Original Article

Risk of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis Associated With Antibiotic Use: A Case-Crossover Study

Toshiki Fukasawa, MS[a,b], Hisashi Urushihara, DrPH[c], Hayato Takahashi, MD, PhD[d], Takayuki Okura, MD[a], and Koji Kawakami, MD, PhD[a] *Kyoto and Tokyo, Japan*

What is already known about this topic? Drugs are the main cause of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), with antibiotics being the most common.

What does this article add to our knowledge? This study provides new evidence for the increased risk of SJS/TEN associated with exposure to lincomycins, glycopeptides, aminoglycosides, fosfomycin, and carbapenems, which accordingly join penicillins, cephalosporins, macrolides, tetracyclines, quinolones, and trimethoprim-sulfamethoxazole (TMP-SMX), as reported in previous studies.

How does this study impact current management guidelines? The risk of SJS/TEN induced by other antibiotics, except TMP-SMX and glycopeptides, appears low. Optimization of the benefit-risk balance of TMP-SMX and glycopeptides based on clinical evidence is desirable.

BACKGROUND: Evidence is lacking on the association between antibiotic use and risk of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) in Asians.

OBJECTIVE: We assessed the risk of SJS/TEN associated with different antibiotic classes in Japanese.

METHODS: We conducted a case-crossover study using a claims database. Firth conditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) of SJS/TEN associated with antibiotic use in a 56-day hazard period versus 3 control periods. We created 18 cohorts for each antibiotic class and calculated 56-day cumulative incidence per 100,000 new users. The association between antibiotic class and SJS/TEN was also evaluated in each case using the ALgorithm of Drug causality for Epidermal Necrolysis (ALDEN).

RESULTS: Our case-crossover study included 170 SJS/TEN cases. Increased ORs were observed for lincomycins (OR, 33.00 [95% CI, 3.74-4332.05]), trimethoprim-sulfamethoxazole (21.20 [6.73-105.98]), penicillins (14.39 [6.95-34.21]), glycopeptides (14.37 [3.17-136.10]), cephalosporins (7.06 [4.25-12.21]), aminoglycosides (6.55 [1.97-26.84]), quinolones (5.98 [3.34-11.20]), fosfomycin (5.40 [1.20-30.97]), carbapenems (5.09 [1.85-15.64]), tetracyclines (4.95 [1.78-15.27]), and macrolides (3.78 [2.13-6.83]). Cumulative incidence of SJS/TEN was 67.4 for trimethoprim-sulfamethoxazole, 86.2 for glycopeptides, and below 10.0 for the others. Despite the high incidence, only 2 cases had a probable causal relationship with glycopeptides.

CONCLUSION: Some antibiotic classes, including lincomycins, glycopeptides, aminoglycosides, fosfomycin, and carbapenems, were newly suggested to be associated with risk of SJS/TEN;

[a]Department of Pharmacoepidemiology, Graduate School of Medicine and Public Health, Kyoto University, Kyoto, Japan
[b]Department of Digital Health and Epidemiology, Graduate School of Medicine and Public Health, Kyoto University, Kyoto, Japan
[c]Division of Drug Development and Regulatory Science, Graduate School of Pharmaceutical Sciences, Keio University, Tokyo, Japan
[d]Department of Dermatology, Keio University School of Medicine, Tokyo, Japan

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Corresponding author: Koji Kawakami, MD, PhD, Department of Pharmacoepidemiology, Graduate School of Medicine and Public Health, Kyoto University, Yoshidakonoe-cho, Sakyo-ku, Kyoto 606-8501, Japan. E-mail: kawakami.koji.4e@kyoto-u.ac.jp.

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Abbreviations used
ALDEN- ALgorithm of Drug causality for Epidermal Necrolysis
CI- Confidence interval
CLR- Conditional logistic regression
CPRD- Clinical Practice Research Datalink
EBV- Epstein-Barr virus
MP- Mycoplasma pneumonia
NSAIDs- Nonsteroidal anti-inflammatory drugs
OR- Odds ratio
SJS- Stevens-Johnson syndrome
TEN- Toxic epidermal necrolysis
TMP-SMX- Trimethoprim-sulfamethoxazole

considered together with the high incidence for trimethoprim-sulfamethoxazole and glycopeptides, these findings warrant caution in clinical practice. © 2023 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2023;11:3463-72)

Key words: *Adverse drug reaction; Antibiotics; Asia; Incidence; Japan; Pharmacoepidemiology; Real-world evidence; Stevens-Johnson syndrome; Toxic epidermal necrolysis; Trimethoprim-sulfamethoxazole*

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe mucocutaneous reactions that cause blistering and epithelial sloughing.[1] SJS/TEN represent different severities of the same disease entity, with TEN being the more severe form. Annual incidence per million in Western and Asian countries ranges from 1 to 7 for SJS and 0.4 to 1.5 for TEN.[1-3]

Drugs are the main cause of SJS/TEN, with antiseizure medications, antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), and allopurinol being common.[4] In recent years, real-world data have been widely used to assess the safety of drugs,[5] and the relative and absolute risks of SJS/TEN for individual drugs have been successively reported.[6-9] In our previous studies, we developed an algorithm to identify patients with SJS/TEN from a claims database and successfully used it to report the risk of SJS/TEN associated with individual antiseizure medications.[10,11]

Causative antibiotics in previous studies in Europe include penicillins,[7,12,13] cephalosporins,[7,12,13] macrolides,[7,13] tetracyclines,[12,13] quinolones,[7,12,13] and sulfonamides.[12,13] The risk of drug-induced SJS/TEN varies by region due to ethnic and genetic influences,[14,15] and these findings cannot be generalized to Asian populations; instead, region-specific studies are needed. Recent studies have reported the involvement of various genetic polymorphisms in the elevated risk of SJS/TEN induced by some drugs, including sulfonamides.[14,16-18] Accordingly, the case-crossover design, which controls for time-invariant, unmeasured confounders within individuals, including genetic predisposition, appears desirable for investigating SJS/TEN with differential risk across ethnic groups.

