting System

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Background. Eosinophilic pneumonia (EP) is a rare adverse event caused by several types of drugs, such as antibiotics; however, its characteristics remain poorly described. This study aimed to analyze the disproportionality between the occurrence of EP and anti–methicillin-resistant *Staphylococcus aureus* (anti-MRSA) agents and to characterize anti-MRSA agent–induced EP events using the Food and Drug Administration Adverse Event Reporting System (FAERS).

Method. Disproportionality linking EP and anti-MRSA agents was analyzed through bayesian confidence propagation neural networks of information components and reporting odds ratio methodologies. The FAERS data set for the fourth quarter of 2012 to the fourth quarter of 2022 was used. We also analyzed the characteristics of EP induced by anti-MRSA agents.

Results. A total of 14 805 795 reports were obtained from FAERS. Disproportionality analysis revealed that the EP signal was detected only in cases with the administration of daptomycin (DAP). This disproportionality signal was consistently detected in the sensitivity analysis. When compared with other reports of DAP-related adverse events, the reports of DAP-related EP were characterized by male sex (odds ratio [OR], 1.94; 95% CI, 1.12–3.37), older age (>70 years; OR, 2.70; 95% CI, 1.68–4.33), and longer duration of treatment (>21 days; OR, 5.08; 95% CI, 3.21–8.05).

Conclusions. This study revealed that among the anti-MRSA agents, disproportionality in the occurrence of EP was observed only with DAP. Our results suggest that sex, age, and treatment duration may affect the occurrence of DAP-induced EP. Clinicians should exercise caution regarding EP during DAP administration.

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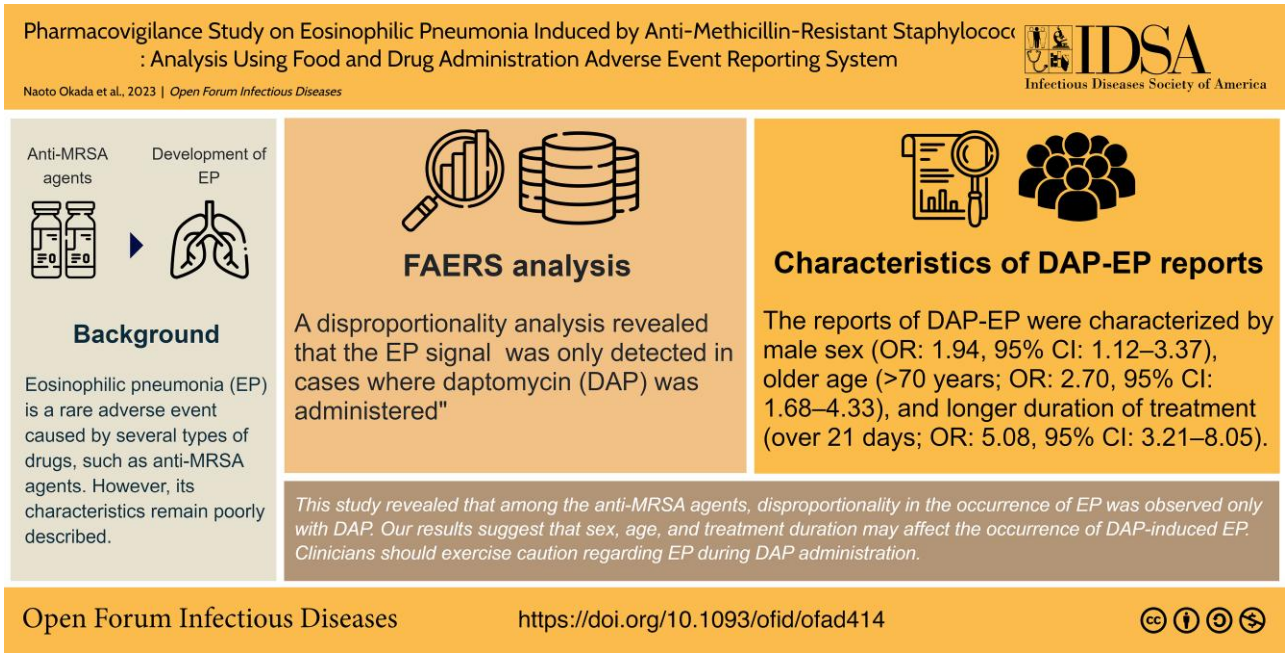
Graphical Abstract



Keywords. Adverse Event Reporting System; daptomycin; eosinophilic pneumonia.

