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Original Article

Correlation between drug–drug interaction-induced Stevens–Johnson syndrome and related deaths in Taiwan

Fu-Jen Cheng [a,*], *Fei-Kai Syu* [b], *Kuo-Hsin Lee* [c], *Fu-Cheng Chen* [a], *Chien-Hung Wu* [a], *Chien-Chih Chen* [a]

[a] *Department of Emergency Medicine, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung County, Taiwan*

[b] *College of Pharmacy, China Medical University, Taichung, Taiwan*

[c] *Department of Emergency Medicine, E-Da Hospital, I-Shou University, Kaohsiung, Taiwan*

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ABSTRACT

Concomitant use of some drugs can lead to interactions between them resulting in severe adverse effects. To date, there are few reports of incidences of Stevens-Johnson syndrome (SJS) associated with combination drug administration. Therefore, we studied the relationship between drug combinations and SJS-related mortality, with the hope that a retrospective study of this nature would provide information crucial for the prevention of future drug-drug interaction related deaths attributable to SJS. This retrospective longitudinal study used mortality cases from 1999 to 2008 that were diagnosed as erythema multiforme (International Classification of Diseases, Ninth Revision, Clinical Modification 695.1) from the National Health Insurance database in Taiwan. Statistical comparisons of the results were performed using analysis of variance (ANOVA), independent sample t-tests, and odds ratio (OR). In this way, the relationship between combinations of SJS-inducing drugs and mortality could be determined. A total of 111 patients who had died, including 63 males and 48 females (66.0 ± 20 and 70.0 ± 17.7 years, respectively), were suspected of having experienced drug-drug interaction-related adverse effects. The associated drug combinations included allopurinol and ampicillin ($p = 0.049$), carbamazepine and sulfamethoxazole/trimethoprim (TMP) ($p < 0.0001$), carbamazepine and phenytoin ($p < 0.0001$), sulfamethoxazole/TMP and phenytoin ($p = 0.015$), sulfadoxine and piroxicam ($p = 0.045$), phenobarbital and cephalexin ($p < 0.0001$), ampicillin and erythromycin ($p < 0.0001$), erythromycin and minocycline ($p < 0.0001$), and vancomycin and ethambutol ($p < 0.0001$) administered 1 month before the patients' deaths. Caution should be exercised when administering any drugs that may possibly induce SJS. In addition, attention should be paid to ensure prompt identification of possible drug-drug interactions, and patients should be closely monitored. Furthermore, medications should be immediately discontinued at the first sign or symptom suggesting the occurrence of drug-related SJS, and then prompt, adequate supportive care should be provided.

* *Corresponding author*. Number 123, Dapi Road, Niaosong Township, Kaohsiung County 833, Taiwan.
E-mail address: a0953283092@yahoo.com.tw (F.-J. Cheng).

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1. Introduction

The skin is the most frequent target of adverse drug reactions, probably because it is the largest organ in the body, which also enables easy detection of these reactions when they occur. Most adverse skin reactions are related to drug hypersensitivity. Therefore, drug-related adverse cutaneous reactions are frequent, affecting 2–3% of all hospitalized patients [1]. Fortunately, only approximately 2% of adverse cutaneous reactions are severe and very few are fatal. According to statistical data from the Institute for Taiwan Drug Relief Foundation [2], a total of 1218 cases reported from 1999 to 2009 could be attributed to adverse drug events, resulting in a cost of N.T. 180 million dollars.

Skin lesions were the primary adverse effect in 337 cases (67%) while Steven–Johnson syndrome (SJS) was observed in 233 cases (46%). SJS is a systemic immune reaction of erythema multiforme. Epidemiologically, the incidence rate of SJS is 1–6 persons per year per million [3,4]. SJS could be attributed to a number of things including drugs, infections, malignant cancers, idiosyncratic characteristics, and food; however, the most common etiology is drug-induced adverse reactions (>50%) [5]. The high-risk factors for SJS include advanced age, frequent readmissions, immune dysfunction diseases, and a combination of several drugs [6–8].