Here, we conducted a case-crossover study using a large Japanese claims database to assess the association of antibiotic use with the risk of SJS/TEN while controlling for potential genetic confounding. Further, we performed a cohort study to estimate the absolute risk of SJS/TEN in patients treated with antibiotics to provide information on the public health impact of the exposure.

METHODS

Data source

We used an insurance claims database managed by JMDC Inc. (Tokyo, Japan).[19-21] The database covers the period from January 1, 2005, to October 31, 2020, and as of August 2020 contained anonymized data from over 10 million employees and family members.[19] It does not include people aged 75 years or older because these are covered by a separate, late-stage medical care system for the elderly.[19] For each insured individual, the database contains information on demographics, in- and outpatient diagnoses, procedures, and drug dispensing. The study was approved by the ethics committee of Kyoto University Graduate School and Faculty of Medicine (approval number: R2867). Informed consent was waived in accordance with the local ethical guidelines for life science and medical research involving human subjects because the information used was anonymous and reidentification was not possible.

Case identification. We identified patients with SJS/TEN using our previously reported algorithm (sensitivity 76.9% and specificity 99.0%; Tables E1-E3, available in this article's Online Repository at www.jaci-inpractice.org),[10] which we applied to reporting the risk of SJS/TEN associated with antiseizure medications using the same claims database[11] Here, we identified case candidates as those having at least 1 disease code for SJS/TEN or similar diseases (Table E2, available in this article's Online Repository at www.jaci-inpractice.org)[10] We then applied the algorithm to the case candidates to filter those having SJS/TEN.[11] Weight data were supplemented by the average weight of respective age groups in the 2012-2019 National Health and Nutrition Survey, as reported previously,[11,22] to calculate the dose of corticosteroids and intravenous immunoglobulin used for SJS/TEN treatment. The onset of SJS/TEN in a single patient was defined as the first date of any of the diagnosis codes listed in Table E2 (available in this article's Online Repository at www.jaci-inpractice.org) during the first event that the algorithm identified

Exposure to antibiotics. We defined drug exposure as a minimum 1-day supply of any of the antibiotics listed in Table E4 (available in this article's Online Repository at www.jaci-inpractice.org) Antibiotics of interest were limited to oral and injectable formulations and classified into 18 groups based on the classification developed by the Antimicrobial Resistance Clinical Reference Center (Tokyo, Japan).[23] During the study period, the only sulfonamide antibiotic available in the Japanese market was a combination preparation of trimethoprim-sulfamethoxazole (TMP-SMX), and neither trimethoprim nor sulfamethoxazole alone was available.

Study design 1: case-crossover substudy

We first performed a case-crossover substudy to estimate odds ratios (ORs) for SJS/TEN associated with antibiotic use.[24] The case-crossover design has been used to assess the effects of transient drug exposures on acute outcomes,[25-27] such as SJS/TEN. This design compares drug exposure status in the hazard period immediately before the outcome and with exposure in earlier control periods within an individual,[25] thereby controlling for time-invariant unknown or unmeasured confounders, such as genetic polymorphisms in human leukocyte antigen that influence the development of SJS/TEN.[14,16] We set a hazard period before the onset date of SJS/TEN to identify potentially causative drug exposure (Figure 1), preceded by 3 consecutive control periods.[28] A 28-day washout period was

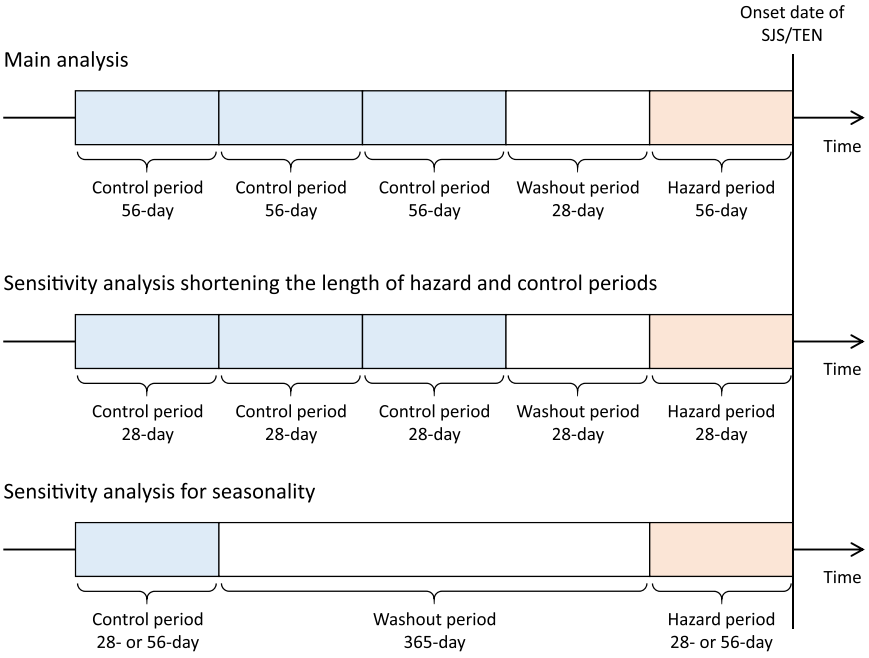

FIGURE 1. Graphical representation of the case-crossover design. *SJS*, Stevens-Johnson syndrome; *TEN*, toxic epidermal necrolysis.

introduced between the hazard and control periods to avoid carryover effects.[29] In primary analysis, the hazard period was 56 days as SJS/TEN is more likely to occur within 56 days after causative drug initiation.[30]

We used the claims records of diagnoses, procedure, and dispensing between April 1, 2012, and October 31, 2020. Because claims records before April 1, 2012, in Japan recorded only month data, and not day data, claims data between January 1, 2005, and March 31, 2012, were used to verify insurance coverage and medication history. Patients who developed SJS/TEN between December 9, 2012 (252 days after April 1, 2012), and October 31, 2020, were eligible for analysis, ensuring continuous enrollment in the database for at least 252 days (sum of hazard, washout, and control periods) before the onset date.