Eosinophilic pneumonia (EP) is a rare adverse event induced by several type of drugs, such as antibiotics and anti-inflammatory agents [1]. Of these, cases induced by daptomycin (DAP), an anti–methicillin-resistant *Staphylococcus aureus* (anti-MRSA) agent, have been reported at a relatively high frequency. However, the number of DAP-related EP cases remains limited [2, 3], while the characteristics of DAP-related EP remain poorly understood.

Although other anti-MRSA agents, such as vancomycin, linezolid, and teicoplanin, are widely used, the association between these agents and the development of EP remains poorly understood. A previous study reported cases of vancomycin-related drug reactions with eosinophilia and systemic symptoms of EP [4, 5], indicating that the increase in eosinophils induced by vancomycin may contribute to the development of EP. Linezolid has high lung penetrability, which may lead to an excessive immune response owing to local linezolid concentration increases in the alveoli [6]. Teicoplanin is currently available in a limited number of regions, making it difficult to assess the risk of EP accurately [7]. Considering that EP is a severe adverse event, analyzing the association between the occurrence of EP and anti-MRSA drugs is an urgent issue. However, as it is rare, the relationship between the development of EP and anti-MRSA drugs is yet to be elucidated.

Databases reporting on spontaneous adverse events have been utilized for postmarketing safety surveillance [8]. The US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) is a worldwide database of spontaneously reported adverse events that reflects the occurrence of adverse events in the real world [9]. The number of reports in the FAERS database enables safety signal detection of rare adverse events through disproportionality analysis [10]. Furthermore, the FAERS database includes baseline patient information, which can help analyze the characteristics of drug-related adverse events. Given the frequency of drug-induced EP, a disproportionality analysis based on the FAERS database may be used to suggest a relationship between anti-MRSA drugs and EP.

This retrospective pharmacovigilance disproportionality analysis based on the FAERS database aimed to investigate whether EP occurs with all anti-MRSA agents. We also aimed to analyze the characteristics of anti-MRSA agent–induced EP reports.

METHODS

Data Sources

Publicly available data were obtained from the FAERS database (https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html). Data from the fourth quarter of 2012 to the fourth quarter of 2022 were used in this study. Duplicate reports from the same patient were excluded, and only the most recent report was included to comply with the FDA guidelines. Two distinct data sets were utilized for disproportionality analysis: the crude and complete data sets. The former consisted of FAERS data from which duplicate cases were

excluded. Meanwhile, the latter was constructed by excluding cases with missing age, sex, and body weight data or those with abnormal age (>130 years) or body weight (>300 kg) from the crude data set [11].

The FAERS data comprise anonymized information. Given the retrospective nature of this observational study, the requirement for informed consent was waived. The study was conducted under the principles of the Declaration of Helsinki.

Target Drugs

The anti-MRSA agents used in this study were DAP, vancomycin, linezolid, and teicoplanin. All the drug names in the data sets were changed to their generic names. Only intravenous formulations of vancomycin and linezolid were considered to maintain consistency in patient characteristics for each drug. The intravenous formulation was defined as the intravenous administration of the drug. Furthermore, to enhance the precision of identifying the EP signal during the use of targeted drugs, a sensitivity analysis was conducted with drugs flagged as *primary suspected* or *secondary suspected* in the drug role code, which represents the drug's roles in an event [12].

Outcome Definition

The adverse events recorded in the FAERS conformed to MedDRA (version 25.0; Medical Dictionary for Regulatory Activities), which was used to define adverse events in this study. EP was defined by using 15 preferred terms associated with "eosinophilic pneumonia" (SMQ: 20000159, Standardized MedDRA Query; Table 1). We defined EP cases as those containing the extracted preferred terms.

