MAJOR ARTICLE

Severe Cutaneous Adverse Reactions Related to Systemic Antibiotics

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Background. Systemic antibiotics are a major cause of severe cutaneous adverse reactions (SCARs). The selection of alternative antibiotics and management for SCARs patients with underlying infections can be challenging.

Methods. We retrospectively analyzed 74 cases of SCARs, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug rash with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP), related to use of systemic antibiotics in Taiwan from January 2006 to January 2012. We analyzed the causative antibiotics, clinical features, organ involvements, and mortality. We also assessed patient tolerability to alternative antibiotics after the development of antibiotic-related SCARs.

Results. The most common causes of SCARs were penicillins and cephalosporins for SJS/TEN and AGEP; glycopeptides for DRESS. Fatality was more frequent in the SJS/TEN group. In patients with SJS/TEN, higher mortality was associated with old age and underlying sepsis before the development of SCARs. The majority of patients with penicillin- or cephalosporin-related SCARs were able to tolerate quinolones, glycopeptides, and carbapenems.

Conclusions. Complicated underlying conditions and infections may increase mortality in patients with antibiotic-related SCARs. The selection of structurally different alternative drugs is important to avoid recurrence.

Keywords. SCARs; systemic antibiotics.

The occurrence of severe cutaneous adverse reactions (SCARs), such as Stevens-Johnson syndrome (SJS), toxic epidermal necrosis (TEN), acute generalized exanthematous pustulosis (AGEP), and drug rash with eosinophilia and systemic symptoms (DRESS), occurs in association with various medications, including some common antibiotics. SJS and TEN are occasionally life-threatening SCARs [1]. Although their incidence is low, SJS and TEN can result in disability or death, with a mortality rate of 10%–40% [2, 3]. DRESS, or drug-induced hypersensitivity syndrome, is characterized by generalized maculopapular eruptions or erythroderma, high fever, lymphadenopathy, eosinophilia, atypical lymphocytes, and visceral involvement; it has a mortality rate of approximately 10% [4]. Acute generalized exanthematous pustulosis (AGEP) is characterized by the sudden occurrence of dozens to hundreds of sterile, nonfollicular, pinhead-sized pustules arising on an edematous erythema. The rash is commonly accentuated in the main folds. Additional skin symptoms can comprise facial edema and unspecific lesions such as purpura, "atypical" targets, blisters, or vesicles. SCARs are T-cell–mediated delayed hypersensitivity reactions. The T-cell–meditated reactions in drug hypersensitivity have been further subclassified according to their distinct clinical presentations and cytokine production, such as increased interleukin (IL) 5 expression in DRESS and elevated IL-8 expression in AGEP, and the participation of different effector cells, such as increased eosinophil

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numbers in DRESS, higher cytotoxic T-cell counts in SJS/TEN, and elevated neutrophil numbers in AGEP, which further cause inflammation and tissue damage [5]. Furthermore, our recent findings revealed that the release of large amounts of granulysin, an extremely potent cytolytic cytokine, from cytotoxic T cells or natural killer cells plays a major role in the widespread destruction of epithelium that characterizes SJS/TEN [6].

Antibiotic-related cutaneous drug reactions represent a common cause of dermatological consultations among hospitalized patients, and it is difficult to verify the major culprit antibiotic because of the concomitant use of multiple systemic antibiotics. Antibiotic allergy may present as immediate or delayed hypersensitivity reactions. Immediate reactions are usually immunoglobulin E (IgE) mediated, whereas SCARs are T-cell–mediated delayed hypersensitivity reactions. With the availability of newer systemic antibiotics and frequent combined antibiotic use for severe infection or sepsis, the appropriate selection of alternative antibiotics for treating antibiotic-related SCARs in patients with underlying infections represents a challenge for physicians. Epidemiologic studies of new systemic antibiotic-related SCARs with large sample sizes have not been conducted. In this study, we retrospectively enrolled patients with SJS, TEN, AGEP, or DRESS in Taiwan over a 6-year period. We analyzed the clinical data of these SCARs associated with the administration of systemic antibiotics. We followed up and analyzed the subsequent alternative antibiotics used for patients after the SCAR episodes.

MATERIALS AND METHODS

Study Design and Study Population

We collected the clinical information of patients with antibiotic-related SCARs, including SJS, TEN, AGEP, and DRESS, from January 2006 to January 2012 at Chang Gung Memorial Hospital in Taiwan. A total of 528 patients with antibiotic-related cutaneous adverse reactions were included in our cutaneous adverse drug reaction registration database, which contained clinical information of diagnosis, photographs, pathologic reports of skin biopsy, assessment of causality, and laboratory investigations. All cases were diagnosed by dermatologists.