Study design 2: cohort substudy

To calculate the 56-day cumulative incidence of SJS/TEN after exposure to antibiotics, we created 18 cohorts of new users of individual antibiotic classes (Table E4, available in this article's Online Repository at www.jaci-inpractice.org) Cohort entry date was defined as the date of the first dispensing of an antibiotic after verifying no preceding dispensing records of the drug in the antibiotic class of interest during a look-back period of at least 196 days, with the earliest date being October 14, 2012 (196 days after April 1, 2012). In addition, the latest entry date of September 5, 2020 (56 days before October 31, 2020), ensured at least a 56-day follow-up period to detect SJS/TEN onset. Patients could be entered into more than 1 antibiotic class cohort if they met the relevant inclusion criteria.

Assessment of drug causality for SJS/TEN

To examine the association between antibiotic use and SJS/TEN in individual cases, we used the ALgorithm of Drug causality for Epidermal Necrolysis (ALDEN).[30] An ALDEN score of $\geq$4 indicates a probable causal relationship with the suspect drug.[30] ALDEN considers drug distribution in the body on the onset date of SJS/TEN based on elimination half-life, kidney and liver function, and possible drug interactions. In addition, we set a 7-day grace period after the final day of drug supply to account for possible leftover drugs.

Statistical analysis

In this case-crossover substudy, the following patient characteristics were summarized (Tables E5 and E6, available in this article's Online Repository at www.jaci-inpractice.org): demographics; comorbidities, including risk factors for SJS/TEN such as *Mycoplasma pneumoniae* (MP), Epstein-Barr virus (EBV), and human immunodeficiency virus (HIV);[31-33] use of high-risk drugs for SJS/TEN, namely allopurinol, carbamazepine, lamotrigine, phenobarbital, and phenytoin, oxicam NSAIDs, sulfonamides (TMP-SMX and sulfasalazine), and nevirapine;[13] and use of drugs other than high-risk drugs The case-crossover substudy estimated the ORs and 95% confidence intervals (CIs) of SJS/TEN associated with antibiotic use in the hazard period in comparison with that in each of the 3 control periods. Given the very low incidence of SJS/TEN and their idiosyncratic nature, complete or quasi-complete separation may occur in conventional conditional logistic regression (CLR) analysis.[34] To address this issue, we used CLR with Firth's penalization.[35-37] Multivariable regression was not feasible because of the small number of cases and therefore not performed. We investigated the proportions of SJS/TEN cases with a probable causal relationship (ALDEN score of $\geq$4) with the drug class of interest.

In the first sensitivity analysis, 28-day hazard and control periods were used to examine robustness against different time window lengths (Figure 1).[25] Cumulative incidence of skin rash within 28 days of the initiation of suspect antibiotic therapy was approximately 93% in SJS and 100% in TEN.[38] The second sensitivity analysis used a single control period 1 year before the onset of SJS/TEN instead of 3 control periods, to control for potential seasonality, which can be problematic in a case-crossover design (Figure 1).[39]

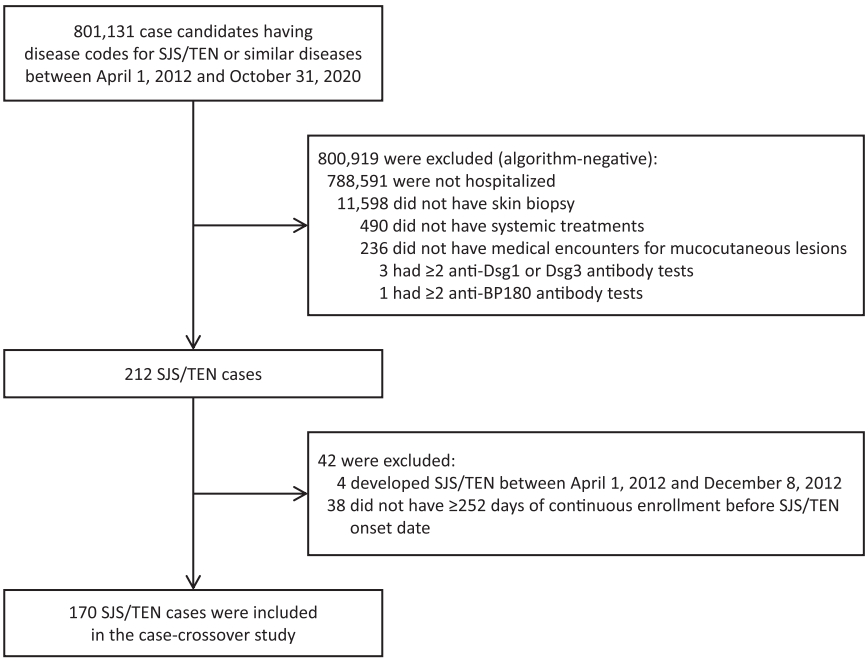

FIGURE 2. Flow diagram for the case-crossover study. *BP*, Bullous pemphigoid; *Dsg*, desmoglein; *SJS*, Stevens-Johnson syndrome; *TEN*, toxic epidermal necrolysis.