Table 1. Definition of Eosinophilic Pneumonia

Code	Term
SMQ 20000157	**Eosinophilic pneumonia**
PT 10008413	Charcot-Leyden crystals
PT 10014952	Eosinophilia myalgia syndrome
PT 10014962	Eosinophilic pneumonia
PT 10024794	Loeffler's syndrome
PT 10035742	Pneumonitis
PT 10035745	Pneumonitis chemical
PT 10037382	Pulmonary eosinophilia
PT 10037457	Pulmonary vasculitis
PT 10048637	Angiolymphoid hyperplasia with eosinophilia
PT 10048643	Hypereosinophilic syndrome
PT 10052832	Eosinophilic pneumonia acute
PT 10052833	Eosinophilic pneumonia chronic
PT 10065563	Eosinophilic bronchitis
PT 10078117	Eosinophilic granulomatosis with polyangiitis
PT 10080148	Eosinophilic pleural effusion

Abbreviations: PT, preferred term; SMQ, standardized Medical Dictionary for Regulatory Activities query.

Characteristics of DAP-Induced EP

DAP-related adverse event reports—constructed by excluding cases where the role code was not classified as primary or secondary suspected and where dates of drug dosing or administration were missing from the complete data set—were used to analyze the characteristics of the reports of DAP-induced EP. These were classified into DAP-induced EP and other DAP-induced adverse events. Age, sex, weight, duration of DAP administration, outcome of the adverse event, and indications for DAP were compared between the groups. The diagnosis of the outcome was dependent on the reporter's judgment, and, if multiple outcomes were indicated for the same patient, the more severe outcome was counted. Indications were compared with data from patients for whom the indication was reported. The time to onset of adverse events was calculated per the following formula: time to onset = (adverse event onset date – start date of DAP use) + 1. Reports with input errors were excluded, such as a start date later than the event date [13]. The year of EP onset was used as the year of DAP-related EP expression.

Statistical Analysis

We used the 2 indicators for disproportionality analysis to reduce the likelihood of false-positive signals: reporting odds ratio (ROR) and bayesian confidence propagation neural network (information component [IC]) [14].

The disproportionality analysis focuses on differences in the proportion of adverse event reports, with ROR and IC as the main algorithms for detecting these differences, commonly referred to as *signals* [15]. ROR and IC were calculated per a previous study [16]. Briefly, ROR, which was usually adopted for signal detection [17], was calculated as follows: $\mathrm{ROR} = (a \times d) / (b \times c)$, where a is the number of reports showing the development of target events with a targeted drug, b is the number of reports showing the development of nontarget events with a targeted drug, c is the number of reports showing the development of the target event with all other drugs, and d is the number of reports showing the development of nontarget events with all other drugs. Moreover, the ROR was adjusted for sex, age, body weight, and concomitant anti-MRSA agents in the complete data set. IC with a statistical shrinkage transformation model [18], which provided effective protection against false associations in signal detection, was calculated as follows: $\mathrm{IC} = \log_2([N_{\mathrm{observed}} + 0.5] / [N_{\mathrm{expected}} + 0.5])$, where N_{expected} is the number of reports expected to identify the target events with a targeted drug, while N_{observed} is the number of reports observing the target events with a targeted drug. For ROR, significant signal detection was defined when the lower limit of the 95% CI exceeded 1. For IC, significant signal detection was defined when the lower limit of 95% CI exceeded 0. To improve the accuracy of the signals and eliminate some false-positive signals, we defined significant signals when they met all criteria

simultaneously in analyses, including 2 data sets and 1 sensitivity analysis.

Differences between the groups were analyzed with the nonparametric Mann-Whitney *U* test. Chi-square or Fisher exact test was used to analyze the nominal scales. The time to onset of DAP-induced EP was compared through Kaplan-Meier plots and log-rank tests. To characterize the reports of DAP-induced EP vs those of other DAP-induced adverse events, a multivariate logistic analysis was performed with age, sex, administration period, and DAP dose as explanatory variables. Data extraction was performed with Alkano software (NTT DATA Mathematical Systems) based on the Python program. The calculation of ROR and IC and statistical analysis were performed with R software (version 4.0.2). The significance level was set at $P < .05$ (2-tailed).