Patients with SJS or toxic epidermal necrolysis tend to show relatively lower N-acetylating capacity, especially in the Caucasian population [9]. Aromatic ring-containing anticonvulsant drugs such as phenytoin, carbamazepine, and phenobarbital frequently exhibit cross-hypersensitivity [10,11], as do some other drug classes such as oxicams including the nonsteroidal anti-inflammatory drugs (NSAIDs) piroxicam and tenoxicam. Therefore, care should be exercised when choosing drugs known to be high-risk SJS-inducing agents.

2. Patients and methods

2.1. Data resource

Taiwan's National Health Insurance Research Database (NHIRD), one of the largest administrative health care databases around the world, has been used widely in academic studies. The NHIRD studies expanded rapidly in both quantity and quality since the first study was published in 2000. Researchers usually collaborated to share knowledge, which was crucial to process the NHIRD data [22]. The NHIRD includes patients' demographics, disease diagnosis, contracted medical care institutions, medical expenditure, and prescription claims data. For each medical expenditure reimbursement (both outpatient and inpatient), the types of medical services, details of medical orders, and costs are recorded. All the individual identification and medical care providers (medical professionals and institutions) were removed by the Bureau of National Health Insurance before the data were transferred to the NHRI. All the related research protocols are pre-approved by the NHRI, and investigators are required to sign an agreement that guarantees patient confidentiality before conducting any study using the NHIRD data set.

2.2. Definitions of variables

The index date was defined as the date when the first skin reaction with a diagnosis of International Classification of Diseases, Ninth Revision, Clinical Modification 695.1 (ICD-9-CM code 695.1), which represents SJS, was observed in the medical records for each of the cases. The age variable was defined as the patients' age at the time of the index date. In our study, we rechecked SJS treated with medicine such as high-dose cortisone to improve SJS diagnosis correction rate.

2.3. Study designs

The study was approved by the Institutional Review Board of the Antai Tian-Sheng Memorial Hospital. A total of 111 SJS cases (ICD-9-CME-code: 695.1) were selected from the 1999–2008 Mortality Statistics File after rejecting records that included nonspecified sex and domicile information. We used a case-controlled, longitudinal, and retrospective study design, and the data from the NHIRD between 1999 and 2008 that were included in our analysis were required to meet the following criteria. Firstly, the data was limited to that of inpatients that were diagnosed with SJS and died during that period. The definition of death cases was patients whose first admission was SJS-related and then who subsequently died at that time. That is, recovery cases were not included in our study. Secondly, the included cases had specific start times for the adverse drug reactions such as SJS, following drug administration.

Therefore, the records were screened for the administration of high-risk drugs like sulfa antibiotics [sulfamethoxazole/trimethoprim (Baktar), sulfadoxine, and sulfasalazine], oxicam derivatives (piroxicam and tenoxicam), anticonvulsants (carbamazepine, phenytoin, phenobarbital, and valproate), an antigout medication (allopurinol), penicillins (amoxicillin and ampicillin), a cephalosporin (cephalexin), a macrolide (erythromycin), a fluoroquinolone (ciprofloxacin), a glycopeptide (vancomycin), tetracyclines (doxycycline and minocycline), and antitubercular medications (rifampin and ethambutol). All records of the use of these drugs were reviewed for 1 year from the beginning of the adverse drug

reactions. As for drug–drug interactions, overlapping combined use over 3 days could be considered as an interaction.

Finally, all the study variables including the drugs, frequency, and duration of drug administration, and the different branches such as the Taipei, North, Central, Southern, Pingtung, and East branches were considered. The difference between the data sets was analyzed on a year-to-year basis.

2.4. *Statistical analysis*

All patients were assessed based on the SJS mortality rate. The Chi-square tests and analysis of variance were used to compare the SJS fatality prevalence between individuals with drug–drug interaction-induced SJS/toxic epidermal necrolysis and the controls. Univariate analysis and multivariate stepwise logistic regression analyses were used to identify the risk factors for mortality, and compare the prognosis of patients who received different drug therapies. The association between highly suspected drugs and risk of SJS fatality cases was estimated using the odds ratio (OR) and the 95% confidence interval (95% CI), which were calculated with unconditional logistic regression with an adjustment for age and sex. All analyses were performed using the statistical package for the social sciences (SPSS Inc., Chicago, IL, USA) version 17.0. All statistical tests were two-sided.

