International Journal of Dermatology

Report

Differences between Stevens-Johnson syndrome versus toxic epidermal necrolysis

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Conflict of interest: None.

Funding source: None.

doi: 10.1111/ijd.15287

Abstract

Background To retrospectively review the outcomes of two rare cutaneous diseases, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), and to question the practice of averaging the mortality rate on the assumption that they are one disease.

Methods A retrospective chart review of all patients diagnosed with SJS and TEN by a dermatologist between January 1, 2000, and January 1, 2020, at our institution was performed. Seventy-one patients were identified (21 pediatric and 50 adults). Pathology slides from 32 adult patients (64%) were evaluated by a blinded board-certified dermatopathologist.

Results Of the adult patients, 31 had SJS, two had SJS-TEN overlap, and 17 had TEN. All 21 patients in the pediatric group were diagnosed with SJS mainly caused by Mycoplasma. Mortality rates were 6.5% for SJS among adults and 35.3% for TEN. Chemotherapy-induced TEN is a trigger with 50% mortality.

Conclusions SJS was more common in adults and pediatric cases than TEN (3:1) and had a much better prognosis and outcome. Combining and averaging the mortality rates of TEN and SJS are not advised as SJS is mainly a mucocutaneous disorder with good prognosis versus TEN, a systemic toxicity of multiple organs with deep skin detachment.

Introduction

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are well-known dermatologic diseases that are rare, life-threatening eruptions. Both entities are considered an adverse reactive process secondary to a drug or infection. SJS is a toxicity of the mucous membranes, including oral and esophageal mucosa, eyes, and genital areas, with mild to moderate skin involvement presenting with targetoid or morbilliform eruptions and minimal skin shedding (Fig. 1). Alternatively, TEN is a severe systemic toxic reaction of multiple organ systems, including kidney, liver, and mucous membranes, with a hallmark of skin toxicity presenting with initial bulla followed by extensive skin detachment (Fig. 2) and epidermal necrosis to the dermal-epidermal junction (DEJ). The trigger is always drug related in TEN and drug or infection related in cases of SJS.

Mortality rates for SJS/TEN have been reported to be as high as 39%.[1,2] Most studies of SJS/TEN assume that SJS and TEN are a spectrum of the same disease. Overlaps between the two entities occur, and hence the tendency to treat both diseases as part of one spectrum dividing them by the extent of body surface area (BSA) of skin detachment.[3] Per the study of Bastuji-Garin *et al.*,[3] which was intended mainly to classify bullous erythema multiforme (EM) or EM major subtypes, percentages were given to the extent of BSA skin detachment. TEN was stratified as detachment more than 30% with or without skin targetoid lesions or skin erythema, and SJS was classified as <10% skin detachment. Between 10 and 30% was referred to as overlap SJS/TEN. Although Bastuji-Garin *et al.*[3] did not conclude in their classification that the two entities are of one spectrum, most studies of SJS/TEN in the literature combine and average the mortality, thus implying they are the same disease. We question this averaging of the mortality rates and find it to be misleading as the mortality rate would be increased for patients with SJS and decreased for patients with TEN.[1,2,4]

Herein we report on our data and experience from one center with 71 patients seen over the past 20 years by the same dermatology hospitalists at two major hospitals with the aim of questioning the rationale of averaging mortality rates of both diseases and to investigate our data of SJS and TEN in

The related article will be available in 10.1111/ijd.15284

Figure 1 (a–d) Representative images from a patient with SJS. Mucosal involvement is often seen in patients with SJS. (a) Oral mucosa, tongue, and lip ulcerations. (b) Lip hemorrhagic crusting. (c) Palmar targetoid lesions. (d) Eyelid and conjunctival inflammation. (e) Histopathologic feature of SJS with many apoptotic keratinocytes with vacuolar interface changes (H&E, ×10)

pediatric and adult patients with regard to any triggers, clinical presentation, treatment, and outcomes.