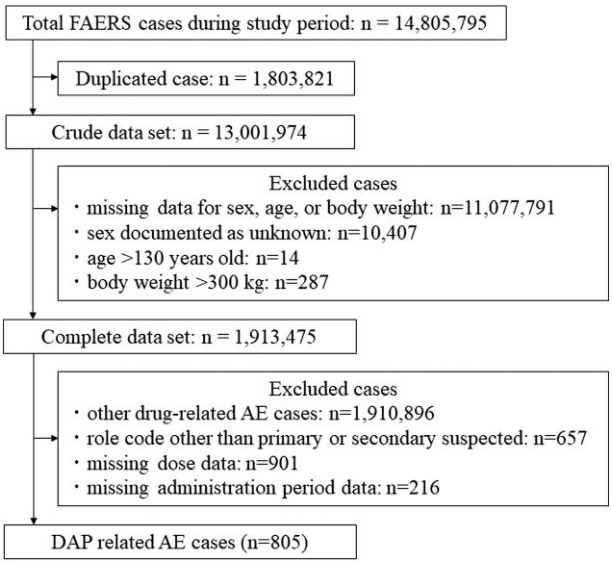


Figure 1. Diagrammatic representation of this study. AE, adverse event; DAP, daptomycin; FAERS, Food and Drug Administration Adverse Event Reporting System.

RESULTS

Disproportionality Analysis for EP

During the study period, 14 805 795 adverse event reports were identified from the FAERS database. After exclusion of the duplicates, 13 001 974 and 1 913 475 cases were included in the crude and complete data sets, respectively (Figure 1). The number of EP reports in the crude and complete data sets was 20 099 and 2579. There were 4 EP reports with concomitant anti-MRSA agents in the complete data set. We performed a disproportionality analysis using these data sets and found disproportional EP signals with DAP (crude data set: IC, 5.55 [95% CI, 5.42–5.64]; ROR, 54.18 [95% CI, 50.05–58.66]; complete data set: IC, 4.90 [95% CI, 4.67–5.06]; ROR, 36.23 [95% CI, 31.46–41.73]). However, no disproportional signals were detected for other anti-MRSA drugs. Furthermore, in analyses adjusted for age, sex, weight, and concomitant anti-MRSA agents, the signal was observed only with DAP (adjusted ROR, 31.90; 95% CI, 27.50–36.90). In the sensitivity analysis (Supplementary Table 1), the disproportional signal was detected only with DAP (crude data set: IC, 5.84 [95% CI, 5.72–5.94]; ROR, 68.22 [95% CI, 62.93–73.95]; complete data set: IC, 5.25 [95% CI, 5.03–5.42]; ROR, 48.88 [95% CI, 42.29–56.50]). Similar results were observed

Table 2. Disproportionality Analysis of Anti-MRSA Agents

	Without Drug		With Drug		ROR (95% CI)		
Agent: Data Set	EP Cases/ Noncases	Proportion (95% CI)	EP Cases/ Noncases	Proportion (95% CI)	Crude	Adjusted	IC (95% CI)
DAP							
Crude	19 418/12 973 478	0.15 (.147–.152)	681/8397	7.50 (6.968–8.063)	54.18 (50.05–58.66)	…	5.55 (5.42–5.64)
Complete	4882/1 906 014	0.26 (.248–.263)	219/2360	8.49 (7.444–9.635)	36.23 (31.46–41.73)	31.90 (27.50–36.90)	4.90 (4.67–5.06)
Vancomycin							
Crude	20 026/12 967 862	0.15 (.152–.156)	73/14 013	0.52 (.406–.651)	3.37 (2.68–4.25)	…	1.72 (1.33–2.00)
Complete	5078/1 902 964	0.27 (.259–.274)	23/5410	0.42 (.269–.635)	1.59 (1.06–2.40)	0.70 (.46–1.07)	0.65 (–.049, 1.14)
Linezolid							
Crude	20 087/12 978 695	0.15 (.152–.157)	12/3180	0.38 (.194–.656)	2.44 (1.39–4.30)	…	1.20 (.22–1.87)
Complete	5095/1 907 037	0.27 (.259–.274)	6/1337	0.45 (.164–.970)	1.68 (.75–3.75)	0.69 (.30–1.56)	0.67 (–.74, 1.58)
Teicoplanin							
Crude	20 082/12 977 879	0.15 (.152–.157)	17/3996	0.42 (.247–.677)	2.75 (1.71–4.43)	…	1.38 (.57–1.95)
Complete	5096/1 907 163	0.27 (.259–.274)	5/1211	0.41 (.134–.957)	1.55 (.64–3.72)	0.55 (.22–1.35)	0.56 (–1.01, 1.54)