3. Results

As shown in Table 1, a total of 111 cases of death including 63 men and 48 women (66.0 ± 20.0 years and 70.0 ± 17.7 years, respectively), resulting from SJS were identified by screening the Taiwan National Health Insurance databank records from 1999 to 2008. The highest and lowest number of mortality cases was 53 and three from the Taipei and Eastern divisions, respectively. Specifically, the mortality prevalence rates were higher in 2007 and 2008 than they were during other years. Most patients were emergently admitted, with hospital stays lasting for 14–15 days on average before their deaths. The drug cost per patients who died increased in 2000 resulting in an increase in total drug costs. Furthermore, over 20% of patients experienced drug–drug interactions before their last admission, including those who were administered allopurinol at least 3 months prior (Table 2; $p = 0.025$). Of these fatalities, the most highly suspected SJS-inducing drugs such as Baktar, piroxicam, tenoxicam, phenobarbital, cephalexin, vancomycin, doxycycline, and minocycline showed an incidence rate of drug–drug combinations that was considerably lower than 10%. Therefore, drug–drug interactions were less likely to lead to SJS-induced mortality. In contrast, SJS appeared to occur following a single use of some agents including carbamazepine, Baktar, sulfadoxine, phenytoin, and ampicillin with five, seven, three, three, and three cases, respectively (31.2%, 43.7%, 18.7%, 18.7%, and 18.7%, respectively, $p = 0.000$). Surprisingly, regarding drug–drug interactions, we found that combinations including allopurinol and ampicillin ($p = 0.049$), carbamazepine and Baktar ($p < 0.000$), carbamazepine and phenytoin ($p < 0.000$), Baktar and phenytoin ($p = 0.015$), sulfadoxine and piroxicam ($p = 0.045$), phenobarbital and cephalexin ($p < 0.000$), ampicillin and erythromycin ($p < 0.000$), erythromycin and minocycline ($p < 0.000$) versus vancomycin and ethambutol ($p < 0.000$) were administered 1 month before the deaths of these patients (Table 3).

The individual end points of the sex- and age-adjusted univariate and multivariate analyses revealed that patients who were administered cephalexin had the highest risk of death resulting from SJS complications (Table 4; OR 13.429, 95% CI 1.141–158.006, $p = 0.009$). In addition, minocycline (OR 13.429, 95% CI 1.141–158.006, $p = 0.009$), followed by Baktar (OR 11.537, 95% CI 3.182–41.829, $p = 0.000$) and allopurinol (OR 3.318, 95% CI 1.116-9.867, $p = 0.025$) had significantly high incidences of SJS-induced mortality.

For comparison of the differences in the area under the curve (AUC), a receiver operating characteristic curve was used. Based on the receiver operating characteristic curve, allopurinol was the best option for reducing SJS-induced deaths with the highest accuracy; the sensitivity and specificity were 88.3% and 80.9%, respectively, with an AUC of 0.88 (Fig. 1). The AUC values for other drugs were 0.77%, 0.74%, and 0.60% for cephalexin, minocycline, and Baktar, respectively, while their sensitivities and specificities were 77.3% and 82.9%, 82.4%, 77.1%, 70.9%, and 72.1%, respectively.

Table 1 – Baseline characteristics of 111 Stevens–Johnson syndrome-induced mortality cases from 1999 to 2008 in the National Health Insurance databank.

Yr	Cases	Age (yr; mean ± SD)	D of acute admission (mean ± SD)	D of chronic admission (mean ± SD)	Total annual cost (N.T. dollars/per person)	Total annual drug cost (N.T. dollars/per person)
1999	8	67.0 ± 28.8	14.4 ± 7.5	0 ± 0	164,901,0000	35,645,2500
2000	6	57.2 ± 27.9	23.1 ± 26.1	0 ± 0	522,811,6667	155,461,5556
2001	8	62.5 ± 24.6	8.4 ± 9.4	0 ± 0	111,582,2500	24,568,8750
2002	8	56.3 ± 28.5	13.7 ± 12.0	0 ± 0	209,861,6154	65,318,2308
2003	6	66.2 ± 24.1	19.0 ± 6.3	0 ± 0	351,826,1667	97,085,6667
2004	12	65.4 ± 21.7	14.3 ± 11.5	0 ± 0	264,409,0769	78,058,1538
2005	12	68.7 ± 14.3	15.2 ± 16.2	0.4 ± 1.1	194,497,5714	47,730,3571
2006	5	75.4 ± 8.8	15.8 ± 13.1	0 ± 0	214,781,7778	51,899,2222
2007	20	70.3 ± 13.5	15.5 ± 14.0	1 ± 4.4	156,656,0714	39,664,5714
2008	26	75.0 ± 14.6	14.4 ± 12.8	0 ± 0	167,165,0294	33,776,9706
Total	111	68.2 ± 19.7	14.8 ± 13.8	0.2 ± 2.0	205,599,1342	52,932,2685

SD = standard deviation.