Methods

We performed a single center, retrospective study of patients of all ages diagnosed with SJS and TEN at the Mayo Clinic, Rochester, MN, between January 1, 2000, and January 1, 2020. Patients were identified from electronic medical record systems by the Biomedical Statistics and Informatics group. A detailed chart review was performed to identify all patients with SJS and TEN, with at least one concurrent dermatology consultation during the acute presentation with the disease.

Detailed medical information including the following parameters were extracted from the medical records: relevant demographics such as age at diagnosis, sex, medical comorbidities, disease presentation including mucosal and ophthalmic involvement and fever, causative agent of SJS and TEN, treatment, and outcomes including mortality and transfers to a burn unit for further care. Causality or trigger of SJS and TEN was determined from the clinical note(s) of the dermatologist(s) treating the patient at the time of the presentation. It was also noted whether the patient had photographic and histologic evidence of disease. Each patient was retrospectively verified to have SJS or TEN by a dermatologist using all available clinical, laboratory, and

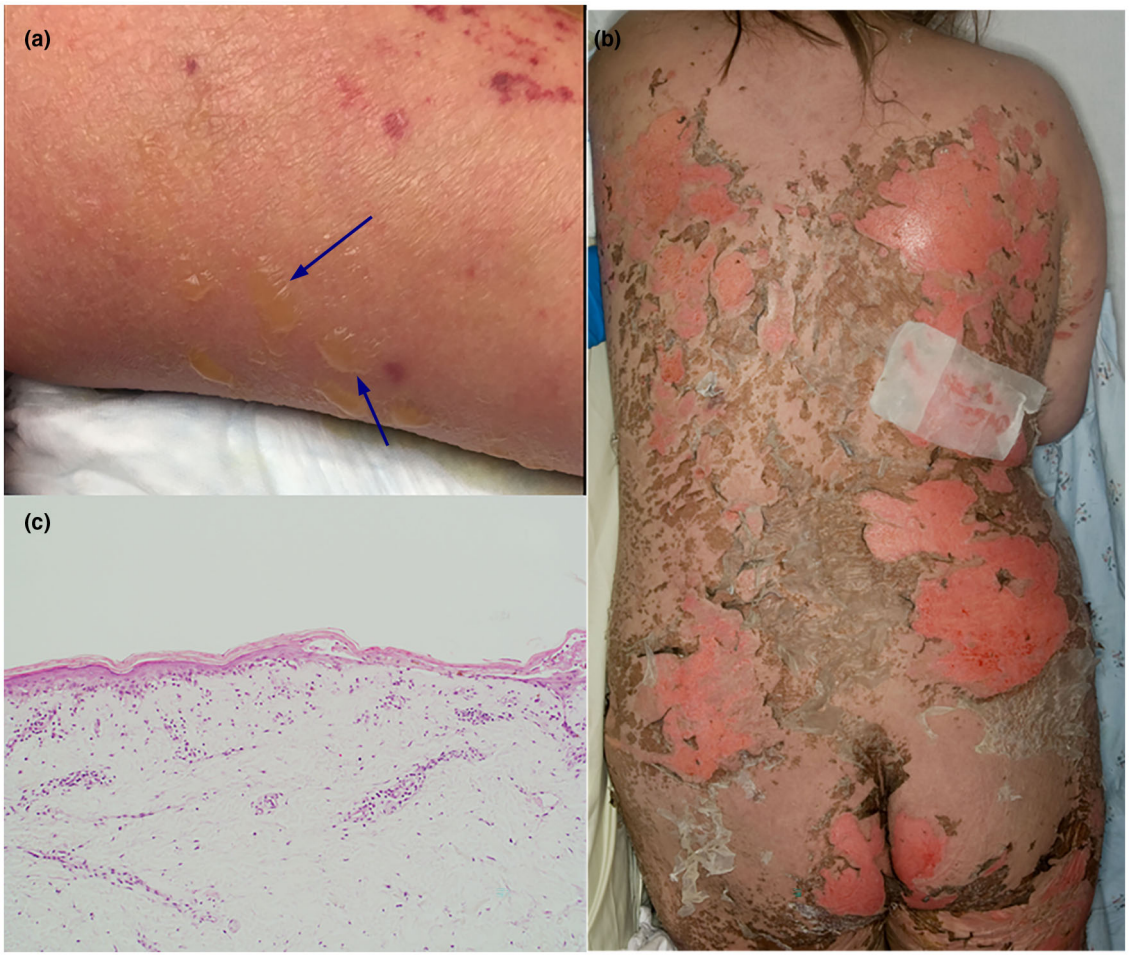

Figure 2 (a–b) Representative images from a patient with TEN. (a) Early TEN with bulla and beginning of detachment. (b) Moderate to severe skin detachment on the back and buttocks. (c) Histopathologic feature of TEN with pauci-inflammatory full-thickness epidermal necrosis (H&E, ×10)

histologic features. Available pathology slides were blindly analyzed by a board-certified dermatopathologist (without access to clinical data) for features of SJS, TEN, or both.