Patient Recruitment and Definition

A consensus definition of SJS/TEN (refers to the collection of SJS, SJS-TEN overlap, and TEN) was applied to diagnose the patients. SJS is characterized by widespread macules or blisters with skin detachment of <10% of the body surface area (BSA). Skin detachment between 10% and 29% of the BSA is categorized as SJS-TEN overlap, and TEN is defined by widespread macules or blisters with skin detachment affecting >30% of the BSA or skin detachment of at least 10% of the BSA without macules (Figure 1). The recruitment of patients with DRESS was performed to the criteria proposed by the European Registry of Severe Cutaneous Adverse Reactions [4, 7]. The inclusion criteria were a suspected drug reaction with an acute skin rash, involvement of at least 1 internal organ, one blood abnormality, and a fever >38°C. The patients who met 3 or more of the aforementioned criteria and who represented probable or definite cases of DRESS were included in the study (Figure 1). The recruitment of patients with AGEP was conducted according to the criteria proposed by the EuroSCAR study group. The AGEP validation score includes morphology, clinical course, and histology findings [8]. All patients were diagnosed and followed up by dermatologists at our hospital.

Drug Causality Assessment

Two methods, the Naranjo algorithm [9] and the algorithm of drug causality assessment for SJS/TEN (ALDEN) [10], were applied to determine the causality of the suspected adverse drug reactions. In brief, the assessment scores include the patients' prior drug reaction history, clinical manifestations of typical drug reactions, chronology or temporal relationships between drug use and the onset of reaction, rechallenge, dechallenge, or improvement after discontinuation of the suspected drugs, and the notoriety of the suspected drugs. The patients with an ALDEN score ≥4, as well as a Naranjo algorithm ≥5 (for SJS and TEN) or a Naranjo algorithm score ≥5 (for AGEP and DRESS), were recruited into this study. The clinical courses, causative antibiotics, time from drug intake to the onset of symptoms (latent period), the extent of organ involvement, complications, treatment, outcomes, and mortality were analyzed. The tolerability of alternative antibiotics was evaluated in patients after antibiotic-related SCAR episodes.

Laboratory Investigations and Organ Involvements

We collected patients' laboratory data and clinical presentations and determined that the liver, kidneys, gastrointestinal tract, and eyes were often involved in the SCARs. Hepatitis was defined as a 2-fold increase from the normal or baseline level of serum glutamic oxaloacetic transaminase, glutamic pyruvate transaminase (GPT), or total bilirubin. An acute kidney injury was defined as >1.5-fold elevation in serum creatinine levels from the normal range of creatinine values. The eye sequelae were judged based on the occurrence of corneal ulcers or symblepharon.

Mortality Assessment

We used the SCORTEN (score of toxic epidermal necrosis) to evaluate the expected mortality rate relative to the observed mortality rate for patients with SJS/TEN. The expected mortality rate predicted by using the SCORTEN score was calculated by using the following formula as described previously [11]: P (death) = elogit/1 + elogit [logit = −4.448 + 1.237(SCORTEN)].