Table 2 – Clinical features of 111 patient death cases.

Characteristics	Total cases N (%)[a]	Drug–drug interaction N (%)[a]	Nondrug –drug interaction N (%)[a]	p
Sex				
Male	63 (56.7)	55 (57.9)	8 (50.0)	0.555
Female	48 (43.2)	40 (42.1)	8 (50.0)	
Age (yr)				
<65	30 (27.0)	26 (27.4)	4 (25.0)	0.844
≥65	81 (73.0)	69 (72.6)	12 (75.0)	
Allopurinol				
No	81 (73.0)	73 (76.8)	8 (50.0)	0.025*
Yes	30 (27.0)	22 (23.2)	8 (50.0)	
Carbamazepine				
No	106 (95.5)	95 (100.0)	11 (68.8)	0.0001**
Yes	5 (4.5)	0 (0)	5 (31.2)	
Baktar				
No	98 (88.3)	89 (93.7)	9 (56.3)	0.0001**
Yes	13 (11.7)	6 (6.3)	7 (43.7)	
Sulfadoxine				
No	108 (97.3)	95 (100.0)	13 (81.3)	0.0001**
Yes	3 (2.7)	0 (0)	3 (18.7)	
Piroxicam				
No	110 (99.1)	94 (98.9)	16 (100.0)	0.680
Yes	1 (0.9)	1 (1.1)	0 (0)	
Tenoxicam				
No	110 (99.1)	94 (98.9)	16 (100.0)	0.680
Yes	1 (0.9)	1 (1.1)	0 (0)	
Phenytoin				
No	108 (97.3)	95 (100.0)	13 (81.3)	0.0001**
Yes	3 (2.7)	0 (0)	3 (18.7)	
Phenobarbital				
No	109 (98.2)	94 (98.9)	15 (93.8)	0.148
Yes	2 (1.8)	1 (1.1)	1 (6.2)	
Ampicillin				
No	108 (97.3)	95 (100.0)	13 (81.3)	0.0001**
Yes	3 (2.7)	0 (0)	3 (18.7)	
Cephalexin				
No	108 (97.3)	94 (98.9)	14 (87.5)	0.009*
Yes	3 (2.7)	1 (1.1)	2 (12.5)	
Erythromycin				
No	110 (99.1)	95 (100.0)	15 (93.8)	0.014*
Yes	1 (0.9)	0 (0)	1 (6.2)	
Vancomycin				
No	106 (95.5)	92 (96.8)	14 (87.5)	0.096
Yes	5 (4.5)	3 (3.2)	2 (12.5)	
Doxycycline				
No	109 (98.2)	94 (98.9)	15 (93.8)	0.148
Yes	2 (1.8)	1 (1.1)	1 (6.2)	
Minocycline				
No	108 (97.3)	94 (98.9)	14 (87.5)	0.009*
Yes	3 (2.7)	1 (1.1)	2 (12.5)	
Ethambutol				
No	110 (99.1)	95 (100.0)	15 (93.8)	0.014*
Yes	1 (0.9)	0 (0)	1 (6.2)	

*$p < 0.05$.
**$p < 0.0001$.
[a] All data were statistical analyzed using Chi-square tests.

Table 3 – Drug–drug interactions.