The patients were divided into four groups: adult patients with SJS, adult patients with TEN, adult patients with SJS-TEN, and pediatric patients with SJS only (zero TEN and SJS/TEN overlap identified in our cohort). A pediatric patient was defined as a patient <18 years of age. This study was approved by the Mayo Clinic Institutional Review Board.

Statistics

Variables were summarized as frequency (percentage) and compared between SJS and TEN groups using Fisher's exact test. All tests were two-sided with alpha level set at 0.05 for statistical significance. The analysis was done using R3.6.2 by a biostatistician in the Division of Biomedical Statistics and Informatics at Mayo Clinic.

Results

A total of 71 patients were identified in our study; 21 pediatric patients with SJS, 31 adult patients with SJS, two adult patients with SJS-TEN, and 17 adult patients with TEN (Table 1). The average age at diagnosis was approximately 42 years in adult patients with SJS, 57 years in adult patients with TEN, and 10 years in the SJS pediatric patients. SJS was more commonly diagnosed in males in both adult and pediatric patients (2:1 males to females). SJS trigger in adults was either infection or drug related, and infection only in pediatric patients. TEN trigger was always drug related.

Table 1 lists the physical findings in patients with SJS and TEN. More than 50% of patients with these cutaneous disorders had ophthalmic and mucosal involvement (Figs. 1 and 2). Most TEN patients (52.9%) presented with fever while 41.9% of adult SJS patients and 71.4% of pediatric patients had fever.

Table 1 Patient demographics, comorbidities, physical findings, treatment, and outcomes (n = 71)