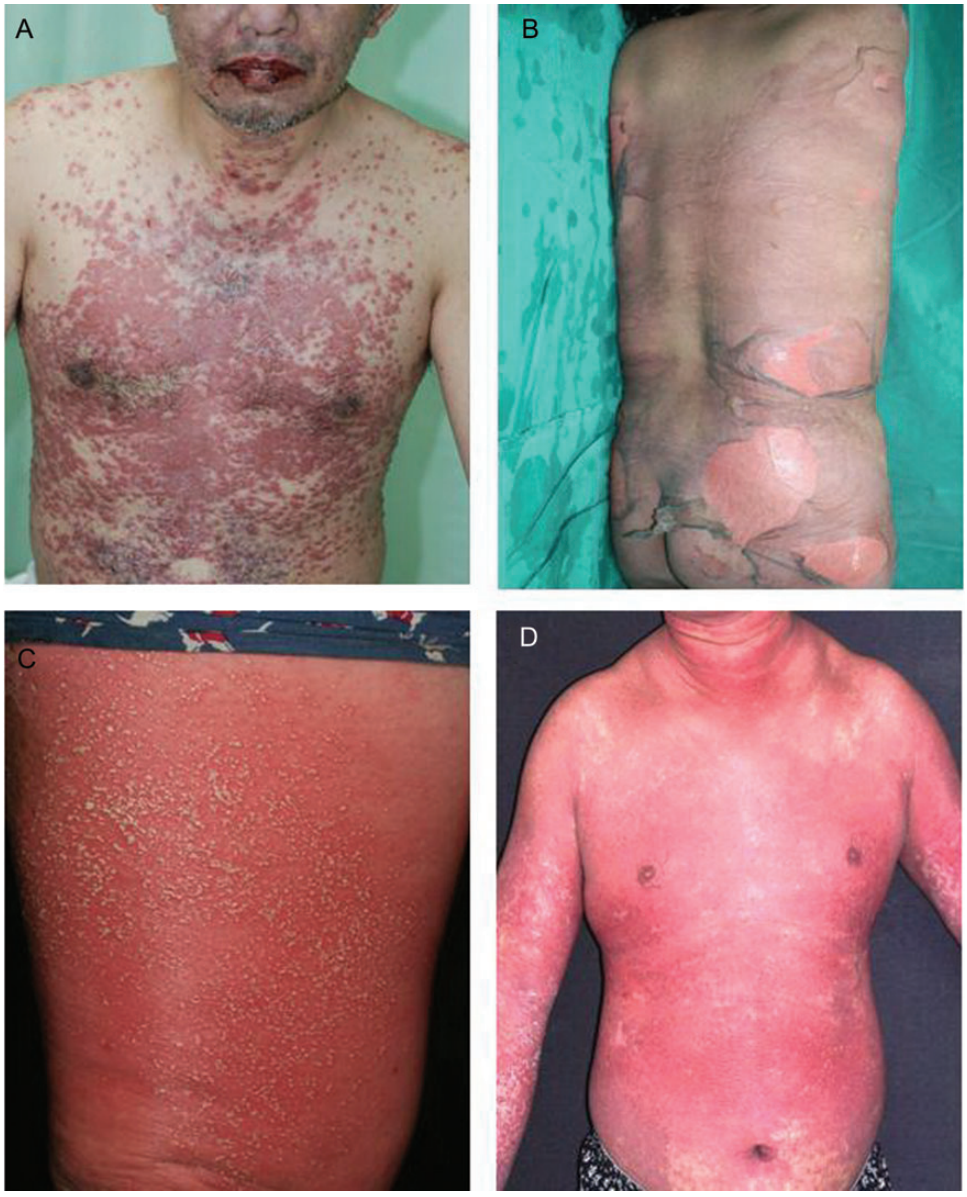

Figure 1. Clinical presentations of severe cutaneous adverse drug reactions. *A*, Typical case of Stevens-Johnson syndrome typified by widespread purpuric to blistering skin lesions with mucosal erosions. *B*, Typical case of toxic epidermal necrosis exhibited by large skin detachment exceeding 30% of the body surface area. *C*, Case of acute generalized exanthematous pustulosis typified by multiple pinhead-sized nonfollicular pustules on an edematous erythematous base. *D*, Case of drug rash with eosinophilia and systemic symptoms denoted by extensive and infiltrated erythema on the trunk and limbs with facial edema and neck lymphadenopathy.

The Charlson comorbidity index was applied to deceased patients with comorbid conditions.

RESULTS

Causative Antibiotics for SCARs

Among the 528 patients with antibiotic-related cutaneous adverse reactions, 74 had antibiotic-related SCARs, including 37 cases of SJS/TEN (25 of SJS or SJS-TEN overlap and 12 of TEN), 12 of AGEP, and 25 of DRESS. We categorized the most frequently prescribed antibiotics into 6 groups (penicillins, cephalosporins, quinolones, glycopeptides, trimethoprim-sulfamethoxazole, and others) and recorded the concomitant use of multiple antibiotics (Table 1). In the 4 groups of SCARs, SJS or SJS-TEN overlap, TEN, AGEP, and DRESS accounted for 33.8%, 16.2%, 16.2%, and 33.8%, respectively, of the antibiotic-related SCARs. In our study, penicillins were the most frequent causative antibiotic class for SJS or SJS-TEN

Table 1. Causative Antibiotics, Demographic Data, and the Latent Period of the Recruited Patients With Severe Cutaneous Adverse Reactions

	Phenotypes, No. (%)			
Culprit Drug and Patients' Characteristics	SJS or SJS-TEN, 25 (33.8)	TEN, 12 (16.2)	AGEP, 12 (16.2)	DRESS, 25 (33.8)
Culprit drug, No. (%)				
Penicillins[a]	9 (36)	4 (33.3)	5 (41.7)	2 (8)
Cephalosporins[b]	5 (20)	3 (25)	4 (33.3)	5 (20)
Quinolones[c]	2 (8)	2 (17)	1 (12.5)	0 (0)
Glycopeptides[d]	3 (12)	1 (12.5)	1 (12.5)	12 (48)
Trimethoprim-sulfamethoxazole	3 (12)	1 (12.5)	0 (0)	0 (0)
Other(s)[e]	2 (8)	0 (0)	0 (0)	2 (8)
Multiple drugs[f]	1 (4)	1 (12.5)	1 (12.5)	4 (16)
Age, y, mean ± SD	56.4 ± 24	53.8 ± 24.9	51.8 ± 23.5	52.8 ± 19.1
Sex, M/F	10/15	5/7	4/8	17/8
Latent period before onset of SCARs, d, mean ± SD (range)	6.52 ± 4.59 (3–17)	5 ± 3.52 (2–12)	4.67 ± 3.23 (2–12)	11.3 ± 8.20 (3–32)

Abbreviations: AGEP, acute generalized exanthematous pustulosis; DRESS, drug rash with eosinophilia and systemic symptoms; SCAR, severe cutaneous adverse drug reaction; SD, standard deviation; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrosis.