TABLE I. Demographic and clinical characteristics of cases with Stevens-Johnson syndrome and toxic epidermal necrolysis

	Cases (n = 170)	
Characteristic	**Hazard period**	**Control periods***
Demographics		
Age, mean (SD) (y)†	45.1 (16.0)	44.8 (16.0)
Female	106 (62.4)	106 (62.4)
Comorbidities		
Mycoplasma pneumoniae	2 (1.2)	1 (0.6)
Epstein-Barr virus	2 (1.2)	1 (0.6)
HIV	1 (0.6)	0
Chronic kidney disease	3 (1.8)	3 (1.8)
Chronic liver disease	17 (10.0)	9 (5.3)
High-risk drug use		
Allopurinol	9 (5.3)	3 (1.8)
Carbamazepine	13 (7.6)	2 (1.2)
Lamotrigine	7 (4.1)	0
Phenobarbital	3 (1.8)	2 (1.2)
Phenytoin	5 (2.9)	2 (1.2)
Oxicam NSAIDs	0	0
Sulfonamides	22 (12.9)	7 (4.1)
Nevirapine	0	0

HIV, Human immunodeficiency virus; *NSAIDs*, nonsteroidal anti-inflammatory drugs; *SD*, standard deviation.
*Comorbidities and high-risk drug use were counted if recorded during at least 1 control period.
†Ages in the hazard and control periods are as of the last day of the respective periods.

Two time window patterns of 56 and 28 days were again set for the hazard and control periods for the second sensitivity analysis. Patients meeting the following criteria were included: (1) development of SJS/TEN between May 27, 2013 (421 days after April 1, 2012), and October 31, 2020; and (2) continuous enrollment in the database for at least 421 days on and before the onset date.

In the cohort substudy, we calculated 56-day cumulative incidence by dividing the number of incident SJS/TEN cases by the number of patients newly exposed to the antibiotic class of interest. Given the short duration of antibiotic use and the possibility that sensitization did not occur during the first course,[40,41] SJS/TEN cases after multiple courses of an antibiotic were also included in calculating cumulative incidence. For SJS/TEN cases, we also calculated cumulative days' supply of the drug class of interest from cohort entry to onset. As a sensitivity analysis, we calculated 56-day cumulative incidences by restricting the numerator to SJS/TEN cases with a probable causal relationship with the drug class of interest.

All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC).

RESULTS

Patient characteristics of SJS/TEN cases

A total of 170 SJS/TEN cases were eligible for the case-crossover substudy (Figure 2) with an average age of 45.1 years (standard deviation, 16.0 years) at the end of hazard period and female sex of 62.4% (Table I). The following risk factors for SJS/TEN were more common in the hazard than the control periods: MP (1.2% vs 0.6%), EBV (1.2% vs 0.6%), HIV (0.6% vs 0%), and use of allopurinol (5.3% vs 1.8%), carbamazepine (7.6% vs 1.2%), lamotrigine (4.1% vs 0%), phenobarbital (1.8% vs 1.2%), phenytoin (2.9% vs 1.2%), and sulfonamide (12.9% vs 4.1%). The frequency of use of drugs other than high-risk drugs in SJS/TEN cases during the hazard and control periods is shown in Table E6 (available in this article's Online Repository at www.jaci-inpractice.org)

TABLE II. Odds ratios for Stevens-Johnson syndrome and toxic epidermal necrolysis associated with antibiotic use with a 56-day time window

Antibiotic class	No. of exposed SJS/TEN cases		Odds ratio (95% CI)	Cases with probable causality (%)‡
	Hazard period*	Control periods†		
Cephalosporins, including β-lactamase inhibitors (n = 75)	56	35	7.06 (4.25-12.21)	10 (17.9)
Quinolones (n = 55)	40	29	5.98 (3.34-11.20)	7 (17.5)
Penicillins, including β-lactamase inhibitors (n = 45)	38	9	14.39 (6.95-34.21)	20 (52.6)
Macrolides (n = 50)	31	30	3.78 (2.13-6.83)	8 (25.8)
Trimethoprim-sulfamethoxazole (n = 23)	21	6	21.20 (6.73-105.98)	15 (71.4)
Carbapenems (n = 15)	10	7	5.09 (1.85-15.64)	1 (10.0)
Tetracyclines (n = 15)	10	6	4.95 (1.78-15.27)	2 (20.0)
Aminoglycosides (n = 12)	9	5	6.55 (1.97-26.84)	0
Glycopeptides (n = 9)	8	3	14.37 (3.17-136.10)	1 (12.5)
Lincomycins (n = 5)	5	0	33.00 (3.74-4332.05)	1 (20.0)
Fosfomycin (n = 6)	4	2	5.40 (1.20-30.97)	0
Lipopeptides (n = 4)	2	2	3.00 (0.46-19.41)	0
Metronidazole (n = 1)	1	0	9.00 (0.48-1313.28)	0
Monobactams (n = 1)	1	0	9.00 (0.48-1313.28)	0
Penems (n = 1)	1	0	9.00 (0.48-1313.28)	0
Polypeptides (n = 2)	1	1	1.73 (0.13-23.71)	0
Chloramphenicols (n = 0)	0	0	N/A	0
Oxazolidinones (n = 0)	0	0	N/A	0

CI, Confidence interval; *N/A*, not available; *SJS*, Stevens-Johnson syndrome; *TEN*, toxic epidermal necrolysis.
*Due to differences in eligibility criteria, some cases dispensed an antibiotic class of interest in the hazard period of the case-crossover substudy were not identical to those identified in the cohort substudy.
†Cases who were dispensed an antibiotic class of interest during at least 1 control period.
‡Cases with an ALgorithm of Drug causality for Epidermal Necrolysis (ALDEN) score of ≥4 for the drug. Denominator is patients dispensed an antibiotic class of interest in the hazard period.