	Adult patients			**Pediatric patients**
	SJS (n = 31)	**SJS-TEN overlap (n = 2)**	**TEN (n = 17)**	**SJS (n = 21)**
Characteristics				
Age (years, mean ± SD)	42.1 ± 17.7	46.5 ± 16.3	56.6 ± 18.0	10.1 ± 4.3
Sex				
Male (%, n)	61.3% (n = 19)	100.0% (n = 2)	41.2% (n = 7)	61.9% (n = 13)
Female (%, n)	38.7% (n = 12)	0.0% (n = 0)	58.8% (n = 10)	38.1% (n = 8)
Medical comorbidities				
Active malignancy (%, n)	3.2% (n = 1)	50.0% (n = 1)	29.4% (n = 5)	0% (n = 0)
Pulmonary disease (%, n)	12.9% (n = 4)	0.0% (n = 0)	29.4% (n = 5)	4.8% (n = 1)
Connective tissue disorder (%, n)	3.2% (n = 1)	0.0% (n = 0)	5.9% (n = 1)	0% (n = 0)
Diabetes mellitus (%, n)	9.7% (n = 3)	0.0% (n = 0)	17.6% (n = 3)	0% (n = 0)
Hyperlipidemia (%, n)	6.5% (n = 2)	50.0% (n = 1)	23.5% (n = 4)	0% (n = 0)
Hypertension (%, n)	25.8% (n = 8)	100.0% (n = 2)	29.4% (n = 5)	0% (n = 0)
Kidney disease (%, n)	9.7% (n = 3)	0.0% (n = 0)	17.6% (n = 3)	0% (n = 0)
Liver disease (%, n)	3.2% (n = 1)	50.0% (n = 1)	0% (n = 0)	0% (n = 0)
Mood disorder (%, n)	19.4% (n = 6)	0.0% (n = 0)	23.5% (n = 4)	0% (n = 0)
Seizure disorder (%, n)	12.9% (n = 4)	50.0% (n = 1)	0% (n = 0)	28.6% (n = 6)
Physical findings				
Ophthalmic involvement (%, n)	51.6% (n = 16)	0.0% (n = 0)	52.9% (n = 9)	76.2% (n = 16)
Mucosal involvement (%, n)	100.0% (n = 31)	100.0% (n = 2)	82.4% (n = 14)	100.0% (n = 21)
Fever (%, n)	41.9% (n = 13)	0.0% (n = 0)	52.9% (n = 9)	71.4% (n = 15)
Cause identified				
Infection (%, n)	16.1% (n = 5)	0.0% (n = 0)	0.0% (n = 0)	52.4% (n = 11)
Mycoplasma (%, n)	100.0% (n = 5)	-	-	90.9% (n = 10)
Other (%, n)	-	-	-	9.1% (n = 1)
Chemotherapy	0.0% (n = 0)	0.0% (n = 0)	23.5% (n = 4)	0% (n = 0)
Adverse drugs				
Antibiotics (%, n)	22.6% (n = 7)	100.0% (n = 2)	41.2% (n = 7)	19.0% (n = 4)
Phenytoin (%, n)	12.9% (n = 4)	0.0% (n = 0)	0.0% (n = 0)	4.8% (n = 1)
Allopurinol (%, n)	3.2% (n = 1)	0.0% (n = 0)	5.9% (n = 1)	0% (n = 0)
Lamotrigine (%, n)	22.6% (n = 7)	0.0% (n = 0)	0.0% (n = 0)	9.5% (n = 2)
NSAID/ACE inhibitors (%, n)	3.2% (n = 1)	0.0.% (n = 0)	0.0% (n = 0)	4.8% (n = 1)
Carbamazepine (%, n)	0.0% (n = 0)	0.0% (n = 0)	0.0% (n = 0)	9.5% (n = 2
Other (%, n)	12.9% (n = 4)	0.0% (n = 0)	23.5% (n = 4)	0% (n = 0)
Unknown (%, n)	6.5% (n = 2)	0.0% (n = 0)	5.9% (n = 1)	0% (n = 0)
SCORTEN on admission (mean ± SD)	-	-	2.9 ± 1.0	-
Treatment				
ICU treatment (%, n)	25.8% (n = 8)	50.0% (n = 1)	76.5% (n = 13)	19.0% (n = 4)
Dialysis (%, n)	9.7% (n = 3)	0.0% (n = 0)	23.5% (n = 4)	0% (n = 0)
IVIG only (%, n)	6.5% (n = 2)	100.0% (n = 2)	23.5% (n = 4)	9.5% (n = 2)
Steroid only (%, n)	51.6% (n = 16)	0.0% (n = 0)	29.4% (n = 5)	38.1% (n = 8)
IVIG and steroid (%, n)	12.9% (n = 4)	0.0% (n = 0)	5.9% (n = 1)	23.8% (n = 5)
Supportive care (%, n)	22.6% (n = 7)	0.0% (n = 0)	41.2% (n = 7)	28.6% (n = 6)
Cyclosporine (%, n)	6.5% (n = 2)	0.0% (n = 0)	11.8% (n = 2)	0% (n = 0)
Biologics (%, n)	6.5% (n = 2)	0.0% (n = 0)	0.0% (n = 0)	4.8% (n = 1)
Transferred to burn unit (%, n)	3.2% (n = 1)	0.0% (n = 0)	17.6% (n = 3)	4.8% (n = 1)
Mortality (%, n)	6.5% (n = 2)	0.0% (n = 0)	35.3% (n = 6)	0.0% (n = 0)

ICU, intensive care unit; IVIG, intravenous immunoglobulin; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.
Values are presented as number and percentage of patients.