[a] Penicillins included penicillin G (n = 1), oxacillin (n = 3), aminopenicillins (n = 7), amoxicillin-clavulanic acid (n = 7), and piperacillin-tazobactam (n = 2).

[b] Cephalosporins included first-generation cephalosporins (cefazolin [n = 5], cephradine [n = 1], cefadroxil [n = 1], cephalexin [n = 2]); second-generation cephalosporins (cefaclor [n = 1], cefuroxime [n = 2]), and third-generation cephalosporins (ceftriaxone [n = 5]).

[c] Quinolones included norfloxacin (n = 1), ciprofloxacin (n = 2), levofloxacin (n = 1), and moxifloxacin (n = 1).

[d] Glycopeptides included vancomycin (n = 15) and teicoplanin (n = 2).

[e] Others included clindamycin (n = 1), monobactam (n = 1), carbapenems (n = 1), and rifampicin (n = 1).

[f] Concomitant use of multiple antibiotics.

overlap, TEN, and AGEP; glycopeptides were the most frequent cause of DRESS. Cephalosporins were the second-most common cause of all 4 SCARs types in this study. We were unable to determine the culprit drugs in 7 cases because of the simultaneous use of multiple (≥2) antibiotics. The average latent period of antibiotic exposure for SCARs was 6.52 ± 4.59, 5 ± 3.52, 4.67 ± 3.23, and 11.3 ± 8.20 days for SJS, TEN, AGEP, and DRESS, respectively.

Average Dosages and Latent Period of Glycopeptide-Related SCARs

Of the 17 cases of glycopeptide-related SCARs, 15 were related to vancomycin, whereas 2 were related to teicoplanin (Table 2). The latent period for vancomycin was 14.47 ± 6.75 days, and that for teicoplanin was 13.00 ± 4.24 days; the average daily doses were 1511.1 ± 822.5 mg of vancomycin and 400 ± 0 mg of teicoplanin. In the vancomycin-related SCAR group, 3 patients had chronic renal insufficiency, and the antibiotic dosage was adjusted according to the creatinine clearance level (Table 2).

Organ Involvement

Of the total 74 antibiotic-related SCARs, the liver (36.5%) was the most frequently involved organ, and kidney injury, gastrointestinal bleeding, and eye sequelae occurred in 18.9%, 10.8%, and 5.4% of patients, respectively (Table 3). Eye sequelae were found in 10.8% of patients in the SJS/TEN group. The AGEP group displayed less organ involvement, excluding the liver (8.3%). Comparing the frequency of organ involvement between SJS/TEN and DRESS, patients with SJS/TEN had a frequency of gastrointestinal bleeding (16.2%), and patients with

Table 2. Average Dosage, Latent Periods, Underlying Chronic Renal Failure, and Mortality of Vancomycin- and Teicoplanin-Related Severe Cutaneous Adverse Reactions

Culprit Drug	SJS/TEN	DRESS	AGEP	Exposure Duration, d, Mean ± SD	Daily Dose, mg, Mean ± SD	Underlying CRF	Mortality
Vancomycin (n = 15)	3	11	1	14.47 ± 6.75	1511.1 ± 822.5	3	2
Teicoplanin (n = 2)	1	1	0	13.00 ± 4.24	400 ± 0	0	0

Abbreviations: AGEP, acute generalized exanthematous pustulosis; CRF, chronic renal failure; DRESS, drug rash with eosinophilia and systemic symptoms; SD, standard deviation; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrosis.

Table 3. Related Organ Involvements in Patients With Antibiotic-Related Severe Cutaneous Adverse Reactions

Organ Involvement	Phenotypes, No. (%)			
	SJS/TEN, 37 (50)	AGEP, 12 (16.2)	DRESS, 25 (33.8)	Total, 74
Hepatitis[a]	6 (16.2)	1 (8.3)	20 (80)	27 (36.5)
GPT, IU/L				
<100	3 (8.1)	0 (0)	7 (28)	10 (13.5)
100–300	2 (5.4)	1 (8.3)	10 (40)	13 (17.6)
>300	1 (2.7)	0 (0)	3 (12)	4 (5.4)
Acute kidney injury[b]	3 (8.1)	0 (0)	11 (44)	14 (18.9)
GI bleeding	6 (16.2)	0 (0)	2 (8)	8 (10.8)
Eye sequelae[c]	4 (10.8)	0 (0)	0 (0)	4 (5.4)

Abbreviations: AGEP, acute generalized exanthematous pustulosis; DRESS, drug rash with eosinophilia and systemic symptoms; GI, gastrointestinal; GPT, glutamic pyruvate transaminase; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrosis.