Demographic and clinical characteristics of SJS/TEN cases exposed to antibiotics during at least the hazard or control periods are shown by antibiotic class in Tables E7A-E7D (available in this article's Online Repository at www.jaci-inpractice.org)

Case-crossover substudy

Table II presents the effect of antibiotic use on the risk of SJS/TEN within a 56-day window. Increased ORs were found for cephalosporins (OR, 7.06 [95% CI, 4.25-12.21]; probable causality, 17.9%), quinolones (5.98 [3.34-11.20]; 17.5%), penicillins (14.39 [6.95-34.21]; 52.6%), macrolides (3.78 [2.13-6.83]; 25.8%), TMP-SMX (21.20 [6.73-105.98]; 71.4%), carbapenems (5.09 [1.85-15.64]; 10.0%), tetracyclines (4.95 [1.78-15.27]; 20.0%), glycopeptides (14.37 [3.17-136.10]; 12.5%), and lincomycins (33.00 [3.74-4332.05]; 20.0%).

The following antibiotic classes yielded increased ORs, but no SJS/TEN cases exposed to them had probable causality (Table II): aminoglycosides (6.55 [1.97-26.84]) and fosfomycin (5.40 [1.20-30.97]). Nonsignificant associations of SJS/TEN were observed with exposure to lipopeptides (3.00 [0.46-19.41]); metronidazole, monobactams, and penems (9.00 [0.48-1313.28]); and polypeptides (1.73 [0.13-23.71]). No SJS/TEN cases exposed to these antibiotic classes had probable causality. No cases had exposure to chloramphenicols or oxazolidinones in the hazard period.

In the sensitivity analysis with shortened 28-day hazard and control periods, the increased risk remained consistent for all antibiotic classes (Table III). The results of the sensitivity analyses adjusted for seasonality were largely consistent with the main findings, except for aminoglycosides (OR, 3.67 [95% CI, 0.73-35.75] for the 28-day window; Table E8, available in this article's Online Repository at www.jaci-inpractice.org) and fosfomycin (OR, 140 [95% CI, 0.27-8.40] for the 56-day window; OR, 2.33 [95% CI, 0.38-24.07] for the 28-day window; Tables IV and E8, available in this article's Online Repository at www.jaci-inpractice.org)

The antibiotics to which patients with SJS/TEN were exposed during the hazard period in the main and sensitivity analyses are shown in Tables E9 and E10 (available in this article's Online Repository at www.jaci-inpractice.org)

Cohort substudy

Because of differences in eligibility criteria, some cases identified in the cohort substudy were not identical to those dispensed an antibiotic class of interest in the hazard period of the case-crossover substudy. Among the antibiotic classes for which the case-crossover substudy suggested a significant risk, 56-day cumulative incidence was high at 67.4 per 100,000 new users (95% CI, 44.0-103.4; 21 cases of 31,143 new users) for TMP-SMX and 86.2 (43.1-172.4; 8 cases of 9279 new users) for glycopeptides, but lower than 10.0 for the other classes (Table V): cephalosporins (1.2 [0.9-1.7]), quinolones (1.4 [0.9-2.0]), penicillins (2.2 [1.6-3.1]), macrolides (1.0 [0.7-1.5]), carbapenems (7.2 [3.8-13.9]), tetracyclines (2.2 [1.1-4.2]), aminoglycosides (0.9 [0.4-2.2]), lincomycins (2.1 [0.7-6.6]), and fosfomycin (0.7 [0.2-2.0]). Among the antibiotic classes for which the case-crossover substudy did not show a significant risk, 56-day cumulative incidence was high at 89.1 per 100,000 new users (95% CI, 12.6-632.7; 1 case of 1122 new users) for

TABLE III. Odds ratios for Stevens-Johnson syndrome and toxic epidermal necrolysis associated with antibiotic use with a 28-day time window

Antibiotic class	No. of exposed SJS/TEN cases		Odds ratio (95% CI)	Cases with probable causality (%)‡
	Hazard period*	Control periods†		
Cephalosporins, including β-lactamase inhibitors (n = 56)	45	20	10.05 (5.41-20.25)	9 (20.0)
Quinolones (n = 45)	36	18	9.09 (4.57-19.90)	6 (16.7)
Penicillins, including β-lactamase inhibitors (n = 42)	37	6	19.56 (8.66-54.00)	20 (54.1)
Macrolides (n = 33)	22	14	5.06 (2.50-10.77)	7 (31.8)
Trimethoprim-sulfamethoxazole (n = 21)	19	7	18.11 (5.62-91.36)	15 (78.9)
Carbapenems (n = 11)	8	4	6.25 (1.89-25.63)	1 (12.5)
Tetracyclines (n = 9)	8	2	15.69 (3.50-147.89)	2 (25.0)
Aminoglycosides (n = 7)	5	3	4.83 (1.07-27.90)	0
Glycopeptides (n = 8)	6	3	6.75 (1.66-37.37)	1 (16.7)
Lincomycins (n = 5)	5	0	33.00 (3.74-4332.05)	1 (20.0)
Fosfomycin (n = 3)	3	0	21.00 (2.04-2828.51)	0
Lipopeptides (n = 3)	2	1	5.00 (0.67-54.64)	0
Metronidazole (n = 1)	1	0	9.00 (0.48-1313.28)	0
Monobactams (n = 1)	1	0	9.00 (0.48-1313.28)	0
Penems (n = 1)	1	0	9.00 (0.48-1313.28)	0
Polypeptides (n = 2)	1	1	3.00 (0.24-36.94)	0
Chloramphenicols (n = 0)	0	0	N/A	0
Oxazolidinones (n = 0)	0	0	N/A	0