The main infection noted was Mycoplasma in 91% of pediatric SJS patients. Infections in adult patients were 16.1% of the total SJS cases, and they were all caused by Mycoplasma. Drug-related triggers were identified in 84.9% of SJS patients. In particular, lamotrigine was the trigger in 22.6% of all the individual adverse drugs in the SJS category. Antibiotics were the most frequent culprit in adult patients with both SJS and TEN (22.6 and 41.2%, respectively). Chemotherapy was the next more frequent trigger of TEN. Of note, the cause of SJS or TEN was not identified in one patient with TEN and two patients with SJS.

Table 2 Pathology impression (n = 32)

	Adult patients		
Pathology read	**SJS**	**TEN**	***P*-value (SJS vs. TEN)**
Slides available for review	58.1% (n = 18)	70.6% (n = 12)	
Dermal-epidermal junction inflammation			$P = 0.52$
None	16.7% (n = 3)	40.0% (n = 4)	$P = 0.16$
Sparse	33.3% (n = 6)	40.0% (n = 4)	$P = 0.71$
Extensive	50.0% (n = 9)	40.0% (n = 4)	$P = 0.60$
Eosinophils			$P = 0.21$
None	61.1% (n = 11)	75.0% (n = 9)	$P = 0.44$
Sparse	16.7% (n = 3)	25.0% (n = 3)	$P = 0.58$
Extensive	22.2% (n = 4)	0.0% (n = 0)	$P = 0.08$
Neutrophils			$P = 0.07$
None	44.4% (n = 8)	58.3% (n = 7)	$P = 0.46$
Sparse	44.4% (n = 8)	8.3% (n = 1)	$P = 0.04$
Extensive	11.1% (n = 2)	33.3% (n = 4)	$P = 0.14$
Necrotic keratosis			$P = 0.47$
Could not be assessed	0.0% (n = 0)	0.0% (n = 0)	-
None	5.6% (n = 1)	0.0% (n = 0)	$P = 0.41$
Sparse	38.9% (n = 7)	25.0% (n = 3)	$P = 0.20$
Extensive	55.6% (n = 10)	75.0% (n = 9)	$P = 0.29$
Necrotic keratosis in upper epidermis			$P = 0.24$
None	38.9% (n = 7)	16.7% (n = 2)	$P = 0.20$
Sparse	16.7% (n = 3)	41.7% (n = 5)	$P = 0.14$
Extensive	44.4% (n = 8)	41.7% (n = 5)	$P = 0.89$
Areas of full-thickness necrosis			$P = 0.73$
None	61.1% (n = 11)	50.0% (n = 6)	$P = 0.55$
Focal	11.1% (n = 2)	8.3% (n = 1)	$P = 0.81$
Extensive	27.8% (n = 5)	41.7% (n = 5)	$P = 0.44$
Subepidermal separation			$P = 0.21$
None	66.7% (n = 12)	41.7% (n = 5)	$P = 0.18$
Focal	5.6% (n = 1)	0.0% (n = 0)	$P = 0.41$
Extensive	27.8% (n = 5)	58.3% (n = 7)	$P = 0.10$
Satellite cell necrosis			$P = 1.00$
None	33.3% (n = 6)	33.3% (n = 4)	$P = 1.00$
Sparse	33.3% (n = 6)	33.3% (n = 4)	$P = 1.00$
Extensive	33.3% (n = 6)	33.3% (n = 4)	$P = 1.00$
Superficial dermal fibrosis			$P = 0.11$
Absent	66.6% (n = 12)	91.7% (n = 11)	$P = 0.12$
Present	33.3% (n = 6)	8.3% (n = 1)	$P = 0.12$

SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis. Values are presented as number and percentage of patients.

SJS in both adults and pediatrics was mainly treated with oral steroids and occasionally with intravenous immunoglobulin (IVIG) (Table 1). With TEN, there was no treatment consensus. The majority of patients with TEN required ICU-level care.