Abbreviations: DAP, daptomycin; EP, eosinophilic pneumonia; IC, information component; MRSA, methicillin-resistant *Staphylococcus aureus*; ROR, reporting odds ratio.

for the adjusted sensitivity analysis (adjusted ROR, 43.40; 95% CI, 37.40–50.30). These results showed that among the anti-MRSA drugs analyzed, a significantly disproportional EP signal was detected only with DAP (Table 2).

Characteristics of DAP-Induced EP

DAP-related adverse event reports were classified into 2 groups —DAP-induced EP (n = 94) and other DAP-induced adverse events (n = 711)—and their characteristics compared (Table 3). Reports of EP were characterized by the male sex ($P = .005$), older age ($P < .001$), and significantly longer duration of DAP administration ($P < .001$) when compared with other adverse events. The DAP dose, the outcome of adverse events, and indications for DAP did not differ between the groups. The number of cases of DAP-related EP showed an increasing trend (Supplementary Figure). The median time to onset of EP and other adverse events was 19 days (95% CI, 16.3–21.7) and 6 days (95% CI, 5.1–6.9), respectively; the time to onset of EP or other adverse events induced by DAP was significantly different ($P < .001$; Figure 2). Multivariate logistic regression analysis revealed that the reports of DAP-related EP were characterized by male sex (odds ratio [OR], 1.94; 95% CI, 1.12–3.37), higher age (>70 years; OR, 2.70; 95% CI, 1.68–4.33), and longer duration of treatment (>21 days; OR, 5.08; 95% CI, 3.21–8.05; Figure 3).

Table 3. Characteristics of the Reports of DAP-Induced EP

Characteristic	No. (%) or Median (IQR)		
	Reports With EP (n = 94)	Reports With Other AEs (n = 711)	*P* Value
Male	75 (79.8)	465 (65.4)	.005[a]
Age, y	73 (68–79)	67 (55–76)	<.001[b]
Body weight, kg	75.0 (62.0–89.0)	75.0 (61.0–91.7)	.99[b]
Dose, mg/kg	7.8 (6.1–9.7)	7.4 (6.0–9.6)	.16[b]
Dose, mg/d	600 (500–800)	500 (368–770)	.17[b]
Administration period, d	22.0 (15.0–25.8)	9.0 (4.0–18.0)	<.001[b]
Preferred term related to EP			
Eosinophilic pneumonia	65 (69.1)	…	…
Eosinophilic pneumonia acute	18 (19.1)	…	…
Pneumonitis	8 (8.5)	…	…
Pulmonary eosinophilia	2 (2.1)	…	…
Pneumonitis chemical	1 (1.1)	…	…
Indications[c]			
Osteomyelitis/ osteitis	8 (8.5)	73 (10.9)	.47[a]
Arthritis Infection	11 (11.7)	54 (8.1)	.24[a]
Endocarditis	10 (10.6)	50 (7.5)	.29[a]
Sepsis	4 (4.3)	59 (8.8)	.16[d]
Device related infection	8 (8.5)	51 (7.6)	.77[a]
Outcome of adverse events due to DAP			
Death	22 (23.4)	117 (16.5)	.094[a]
Life-threatening	15 (16.0)	95 (13.4)	.49[a]
Hospitalization or disability	47 (50.0)	289 (40.6)	.84[a]

Abbreviations: AE, adverse event; DAP, daptomycin; EP, eosinophilic pneumonia.

[a]Chi-square test.

[b]Mann-Whitney test.

[c]Reports with EP, n = 94; reports with other AEs, n = 667.

[d]Fisher exact test.