[a] Hepatitis was defined as a 2-fold increase from normal or baseline levels of serum glutamic oxaloacetic transaminase, GOT, glutamic pyruvate transaminase, GPT, or total bilirubin.

[b] An acute kidney injury was defined as a >1.5-fold elevation of serum creatinine from the normal range of creatinine levels.

[c] Complications of corneal ulcer or symblepharon.

Table 4. Treatment and Prognosis of Antibiotic-Related Severe Cutaneous Adverse Reactions

Antibiotic-Related SCARs, No. (%) Subgroup of SCARs, n (%)	Treatment Group, Fatalities, No. (%)		
	Corticosteroids	Supportive Care	IVIG
SJS or SJS-TEN, 25	16	9	0
Mortality rate: 20%	2 (12.5)	3 (33.3)[a]	
TEN, 12	7	4	1
Mortality rate: 66.7%	4 (57.1)	3 (75)[b]	1 (100)
AGEP, 12	9	3	0
Mortality rate: 0 %	0 (0)	0 (0)	
DRESS, 25	20	5	0
Mortality rate: 12 %	3 (15)	0 (0)[c]	
Total, 74	9 (17.3)	6 (28.6)	1 (100)
Overall mortality: 21.6%			

Abbreviations: AGEP, acute generalized exanthematous pustulosis; DRESS, drug rash with eosinophilia and systemic symptoms; IVIG, intravenous immunoglobulin; SCAR, severe cutaneous adverse drug reaction; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrosis.

[a] Fisher exact test ($P = .312$).

[b] Fisher exact test ($P = .53$).

[c] Fisher exact test ($P = .496$).

DRESS exhibited a significantly higher frequency of liver (80%, $P = 8.4 \times 10^{-7}$, odds ratio [OR] = 20.7) and kidney (44%, $P = .0015$, OR = 8.9) damage. Furthermore, there were more cases of severe liver function impairment (GPT ≥ 300 IU/L) in the DRESS group (12%) than in the SJS/TEN group (2.7%) (Table 3).

Treatment and Prognosis of Antibiotic-Related SCARs

We separated the enrolled patients into 3 treatment groups of supportive care, corticosteroids, and intravenous immunoglobulin (IVIG) (Table 4). A large portion of patients with SCARs received corticosteroids (70.3%). In total, 28.4% of patients were managed only with supportive care, and only 1.3% of patients received IVIG. The overall mortality rate was 21.6% (16/74) among patients with antibiotic-related SCARs. Relatively higher mortality rates were observed for TEN (66.7%) and SJS or SJS-TEN overlap (20%), compared with 0% for AGEP and 12% for DRESS (Table 4). Mortality did not differ according to corticosteroid treatment or supportive care among the different SCAR subgroups. Most patients who died had underlying comorbidities, including congestive heart failure, chronic renal failure or end-stage renal disease, diabetes mellitus, and cancer (Table 5).

One case of piperacillin-tazobactam–related TEN involved inadvertent exposure to piperacillin-tazobactam 6 months after the first episode of TEN, and the patient developed more fulminant TEN (progressed into TEN in 2 days) again and died because of the second episode.

Comparison of Surviving and Deceased Patients With SJS/TEN

The mean age of the surviving and deceased patients were 48.71 ± 24.21 and 66.46 ± 19.97 years, respectively ($P < .05$) (Table 6). The average SCORTEN score of surviving patients was 1.25 (predicted mortality: 5.2%), compared with 2.77 (predicted mortality: 26.5%) for deceased patients (Table 6). In patients with SJS/TEN, higher mortality was significantly associated with underlying sepsis before the development of severe skin reactions ($P < .0001$) (Table 6). Eight of 13 patients in the deceased group (61.5%) displayed sepsis before the development of SCARs, compared with no patients (0%) in the surviving group. There was no difference in mortality according to treatment with systemic corticosteroids or supportive care ($P = .1713$; Table 6).