Table 3 SJS vs. TEN: are they the same disease?

		SJS	TEN
1	Erythema multiforme lesions on skin or palm	Yes	Occasionally
2	Prognosis	Good	Morbid
3	Skin detachment	Mild	Severe
4	Infection or drug	Both	Drug
5	Skin + mucous membranes or systemic	Mainly skin/ MM	Systemic
6	Pathology diagnosis	Requires CPC	Requires CPC

CPC, clinical pathological correlation; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

Supportive care was necessary for the treatment of multi-organ injury including skin injury which was treated with Vaseline gauze or topical steroids with wet dressings. Of the patients diagnosed with TEN, 23.5% received IVIG treatment, 29.4% received steroids only, and 5.9% received both IVIG and steroids. Other treatments included dialysis, cyclosporine, and a biologic (etanercept). Three adult patients with TEN (17.6%), one (3.2%) adult patient with SJS, and one (4.8%) pediatric patient with SJS were transferred to a burn center for further care.

In our cohort, we had 35.3% mortality for TEN and 3.8% for adult and pediatric patients with SJS, and 6.5% for adults only with SJS. Survival was 100% in pediatric patients with SJS. Two of the adult patients with SJS died likely because of the complications related to disseminated intravascular coagulopathy (DIC). None with SJS-TEN overlap succumbed to their disease. Mortality was highest in patients with TEN (35.3%, n = 6). Table 1 shows that patients with chemotherapy-induced TEN had 50% mortality (n = 2 of 4). The SCORTEN on admission was 3.5. All four patients required ICU-level care and were treated with IVIG, dialysis, or cyclosporine. One patient was transferred to the burn unit. The most frequent cause of death was caused by multi-organ failure. Of the four patients on chemotherapy, two succumbed to multi-organ failure and one of the two also developed DIC.

Table 2 shows the pathology results of the 32 slides (64%) from 50 adult patients that were available for review. No statistically significant histopathological marker differentiating SJS or TEN was identified in our study.

Discussion

This study represents one of the largest single-center studies of patients with SJS and TEN. It is generally believed that SJS/TEN have high morbidity and mortality. Most of the literature tends to add the two entities together and come up with one average figure. In our cohort, we had 35.3% mortality for TEN and 6.5% for adults with SJS. If we averaged them, it would be

16.0% overall mortality for adults which is misleading especially for SJS and gives the impression to other medical services of a morbid disease. This is why we believe these two entities should not be compiled together as SJS has low mortality and better prognosis than TEN.

The question of the overlap needs to be addressed. Most studies of SJS/TEN report findings of patients with SJS, SJS/TEN overlap, and TEN retrospectively, given the rarity of these diseases. The study by Bastuji-Garin *et al.*[3] classified these entities by percentages of the extent of BSA skin detachment. Even though this was reported in the early 1990s, it is still currently used to separate one disease from the other. TEN was stratified as >30% detachment and SJS <10% detachment. Whereas this stratification of the two diseases created a "go in between" overlap syndrome, it implied that SJS and TEN are a spectrum of the same disease. The use of an "overlap" referred to as SJS/TEN may be the reason that these entities are considered as one. It is possible that the "overlap definition" may also imply a difficulty in decisionmaking regarding the clinical presentation; early skin disease may have 10% involvement, but a day or so later it may be 30%. Progression from early skin detachment with associated systemic manifestation is TEN and not an overlap. It is also quite possible that features of both severe SJS and TEN are occurring at the same time. Whether the two entities are a spectrum of one disease or not will remain controversial.

In our cohort, we separated SJS and TEN based on the Bastuji-Garin *et al.*[3] detachments. The two diseases are similar in that they are adverse reactive processes that occur as a result of a provoking agent. The main differences, as suggested in Table 3, are in percentage of skin detachment and outcomes. The outcomes are related to the amount of systemic organ damage. SJS is mainly a skin and mucous membrane disease caused by a drug with mild systemic involvement, and TEN is a severe multi-organ systemic toxicity with skin being one of the organs.