DISCUSSION

This study revealed that among the anti-MRSA agents analyzed, disproportionality in the occurrence of EP was observed only with DAP. Moreover, our results indicated that reports of DAP-related EP were characterized by male sex, older age, and extended duration of therapy as compared with other DAP-related reports. These results highlight the importance of the development of EP during the administration of DAP.

Disproportionality analysis revealed that among the anti-MRSA agents analyzed, a significant EP signal was detected only with DAP, which was consistently detected in the sensitivity analysis. Although the incidence of drug-related EP is rare, DAP has a relatively higher frequency of EP development than other drugs [1], and our results support previous research. The previous study showing the disproportionality of DAP-induced EP had limitations for accuracy owing to the small sample size and methodology for signal detection [2]. Chen et al examined the disproportionality of DAP-induced EP but not the relationship between the occurrence of EP

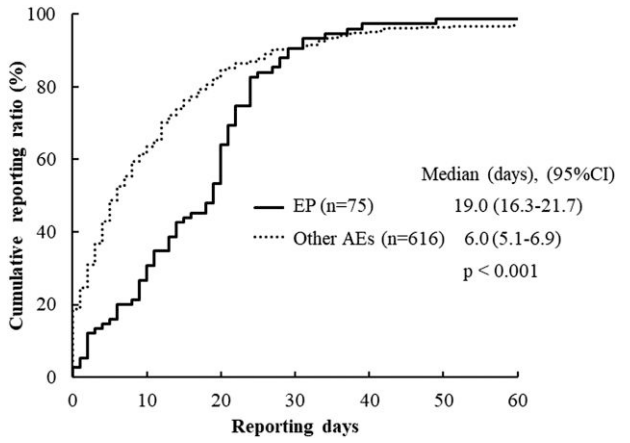


Figure 2. Reporting time of DAP-induced AEs. The reporting time (days) was calculated with the available data. *P* values were calculated per the log-rank test. Solid line, DAP-induced EP (n = 75); dashed line, other DAP-induced AEs (n = 616). Reports with input errors were excluded (n = 114). AE, adverse event; DAP, daptomycin; EP, eosinophilic pneumonia.

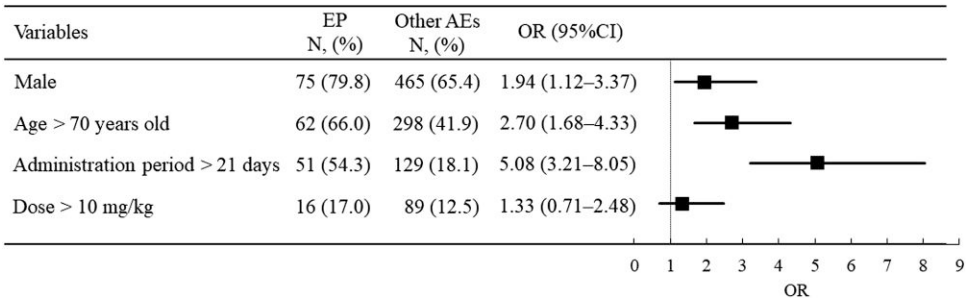


Figure 3. Logistic regression analysis of the cases reporting DAP-related EP. A logistic model was constructed with the following factors as explanatory variables: male sex, age >70 years, administration period >21 d, and dose >10 mg/kg. AE, adverse event; DAP, daptomycin; EP, eosinophilic pneumonia; OE, odds ratio.

and other anti-MRSA agents [19]. Our study overcame these points by using the most recent data set and the robust methodology for signal detection, and it showed the robustness of the disproportionality signal of anti-MRSA agent–related EP. In contrast, although an EP signal was observed for vancomycin in some data sets, this result was inconsistent. In the sensitivity analysis based only on cases with targeted drugs suspected to cause EP occurrence, the number of vancomycin-related EP cases decreased (Table 2). This indicated that vancomycin was not predominantly considered a suspected drug but a concomitant drug in most cases of vancomycin-related EP in the FAERS database. However, the relationship between EP and vancomycin requires further study, as a case of vancomycin-related EP has been reported [4]. No EP signal was detected with the other drugs, indicating that linezolid and teicoplanin did not affect the development of EP. Anti-MRSA agents are key drugs for MRSA infection, and our study highlights that clinicians should exercise caution regarding EP during the administration of DAP.