CI, Confidence interval; *N/A*, not available; *SJS*, Stevens-Johnson syndrome; *TEN*, toxic epidermal necrolysis.
*Due to differences in eligibility criteria, some cases dispensed an antibiotic class of interest in the hazard period of the case-crossover substudy were not identical to those identified in the cohort substudy.
†Cases who were dispensed an antibiotic class of interest during at least 1 control period.
‡Cases with an ALgorithm of Drug causality for Epidermal Necrolysis (ALDEN) score of ≥4 for the drug. Denominator is patients dispensed an antibiotic class of interest in the hazard period.

lipopeptides and 170.6 (24.0-1211.5; 1 case of 586 new users) for polypeptides.

In a sensitivity analysis, 56-day cumulative incidences of SJS/TEN cases with probable causality (Table VI) were 45.0 (26.6-75.9) for TMP-SMX and 21.6 (5.4-86.2) for glycopeptides.

The numbers of SJS/TEN patients by each antibiotic agent with exposure during the risk period are listed in Table E11 (available in this article's Online Repository at www.jaci-inpractice.org)

Median cumulative antibiotic exposure days to SJS/TEN onset ranged from 1 to 21 days in the main analysis and from 6 to 17 days in the sensitivity analyses (Tables V and VI).

DISCUSSION

This case-crossover study using a large-scale claims dataset provides new evidence for the increased risk of SJS/TEN associated with the use of aminoglycosides, carbapenems, fosfomycin, glycopeptides, and lincomycins, which accordingly join penicillins, cephalosporins, macrolides, tetracyclines, quinolones, and TMP-SMX, as reported in previous studies. Except for population exposed to TMP-SMX and glycopeptides, cumulative incidence of SJS/TEN in the population exposed to antibiotics was not much higher than in the general population.[3] The time from antibiotic initiation to the onset of SJS/TEN was similar to that previously reported.

TMP-SMX was identified as a risk drug for SJS/TEN in our study, as in other studies,[12,13] despite differences in genetic predisposition and frequency of drug use among countries. Our study adds higher estimates of TMP-SMX-induced absolute risk among antibiotics to the accumulated evidence of risk factors for SJS/TEN, and underpins the increased ORs reported in previous case-control studies.[12,13] A previous Japanese study reported a 4-month cumulative incidence of 77 per 100,000 sulfonamide users.[42] In that study, however, no effort was made to validate the International Classification of Diseases, Tenth Revision (ICD-10) codes used to identify SJS/TEN cases, and a new user design was not used. The results were therefore highly susceptible to a variety of biases resulting from the potential misclassification of exposure and outcome.[42,43] In contrast, a UK cohort study using the Clinical Practice Research Datalink (CPRD) reported an 84-day cumulative incidence per 100,000 new users of zero for TMP-SMX or all anti-infective sulfonamides excluding trimethoprim and 1.32 for trimethoprim.[7] The results of the CPRD study challenge the common belief that anti-infective sulfonamides are the leading cause of SJS/TEN in Europeans and Asians.[12,13,15] Because the CPRD is based on primary care practice by general practitioners, its source may be limited in assessing SJS/TEN in relation to antibiotic use in inpatient settings.[44]

Glycopeptides showed the second highest absolute risk of SJS/TEN among antibiotic classes. Among 8 patients with SJS/TEN exposed to glycopeptides in the cohort substudy, only 2 had a probable causal relationship with vancomycin. Of the remaining 6, 5 had a probable causal relationship with other culprit drugs, and 1 had used glycopeptides more than 30 times after SJS/TEN onset, indicating an unlikely relationship with glycopeptides. Reports of SJS/TEN due to glycopeptides are limited,[45-49] and

TABLE IV. Odds ratios for Stevens-Johnson syndrome and toxic epidermal necrolysis associated with antibiotic use with a 56-day time window, adjusted for seasonality

Antibiotic class	No. of exposed SJS/TEN cases		Odds ratio (95% CI)	Cases with probable causality (%)‡
	Hazard period*	Control periods†		
Cephalosporins, including β-lactamase inhibitors (n = 58)	50	11	5.59 (2.84-12.46)	10 (20.0)
Quinolones (n = 45)	39	12	5.15 (2.38-13.13)	7 (17.9)
Penicillins, including β-lactamase inhibitors (n = 34)	32	3	12.60 (4.20-61.68)	15 (46.9)
Macrolides (n = 32)	26	10	3.46 (1.53-9.04)	6 (23.1)
Trimethoprim-sulfamethoxazole (n = 22)	21	1	14.33 (3.70-128.85)	15 (71.4)
Carbapenems (n = 10)	10	1	19.00 (2.14-2449.40)	1 (10.0)
Tetracyclines (n = 10)	9	1	6.33 (1.46 to 59.04)	2 (22.2)
Aminoglycosides (n = 9)	9	2	15.00 (1.83-1946.73)	0
Glycopeptides (n = 8)	8	1	15.00 (1.83-1946.73)	1 (12.5)
Lincomycins (n = 5)	5	0	11.00 (1.25-1444.02)	1 (20.0)
Fosfomycin (n = 5)	3	2	1.40 (0.27-8.40)	0
Lipopeptides (n = 2)	2	0	5.00 (0.41-689.61)	0
Metronidazole (n = 1)	1	0	3.00 (0.16-437.76)	0
Monobactams (n = 1)	1	0	3.00 (0.16-437.76)	0
Penems (n = 1)	1	0	3.00 (0.16-437.76)	0
Polypeptides (n = 1)	1	0	3.00 (0.16-437.76)	0
Chloramphenicols (n = 0)	0	0	N/A	0
Oxazolidinones (n = 0)	0	0	N/A	0