	Allopurinol[a]	Carbamazepine[a]	Sulfamethoxazole/TMP[a]	Sulfadoxine[a]	Piroxicam[a]	Tenoxicam[a]	Phenytoin[a]	Phenobarbital[a]
Allopurinol	—	$p = 0.695$	$p = 0.782$	$p = 0.783$	$p = 0.695$	$p = 0.167$	$p = 0.695$	$p = 0.308$
Carbamazepine	$p = 0.695$	—	$p = .0001^*$	$p = 0.662$	$p = 0.697$	$p = 0.848$	$p = 0.0001^*$	$p = 0.785$
Sulfamethoxazole/TMP	$p = 0.782$	$p = 0.0001^*$	—	$p = 0.409$	$p = 0.463$	$p = 0.717$	$p = 0.015^*$	$p = 0.607$
Sulfadoxine	$p = 0.783$	$p = 0.662$	$p = 0.409$	—	$p = 0.045^*$	$p = 0.829$	$p = 0.662$	$p = 0.759$
Piroxicam	$p = 0.695$	$p = 0.697$	$p = 0.463$	$p = 0.045^*$	—	$p = 0.848$	$p = 0.697$	$p = 0.785$
Tenoxicam	$p = 0.167$	$p = 0.848$	$p = 0.717$	$p = 0.829$	$p = 0.848$	—	$p = 0.848$	$p = 0.893$
Phenytoin	$p = 0.695$	$p = 0.0001^*$	$p = 0.015^*$	$p = 0.662$	$p = 0.697$	$p = 0.848$	—	$p = 0.785$
Phenobarbital	$p = 0.308$	$p = 0.785$	$p = 0.607$	$p = 0.759$	$p = 0.785$	$p = 0.893$	$p = 0.785$	—
Ampicillin	$p = 0.049^*$	$p = 0.601$	$p = 0.324$	$p = 0.557$	$p = 0.601$	$p = 0.797$	$p = 0.601$	$p = 0.714$
Cephalexin	$p = 0.695$	$p = 0.697$	$p = 0.463$	$p = 0.662$	$p = 0.697$	$p = 0.848$	$p = 0.697$	$p = 0.0001^*$
Erythromycin	$p = 0.473$	$p = 0.848$	$p = 0.717$	$p = 0.829$	$p = 0.848$	$p = 0.925$	$p = 0.848$	$p = 0.893$
Vancomycin	$p = 0.962$	$p = 0.630$	$p = 0.364$	$p = 0.588$	$p = 0.630$	$p = 0.812$	$p = 0.630$	$p = 0.736$
Doxycycline	$p = 0.308$	$p = 0.785$	$p = 0.091$	$p = 0.759$	$p = 0.785$	$p = 0.893$	$p = 0.785$	$p = 0.848$
Minocycline	$p = 0.695$	$p = 0.697$	$p = 0.463$	$p = 0.662$	$p = 0.697$	$p = 0.848$	$p = 0.697$	$p = 0.785$
Ethambutol	$p = 0.167$	$p = 0.848$	$p = 0.717$	$p = 0.829$	$p = 0.848$	$p = 0.925$	$p = 0.848$	$p = 0.893$

*$p < 0.05$.
TMP = trimethoprim.
[a] All data were tested using analysis of variance.

4. Discussion

Our study is the first population-based, nested case-control study using a data set of 111 SJS-induced fatality patients

Table 4 – Univariate and multivariate methods (sex- and age-adjusted).

Items	Odds ratio[a]	95% CI[a]	*p* (univariate)	*p* (multi-variate)
Sex	1.375	0.476–3.974	0.047	0.560
Age	1.130	0.334–3.822	0.570	0.845
Allopurinol	3.318	1.116–9.867	0.013*	0.025*
Carbamazepine	0.104	0.059–0.182	0.493	0.0001*
Baktar	11.537	3.182–41.829	0.0001*	0.0001*
Sulfadoxine	0.120	0.072–0.200	0.0001*	0.0001*
Piroxicam	0.855	0.791–0.923	0.605	0.683
Tenoxicam	0.855	0.791–0.923	0.605	0.683
Phenytoin	0.120	0.072–0.200	0.047	0.0001*
Phenobarbital	6.267	0.372–105.648	0.549	0.151
Ampicillin	1.200	0.131–10.999	0.606	0.873
Cephalexin	13.429	1.141–158.006	0.0001*	0.009*
Erythromycin	0.136	0.085–0.218	0.060	0.014*
Vancomycin	4.381	0.672–28.581	0.881	0.097
Doxycycline	6.267	0.372–105.648	0.003*	0.151
Minocycline	13.429	1.141–158.006	0.303	0.009*
Ethambutol	0.136	0.085–0.218	0.0001*	0.014*

*$p < 0.05$ was significant.
All data were tested using unconditional logistic regression; CI = confidence interval.