Safety and Tolerability of Alternative Antibiotics for Patients With Antibiotic-Related SCARs

Most of the patients with SCARs were prescribed structurally different alternative antibiotics. Among the 14 cases of penicillin-related SCARs, a quinolone was used as the alternative antibiotic, and it was well tolerated in 6 patients. Glycopeptides were used in 3 patients, cephalosporins were used in 2 patients, and carbapenems were used in 2 patients (Table 7). A patient with amoxicillin-clavulanic acid–related SJS developed maculopapular eruptions after levofloxacin use. Among the 12 cases of

Table 5. Clinical Features of Fatal Cases of Antibiotic-Related Severe Cutaneous Adverse Reactions

Phenotypes	SCORTEN of SJS/TEN Patient	Age, y/Sex	Interval Between Onset and Death, d	Charlson Comorbidity Index	Indication for Antibiotics	Causative Antibiotics	Lethal Complications	Treatment
SJS or SJS-TEN	2	71/M	21	8	BTI	Ceftriaxone	Sepsis	Supportive care
	3	68/F	5	8	UTI	Ciprofloxacin	Sepsis	Corticosteroids
	2	91/F	15	8	Pneumonia	Ciprofloxacin	Respiratory failure	Corticosteroids
	3	81/F	8	8	Pneumonia	Vancomycin	Sepsis, GI bleeding	Supportive care
	3	73/F	60	8	Pneumonia	Aztreonam	Pneumonia	Supportive care
TEN	4	77/M	4	6	Pneumonia	Piperacillin-tazobactam	Septic shock, multiple organ failure	Supportive care
	1	9/M	21	0	Acute tonsillitis	Amoxicillin	ARDS, acute renal failure	IVIG
	3	75/F	15	7	UTI	Cefadroxil	Respiratory failure	Supportive care
	2	57/F	5	7	Empyema, peritonitis	Ceftriaxone	Sepsis, massive GI bleeding	Corticosteroids
	3	65/F	13	5	UTI	Ceftriaxone	Sepsis	Supportive care
	4	74/F	6	8	UTI	TMP-SMX	Sepsis	Corticosteroids
	3	51/M	17	6	Cellulitis	Vancomycin	Sepsis	Corticosteroids
	3	72/M	12	9	Pneumonia	Levofloxacin	Sepsis, hepatic failure	Corticosteroids
DRESS		80/M	60	7	Pneumonia	Piperacillin-tazobactam	Sepsis	Corticosteroids
		46/M	18	4	AV shunt Infection	Multiple drug[a]	Massive GI bleeding	Corticosteroids
		87/F	23	7	Pneumonia	Multiple drug[b]	Sepsis	Corticosteroids

Abbreviations: ARDS, acute respiratory distress syndrome; AV, arteriovenous; BTI, biliary tract infection; DRESS, drug rash with eosinophilia and systemic symptoms; GI, gastrointestinal; IVIG, intravenous immunoglobulin; SCORTEN, score of toxic epidermal necrosis; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrosis; TMP-SMX, trimethoprim-sulfamethoxazole; UTI, urinary tract infection.

[a] Combined simultaneous use of vancomycin and ceftriaxone.

[b] Combined simultaneous use of moxifloxacin and ceftriaxone.

cephalosporin-related SCARs, penicillins were tolerated in 4 patients, quinolones were tolerated in 4 patients, and glycopeptides were tolerated in 3 patients. A patient with cefadroxil-related DRESS displayed cross-reactivity with ampicillin and developed maculopapular eruption. Among the 14 cases of glycopeptide-related SCARs, cephalosporins were tolerated in 6 patients, carbapenems were tolerated in 4, and glycopeptides were tolerated in 2. The 2 patients with vancomycin-related SCARs tolerated teicoplanin.

DISCUSSION

Among the various classes of antibiotics, β-lactams (penicillins and cephalosporins), co-trimoxazole, and quinolones are among the most common causes of antibiotic allergy [12]. Systemic antibiotic–related adverse cutaneous drug eruptions are common, and consultations regarding antibiotic-related adverse cutaneous drug reactions are frequently encountered in hospitals. In our study, penicillins were the leading cause of SJS/TEN and AGEP, and this could be related to the frequent prescription of penicillins as first-line antibiotics by physicians. Glycopeptides were the major cause of DRESS. We were unable to identify the culprit drugs in 7 cases due to the simultaneous use of multiple antibiotics. The use of multiple antibiotics often makes it difficult to determine the offending drug.