CI, Confidence interval; *N/A*, not available; *SJS*, Stevens-Johnson syndrome; *TEN*, toxic epidermal necrolysis.
*Due to differences in eligibility criteria, some cases dispensed an antibiotic class of interest in the hazard period of the case-crossover substudy were not identical to those identified in the cohort substudy.
†Cases who were dispensed an antibiotic class of interest during at least 1 control period.
‡Cases with an ALgorithm of Drug causality for Epidermal Necrolysis (ALDEN) score of ≥4 for the drug. Denominator is patients dispensed an antibiotic class of interest in the hazard period.

this is the first study to report the absolute risk. This association should be monitored on an ongoing basis.

Our results support previous findings on the risk of SJS/TEN associated with the use of penicillins,[7,12,13] cephalosporins,[7,12,13] macrolides,[7,13] tetracyclines,[12,13] and quinolones[7,12,13] in several European case-control studies. Because case-control designs compare risk between individuals, whereas case-crossover designs compare risk within individuals,[50] the estimates cannot be directly compared, but the ORs from both designs were nonetheless similar in direction. The estimates of absolute risk with these antibiotics do not appear particularly high, considering the benchmark annual prevalences of approximately 0.25 for SJS and 0.1 for TEN per 100,000 population in the general Japanese population.[3] Our estimates were also similar to those from a UK cohort study using the CPRD, which had an 84-day cumulative incidence of 1.31 per 100,000 new users for penicillins, 0.97 for cephalosporins, 1.25 for macrolides, and 1.15 for quinolones.[7] The absolute risk of tetracyclines in the previous study was 0.23, which was lower than in our study.[7] Although the CPRD and our database target different medical area levels,[19,44] the impact of these classes on the incidence of SJS/TEN in populations exposed to them appears to be low.

Our study provides the first information on an increased risk of SJS/TEN associated with the use of carbapenems and lincomycins, albeit that only 1 case for each drug class was rated probable in the ALDEN score. The absolute risk of carbapenems and lincomycins was slightly higher than or similar to that of cephalosporins, quinolones, penicillins, macrolides, and tetracyclines. Our study provides weak evidence on the association of these 2 drug classes with SJS/TEN, given the scarcity of reports involving lincomycins and carbapenems.[51]

After adjusting for seasonality in sensitivity analysis, most associations of the studied antibiotic classes with the increased risk of SJS/TEN were weakened but remained significant, except for aminoglycosides and fosfomycin, suggesting that strong time-dependent bias due to seasonality may be present. In the case-crossover design, seasonality could increase the relative frequency of antibiotic use in the hazard period to a greater extent than in the control periods, which could create an apparent association between antibiotic use and SJS/TEN even though no true association was present. No patients with SJS/TEN exposed to aminoglycosides and fosfomycin were rated probable, and it would therefore be considered rare for these drugs to cause SJS/TEN, if ever, given the almost complete absence of previous reports.

In our study, a probable causal relationship was not found in the following 7 antibiotic classes, either in the case-crossover analysis or in the ALDEN assessment: lipopeptides, metronidazole, monobactams, penems, polypeptides, chloramphenicols, and oxazolidinones. When probable causality is absent, it is more appropriate to consider the causal relationship as unknown rather than nonexistent. However, to our knowledge, no previous study has reported an association between these antibiotics and SJS/TEN, suggesting that the risk, if it exists, is very rare.

Six limitations of our study warrant consideration. First, performance of the identification algorithm for SJS/TEN cases in this study may have differed from that developed for SJS/TEN cases at a single university hospital. In our present study, the

TABLE V. The 56-day cumulative incidence of Stevens-Johnson syndrome and toxic epidermal necrolysis among new users of antibiotics

Antibiotic class	No. of new users	No. of SJS/TEN cases*	56-day cumulative incidence per 100,000 new users (95% CI)	Median cumulative antibiotic exposure days to SJS/TEN onset (IQR)
Cephalosporins, including β-lactamase inhibitors	3,069,983	38	1.2 (0.9-1.7)	8.5 (5.0-15.0)
Quinolones	1,985,479	27	1.4 (0.9-2.0)	10.0 (6.0-20.0)
Penicillins, including β-lactamase inhibitors	1,562,827	35	2.2 (1.6-3.1)	7.0 (5.0-9.0)
Macrolides	2,595,243	26	1.0 (0.7-1.5)	9.5 (6.0-31.0)
Trimethoprim-sulfamethoxazole	31,143	21	67.4 (44.0-103.4)	15.0 (12.0-48.0)
Carbapenems	124,643	9	7.2 (3.8-13.9)	6.0 (4.0-19.0)
Tetracyclines	410,214	9	2.2 (1.1-4.2)	5.0 (4.0-11.0)
Aminoglycosides	537,241	5	0.9 (0.4-2.2)	3.0 (1.0-5.0)
Glycopeptides	9279	8	86.2 (43.1-172.4)	14.0 (8.0-27.5)
Lincomycins	140,107	3	2.1 (0.7-6.6)	1.0 (1.0-7.0)
Fosfomycin	456,506	3	0.7 (0.2-2.0)	4.0 (3.0-16.0)
Lipopeptides	1122	1	89.1 (12.6-632.7)	9.0 (9.0-9.0)
Metronidazole	54,299	1	1.8 (0.3-13.1)	6.0 (6.0-6.0)
Monobactams	1009	0	0	N/A
Penems	191,362	0	0	N/A
Polypeptides	586	1	170.6 (24.0-1211.5)	21.0 (21.0-21.0)
Chloramphenicols	621	0	0	N/A
Oxazolidinones	1104	0	0	N/A

CI, Confidence interval; *IQR*, interquartile range; *N/A*, not available; *SJS*, Stevens-Johnson syndrome; *TEN*, toxic epidermal necrolysis.
*Due to differences in eligibility criteria, some cases identified in the cohort substudy were not identical to those dispensed an antibiotic class of interest in the hazard period of the case-crossover substudy.