Given the fact that a drug is the causative agent of TEN, it should be understood that the drug is not just an adverse medication but a toxic agent not only to the skin and mucous membranes but to other organs, including kidney, liver, and lungs, leading to multiple organ injury. In fact, the SCORTEN is based partly on the extent of kidney damage in addition to age and other comorbidities. A TEN patient without any kidney damage would have a much better prognosis. Death is usually caused by resulting multi-organ damage. Early and rapid mechanisms such as dialysis to extract the causative drug can be life-saving to these patients as described previously.[5,6]

No statistically significant histopathological marker of SJS or TEN was identified in our study (Table 2). This may be related to a shared pathogenesis, or a small sample size may have limited the statistical power to detect any difference that may be clinically important. TEN tended to have a higher percentage than SJS in tissue necrosis, and SJS has higher percentages in the inflammatory component. TEN could not be clearly identified from pathology alone. Until a large cohort multicenter study of the pathology of TEN and SJS is done, we can only conclude that pathology reads on their own are insufficient for diagnosis and are best used for confirming the clinical diagnosis by utilizing clinical pathological correlation (CPC).

The triggers identified in our study, including medications and pathogens, were similar to those reported previously.[4,7] Our patients underwent standard treatment approaches as reported previously, including supportive care, IVIG, and steroids.[4,8] We identified two triggers, lamotrigine and chemotherapeutic drugs, that dermatologists need to be aware of. Lamotrigine is a very good drug for psychiatric patients, but its adverse reaction can be quite severe and toxic. One of the patients who died with SJS and DIC was on lamotrigine.

Our TEN patient cohort includes four patients with chemotherapy-related TEN. Chemotherapy is not reported in any mortality rate in the literature; hence, to make our comparative mortality rate, it is actually 26.7%, which is comparable to those reported in the literature. In a study from Europe, the mortality rate for SJS was 13%, SJS-TEN overlap 21%, while TEN was as high as 39%.[9] These numbers are about the highest numbers and show that even though SJS is 13%, it is still much lower than the 39% of TEN. From our study, SJS patients rarely have mortality as shown in a previous study from our institution,[10] whereas TEN patients frequently do. In our group, SJS data from adults showed 6.5% (two patients) mortality. Those two patients that succumbed to SJS also had DIC, which is most likely the cause of death. The 0% mortality in our pediatric patients was also comparable to previous reports.[11,12] TEN showed 35.3% mortality rate in our adult TEN patient cohort. Mortality in TEN patients was associated with significant BSA involvement. In general, a high SCORTEN is a predictor of TEN-associated mortality, which is in agreement with previous reports.[2,13]

Conclusion: key points

- SJS is more common than TEN, with a ratio of 3:1
- Pediatric patients were diagnosed exclusively with SJS. Adults with SJS are 2:1 male to female and are younger than adults with TEN
- Mortality rates were 6.5% for SJS among adults and 35.3% for TEN. Thus, mortality percentages should be separated for SJS and TEN.
- Prognosis, treatment, and outcome differ for SJS and TEN.
- Mycoplasma is a frequent trigger of SJS in pediatric patients.
- Chemotherapy is a trigger for TEN and chemotherapy-induced TEN is associated with high mortality and morbidity.
- Lamotrigine usage is associated with TEN.

The limitations of this study include its retrospective nature, difficulty in accounting for all triggers and confounders, and

assessing the effectiveness of the therapies that the patients were subjected to. Further prospective research is necessary to develop evidence-based treatment guidelines including supportive care protocols and recommendations. Our study encompassed patients receiving treatment at the Mayo Clinic, Rochester, Minnesota, over the last 20 years. Over this time, new biologics have been developed to treat cutaneous dermatologic conditions such as SJS/TEN. However, given the relatively low incidence of these diseases and the absence of set treatment guidelines, the efficacy of these biologics cannot be accurately determined by our study. Identification of the vulnerable patient population and triggers will aid us in appropriately treating SJS and TEN patients to reduce morbidity and mortality. Further work is warranted in these avenues.

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