The use of systemic corticosteroids in the management of SJS/TEN remains controversial. The largest series of cases with SCARs was reported by the EuroScar study group, and it involved the retrospective analysis of 281 patients enrolled from France and Germany [13]. The study reported no significant benefits of any management method, including supportive care, IVIG, corticosteroids, or IVIG plus corticosteroids. Compared to patients with SJS/TEN, those with DRESS required longer treatment with corticosteroids. Rapidly decreasing the dose of corticosteroids may cause relapses of rashes and hepatitis in patients with DRESS [14]. The use of systemic steroids and the complicated underlying conditions of patients with antibiotic-related SCARs may increase the risk of mortality

Table 6. Comparison of the Surviving and Deceased Patients With Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis

Characteristic	Alive	Died	*P* Value
No. of patients (%)	24 (64.9%)	13 (35.1%)	
Age, y, mean ± SD	48.71 ± 24.21	66.46 ± 19.97	.0234*
SCORTEN[a], mean	1.25	2.77	.1742*
Predicted mortality[b]	5.21%	26.5%	
Sepsis before SCAR episode	0	8	<.0001**
Treatment with systemic steroid	17	6	.1713**

Abbreviations: SCAR, severe cutaneous adverse drug reaction; SD, standard deviation; SCORTEN, score of toxic epidermal necrosis.

[a] SCORTEN includes the following 7 independent predictive factors: (1) age ≥40 years, (2) presence of malignancy, (3) skin detachment of at least 10% of the body surface area, (4) heart rate of at least 120 beats/min, (5) serum glucose level exceeding 14.0 mmol/L (252 mg/dL), (6) serum bicarbonate level of <20 mmol/L (20 mEq/L), and (7) serum urea nitrogen level exceeding 9.6 mmol/L (27 mg/dL). Each factor holds equal weight in the score, giving score ranging from 0 to 7.

[b] Predicted mortality was calculated using the formula (P (death) = elogit/1 + elogit [logit = –4.448 + 1.237(SCORTEN)]) on the first day of hospitalization.

* Unpaired *t* test.

** Fisher exact test.

and morbidity. Our study observed an extremely high mortality rate (66.7%) in patients with antibiotic-related TEN, and the mortality rate was 2.3-fold higher than that predicted by using the SCORTEN (2.875). The mortality rate of patients with antibiotic-related SCARs (21.6%) was higher than our previous findings in patients with antiepileptic-related SCARs (6.49%) [15]. Sepsis was the major cause of mortality in these patients (68.8%), and sepsis was caused by underlying infections before SCAR episodes in the more than half (54.5%) of these patients. The majority of patients with antibiotic-related SCARs need alternative antibiotics to control their underlying infections; some patients require more broad-spectrum antibiotics to treat the initial infections and possible sequential skin wound infections. Because the cross-reactivity of antibiotics has been reported, the cautious selection of alternative antibiotics with structurally different drugs is essential for avoiding SCAR recurrences.

Drugs in the same class may share structural similarities and differences in side chains. The immune system reactivity to one compound of the drug class may result in cross-reactivity to related compounds. This cross-reactivity with structurally similar drugs depends on structural similarity and the precursor

Table 7. Safety and Tolerability Follow-up of Alternative Antibiotic Use in Patients With Antibiotic-Related Severe Cutaneous Acute Reactions (n = 43)

		Alternative Antibiotics Prescribed After SCAR, No.				
Type of Antibiotic, No.	Subgroup of SCARs (No.)	Quinolones, 12	Penicillins, 6	Cephalosporins, 8	Glycopeptides, 9	Carbapenems, 8
Penicillins, 14	SJS/TEN (10)	4 1 (H)[b]		2[a]	2	1
	AGEP (2)	1			1	
	DRESS (2)	1				1
Cephalosporins, 12	SJS/TEN (5)	1	1[c]		3	
	DRESS (5)	2	2[c] 1(H)[d]			
	AGEP (2)	1	1[c]			
Glycopeptides, 14	SJS/TEN (3)	1		1	1[e]	
	DRESS (10)		1	4	1[e]	4
	AGEP (1)			1		
Quinolones, 3	SJS/TEN (2)				1	1
	AGEP (1)					1

Abbreviations: AGEP, acute generalized exanthematous pustulosis; DRESS, drug rash with eosinophilia and systemic symptoms; SCAR, severe cutaneous adverse drug reaction; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrosis.

[a] Denotes a case of amoxicillin-clavulanic acid–related SJS in a patient who tolerated cefadroxil and a case of amoxicillin-related TEN in a patient who tolerated cefazolin.

[b] Denotes a case of amoxicillin-clavulanic acid–related SJS that developed into a maculopapular eruption after levofloxacin use.

[c] Denotes a case of cefazolin-related SJS in a patient who tolerated amoxicillin; a case of cefuroxime-related DRESS in a patient who tolerated Augmentin; a case of ceftriaxone-related DRESS in a patient who tolerated amoxicillin; and a case of cefazolin-related AGEP in a patient who tolerated amoxicillin.

[d] Denotes a case of cefadroxil-related DRESS in a patient with cross-reactivity to ampicillin that developed into a maculopapular eruption.