TABLE VI. The 56-day cumulative incidence of Stevens-Johnson syndrome and toxic epidermal necrolysis among new users of antibiotics (limited to cases with probable causality according to ALDEN)

Antibiotic class	No. of new users	No. of SJS/TEN cases*	56-day cumulative incidence per 100,000 new users (95% CI)	Median cumulative antibiotic exposure days to SJS/TEN onset (IQR)
Cephalosporins, including β-lactamase inhibitors	3,069,983	10	0.3 (0.2-0.6)	13.0 (7.0-22.0)
Quinolones	1,985,479	6	0.3 (0.1-0.7)	11.0 (7.0-12.0)
Penicillins, including β-lactamase inhibitors	1,562,827	19	1.2 (0.8-1.9)	7.0 (5.0-9.0)
Macrolides	2,595,243	7	0.3 (0.1-0.6)	7.0 (4.0-8.0)
Trimethoprim-sulfamethoxazole	31,143	14	45.0 (26.6-75.9)	17.0 (12.0-48.0)
Carbapenems	124,643	2	1.6 (0.4-6.4)	6.0 (6.0-6.0)
Tetracyclines	410,214	1	0.2 (0.03-1.7)	11.0 (11.0-11.0)
Aminoglycosides	537,241	0	0	N/A
Glycopeptides	9279	2	21.6 (5.4-86.2)	16.5 (9.0-24.0)
Lincomycins	140,107	1	0.7 (0.1-5.1)	7.0 (7.0-7.0)
Fosfomycin	456,506	0	0	N/A
Lipopeptides	1122	0	0	N/A
Metronidazole	54,299	0	0	N/A
Monobactams	1009	0	0	N/A
Penems	191,362	0	0	N/A
Polypeptides	586	0	0	N/A
Chloramphenicols	621	0	0	N/A
Oxazolidinones	1104	0	0	N/A

ALDEN, ALgorithm of Drug causality for Epidermal Necrolysis; *CI*, confidence interval; *IQR*, interquartile range; *N/A*, not available; *SJS*, Stevens-Johnson syndrome; *TEN*, toxic epidermal necrolysis.
*Due to differences in eligibility criteria, some cases identified in the cohort substudy were not identical to those dispensed an antibiotic class of interest in the hazard period of the case-crossover substudy.

algorithm was applied to patients admitted to university or other hospitals that may have differed by medical area level, size, and specialty. Disease misclassification could still have occurred. However, because the algorithm was developed in accordance with the clinical practice guidelines for SJS/TEN,[52] it is unlikely to be influenced by differences in institutional practice. Imperfect sensitivity may have led to underestimation of incidence rates. Second, the case-crossover design is susceptible to time-

varying confounders such as concomitant high-risk drugs.[25] However, as in previous studies,[6-8,11] we were unable to perform multivariable analyses to control for these confounders because of the limited number of cases. The ALDEN score was used to account for the potential influence of other concomitant high-risk drugs; nevertheless, other potential time-varying confounders such as comorbidities remain to be addressed.[30] Third, NSAIDs marketed as over-the-counter drugs are potential causative agents of SJS/TEN, but the JMDC claims database did not include them. Fourth, our finding might have been affected by potential bias that MP and EBV, which can induce SJS/TEN, lead to antibiotic use before SJS/TEN onset.[53,54] Almost no effect on the present results is expected because only 2 patients had a claim with a diagnosis of these infections during the hazard period. In addition, although HIV-infected patients have a reportedly 100-fold higher incidence of SJS/TEN than noninfected patients,[33] our study included only 1 HIV-infected patient with SJS/TEN, and the impact of this case on our results is accordingly expected to be small. Fifth, antibiotics may be used for patients with SJS/TEN complicated by serious infections,[3] and if a definitive diagnosis of SJS/TEN were made and dated after the initiation of treatment with antibiotics in the database, this might have led to reverse causality and overestimation of ORs and cumulative incidence rates. Finally, ALDEN scored lower for antibiotics apart for TMP-SMX, which is consistent with a previous study.[30] ALDEN is designed to score low when the time from drug initiation to SJS/TEN onset is 1 to 4 days to exclude patients with fever or skin infection who have been treated with antibiotics and are initially without a diagnosis of SJS/TEN. SJS/TEN could occur within a short period after the initiation of culprit drugs to which patients had been sensitized before enrollment into the study database, leading to underestimation of the causal relationship with the suspect drug. In this study, actual medication use was unknown, which may have resulted in over- or underestimation of the ALDEN score.

In conclusion, our case-crossover study found significant associations between the following antibiotic classes and SJS/TEN: cephalosporins, quinolones, penicillins, macrolides, TMP-SMX, tetracyclines, glycopeptides, and lincomycins. Only TMP-SMX and glycopeptides showed a high absolute risk of SJS/TEN. Given the risk observed in our study, concern about SJS/TEN should play a crucial role in clinical decision-making about treatment with TMP-SMX and glycopeptides.

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