When compared with reports of other DAP-related adverse events, those of DAP-related EP were characterized by male sex, older age (>70 years), and longer duration of treatment (>21 days). Previous studies identified sex and age as risk factors for DAP-induced EP, and the present analysis results are consistent, confirming the reproducibility of the results [20–23]. Although the mechanism underlying the association between these factors and DAP-induced EP remains unclear, sex differences in pharmacokinetic parameters and senescent changes in the lungs may lower the threshold for the development of EP during the administration of DAP [24, 25]. Conversely, whether the duration or dose of DAP is associated with DAP-related EP is uncertain [26]. Our study indicates that the disproportionality of EP development may be influenced by DAP administration duration rather than DAP dosage. Although the duration of antibiotic treatment for osteomyelitis, arthritis infection, or endocarditis is longer than that for other infections [27], the indication for DAP administration between the groups was not significantly different. The development of EP should be carefully monitored during long-term administration of DAP, regardless of the site of infection. Our results also indicate a disparity in time to onset between DAP-associated EP and other adverse events. An increase in the creatine kinase level is a well-known adverse event of DAP administration [28], and a previous study determined that the median duration of creatine kinase elevation after the initiation of DAP therapy was 4 to 5 days [29]. This emphasizes the necessity to determine the distinction in onset timing between these adverse events. Deaths accounted for 23.4% of the outcomes of DAP-related EP, indicating the severity of the adverse event. Our study analyzed the most significant number of DAP-related EP reports to date and provides valuable insights into the characteristics of DAP-related EP that can be applied in a clinical context.

This study had several limitations. First, the FAERS database includes spontaneously reported adverse events with inherent flaws, such as incomplete information and the inability to exclude duplicate cases by another reporting source. As the overall population using anti-MRSA drugs is unknown, it is not feasible to calculate the risk of EP development for each agent. Further analysis is required to determine whether the features of the DAP-induced EP reports obtained from this analysis represent risk factors for DAP-induced EP in clinical settings. We should also consider the probability that the dose of DAP may not have been related to the development of EP in this analysis owing to other DAP-related adverse events being dose related. Second, the number of reports is influenced by several sources of bias. DAP-related EP cases increased in 2017 following the FDA's notification regarding DAP-related EP that same year (Supplementary Figure) [30]. Thus, the possibility that a reporting bias may have affected this result should be considered. We cannot rule out the existence of a potential study time selection bias or a misclassification bias due to the inherent characteristics of the FAERS database. Third, owing to the lack of detailed patient background data, the association between

baseline allergic predisposition, such as a history of asthma, and DAP-related EP could not be analyzed. Additionally, insufficient diagnostic data—including laboratory diagnostic tests such as computed tomography scans or blood tests—precluded the accurate evaluation of the diagnosis of DAP-related EP. Last, the cumulative DAP dose at the onset of EP, which is associated with the dose and administration period, could not be analyzed owing to a lack of data. Despite these limitations and given the rare incidence of DAP-related EP, this study provides important insights into the characterization of DAP-induced EP and can serve as a reference basis for further research to resolve these limitations.

CONCLUSION

Using a large-scale database, our study revealed that among the anti-MRSA agents analyzed, disproportionality in the occurrence of EP was observed only with DAP. In addition, our results suggest that sex, age, and treatment duration may affect the occurrence of DAP-induced EP. Clinicians should exercise caution regarding EP during the administration of DAP.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Author contributions. All authors contributed to the conception and design of the study. N. O. was responsible for data acquisition and statistical analysis. T. N. provided technical support for the analysis. N. O. drafted the manuscript with support from A. S., Y. K., K. I., and T. K. All the authors reviewed and approved the final manuscript.

Patient consent statement. The FAERS data comprise anonymized information. Given the retrospective nature of this observational study, which utilized the FAERS data, the requirement for informed consent was waived.

Data availability. Publicly available data sets were analyzed in this study and are available from https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html.

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Potential conflicts of interest. All authors: No reported conflicts.

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