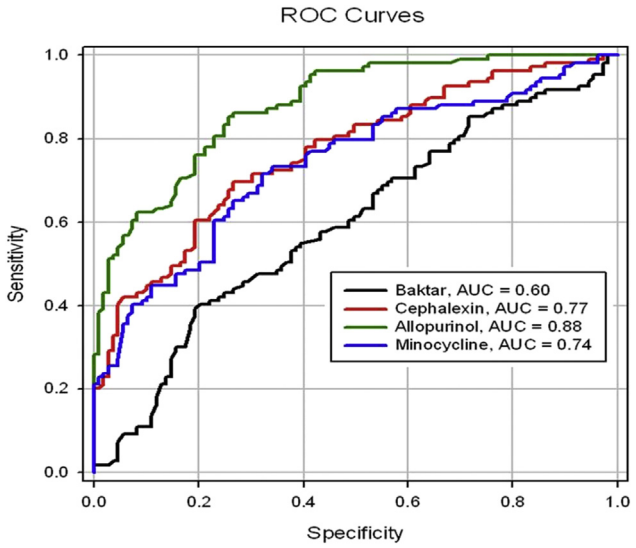

Fig. 1 – Receiver operating characteristics curve for diagnosis of high-risk Stevens–Johnson syndrome-inducing drugs. Receiver operating characteristics of allopurinol, cephalexin, minocycline, and Baktar are shown. Allopurinol has a sensitivity of 0.883 and specificity of 0.809 and, therefore, could be considered to exhibit most risk for inducing SJS. AUC = area under the curve; ROC = receiver operating characteristics.

with their complete prescriptions and diagnoses over a 10-year period. Based on this extensive data sample, we were able to include enough patients from the same population with incidences of SJS to examine the exposure to high-risk drugs, especially allopurinol and cephalexin. We found that with modified effects from age or sex, allopurinol, cephalexin, minocycline, and Baktar were associated with higher risks of SJS in patients than the other drugs were. The relationship between allopurinol and SJS is more established [12] than that of the other drugs. Moreover, our finding provides evidence to support a relationship between the single-use of allopurinol and SJS. The issue of drug–drug interaction has emerged as a cause of increasing concern because of the increased likelihood of combined drug treatment for numerous patients. We analyzed the risks of the multiple combinations including allopurinol and ampicillin, carbamazepine and Baktar, carbamazepine and phenytoin, Baktar and phenytoin, sulfadoxine and piroxicam, phenobarbital and cephalexin, ampicillin and erythromycin, erythromycin and minocycline, and vancomycin and ethambutol. As for combined exposure and then increasing SJS incidence rate in a study by Lawrence and Dahl [21], seven patients were treated with low dose of methotrexate and NSAIDs for psoriatic plaque and pre-existing dermatitis. However, the fact that fewer patients were exposed to these combinations in our study might explain the contrast between our results and those of a recent study in Taiwan. The results of that study, which involved the analysis of increased risk of skin reactions following the administration of a combination of the two mood stabilizers, implied that lamotrigine, similar to carbamazepine and valproate may cause SJS. In addition, co-administration with valproate may further increase the risk [13,14]. Surprisingly, we did not find an increased risk of SJS for the use of carbamazepine, which is the drug most known to induce SJS [4,15–19].

A European study examining the risk of SJS with some antipyretics and analgesics such as NSAIDs (salicylates) and acetaminophen across several countries revealed mixed results [20]. Our finding that there is a significant association between piroxicam and SJS independent of sulfadoxine supports the case-control study. Furthermore, we found significant risks with the single use of allopurinol, cephalexin, minocycline, and Baktar possibly resulting in SJS.

5. Conclusion

Based on the results of our analysis, we strongly recommend that caution should be exercised in the use of any drugs that may possibly induce SJS. In addition, patients administered these suspected drugs should be observed and monitored for possible drug–drug interactions. Furthermore, the suspected medications should immediately be discontinued at the first signs of SJS, and supportive care should be provided promptly. In particular, patients who have experienced SJS should avoid future contact with the implicated drugs.

Conflicts of interest

The authors have nothing to disclose.

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