[e] Denotes cases of vancomycin-related SCARs in patients who tolerated teicoplanin.

frequency of drug-specific T cells. Drugs that differ by only an OH group induce greater cross-reactivity than drugs that differ in side-chain length. In previous studies, T-cell clones (TCCs) that reacted with amoxicillin also reacted with ampicillin, as these therapies differ only by an OH group [16], whereas only a fraction of these TCCs cross-reacted with penicillin G, with even fewer cross-reacting with piperacillin. No cross-reactivity of these amoxicillin-specific TCCs with cephalosporins was observed. However, a previous study suggested that the T-cell reactions in delayed hypersensitivity do not apply to IgE-mediated reactions [17].

For IgE-mediated reactions, previous case reports demonstrated up to a 20% incidence in cross-reactivity between penicillins and cephalosporins in vitro [18]. The reported cross-reactivity for the IgE-mediated hypersensitivity between cephalosporins and penicillins in patients with an IgE-mediated penicillin allergy of 5%–10% was based on early studies from the 1970s involving patients with a history of penicillin allergy who displayed allergic reactions to cephalexin, cephalothin, and cephaloridine [19]. These first-generation cephalosporins have side chains that are structurally similar to the benzyl penicillin, which may explain the high incidence of cross-reactivity [20]. Previous reports also revealed that penicillin can be administered safely to cephalosporin-allergic patients who have a negative skin test result to penicillin determinants [21]. However, the usefulness of a skin test of penicillin determinants for patients with cephalosporin-related SCARs is not well studied. The carbapenems, including imipenem and meropenem, contain a bicyclic nucleus with a β-lactam ring. Recent prospective studies in adults and children with penicillin (predominantly amoxicillin) IgE-mediated allergy indicated that the cross-reactivity based on positive skin tests to imipenem-cilastatin [22] and meropenem [23, 24] was 0.9%. For delayed reactions to carbapenems, the cross-reactivity with penicillins was 5.5% based on patients with a cell-mediated allergy to penicillins with positive patch test results to at least 1 penicillin reagent and imipenem-cilastatin [12]. In this study, there was no cross-reactivity observed in patients with penicillin-related SCARs who received carbapenems.

Teicoplanin and vancomycin are types of glycopeptides, and teicoplanin was suggested to cause fewer side effects than vancomycin [25]. There have been reports of cross-reactivity between individuals with vancomycin and teicoplanin allergies [26–30], but there have also been reports of patients with teicoplanin allergy who tolerated vancomycin [31, 32]. In our study, of the 12 cases of glycopeptides-related DRESS, 11 cases (91.6%) were related to vancomycin, and 1 case was related to teicoplanin. Two of the patients with vancomycin-related SCARs tolerated teicoplanin.

Despite their involvement in the same T-cell–mediated reactions, different phenotypes of T cells involved or immune mediators released in SCARs may have significant clinical effects. The T helper 2 T cells with increased expression of IL-4, IL-5, and IL-13 leads to inflammation involving eosinophils, which is the characteristic inflammatory cell type in maculopapular exanthema in response to DRESS [5]. $CD8^+$ T-cell-mediated cytotoxicity is associated with increased expression of perforin and granzyme B and the production of large amounts of granulysin, which plays a major role in the widespread destruction of epithelium, a characteristic of SJS/TEN [6].

Antibiotics may cause various types of allergic drug reactions ranging from mild to serious cutaneous reactions, organ-specific reactions, or systemic reactions [12]. Careful clinical monitoring for early sign of SCARs and immediate withdrawal of the suspected drugs are the most important steps for the management of these conditions. Systemic immunomodulatory drugs may be helpful to suppress severe cutaneous and systemic reactions; however, the underlying infectious condition of patients with SCARs may hinder the use of systemic corticosteroids. Because patients with antibiotic-related SCARs often require alternative antibiotics to control their initial and subsequent infections, the selection of structurally different alternative drugs is important for the avoidance of SCAR recurrences.

This study reports that the most frequent antibiotic causes of SCARs were penicillins and cephalosporins for SJS/TEN and AGEP and glycopeptides for DRESS. The patients with antibiotic-related SJS/TEN had a higher mortality rate than predicted by using SCORTEN. The majority of patients with penicillin- or cephalosporin-related SCARs tolerated glycopeptides and carbapenems. The complicated underlying conditions and infections may increase the risk of mortality in patients with antibiotic-related SCARs. The selection of structurally different alternative drugs is important to avoid the recurrence of SCARs.

Notes

Author contributions. W.-H. C. designed the research and interpreted data. C.-H. Y., H. S., J.-Y. L., R.-C.-Y. H., Y.-C. T., T.-S. W., C.-T. H., K.-C. K., H.-C. H., and C.-H. C. collected the cases and data. Y.-F. L., W.-H. C., and S.-I. H. drafted and wrote the manuscript.

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