A clinicoetiological analysis of patients with Stevens–Johnson syndrome and toxic epidermal necrolysis treated at Sohag University Hospital, Egypt

Mohammed Abu El-Hamd, Reham Ezz El-Dawla and Wafaa Abd Elmagid

Department of Dermatology, Venereology and Andrology, Faculty of Medicine, Sohag University, Sohag, Egypt

Correspondence to Mohammed Abu El-Hamd, MD, Department of Dermatology, Venereology and Andrology, Faculty of Medicine, Sohag University, Sohag, Egypt
Tel: +20 100 413 9060;
e-mail: mohammedadva@yahoo.com

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Background
Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are characterized by widespread epidermal necrosis and mucosal involvement secondary to keratinocyte apoptosis induced mostly by drugs and associated with high mortality.
Objective
To examine the prevalence, etiology, clinical presentations, and outcome of SJS/TEN in patients admitted in the Department of Dermatology, Venereology, and Andrology, Faculty of Medicine, Sohag University, Sohag, Egypt.
Patients and methods
This observational study included all patients with SJS/TEN admitted in the Department of Dermatology, Venereology, and Andrology, Faculty of Medicine, Sohag University, Sohag, Egypt, between September 2013 and September 2014. All patients with SJS/TEN were subjected to complete medical history and examinations to evaluate the extent of skin and mucous membrane involvement, complications, and other system affections. They also underwent complete laboratory investigations. The severity-of-illness score for toxic epidermal necrolysis was used to evaluate all patients within the first 24 h of admission.
Results
Of the 500 patients admitted, 21 (4.2%) were diagnosed with SJS/TEN (six men and 15 women; mean age 30.4 years). Fourteen patients were diagnosed with SJS ($n=14$; 66.7%), three with SJS/TEN overlap ($n=3$; 14.3%), and four with TEN ($n=4$; 19%). Nineteen patients (90.5%) had a history of drug intake. The most common causative drugs were carbamazepine (33.3%) and antibiotics + NSAIDs (28.57%).
Limitations
The main limitations of our study were the small sample size.
Conclusion
SJS and TEN are uncommon diseases. Most of the cases of SJS/TEN were drug-induced. The most common offending drugs were carbamazepine, NSAIDs, and antibiotics.

Keywords:
cutaneous drug eruption, Stevens–Johnson syndrome, toxic epidermal necrolysis

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Introduction

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are acute life-threatening skin diseases characterized by extensive epidermal sloughing at the dermoepidermal junction resulting from keratinocyte apoptosis [1]. Both TEN and SJS are rare, affecting approximately one or two individuals per 1 000 000 populations annually, and are considered medical emergencies, as they are potentially fatal [2].

The exact molecular pathogenesis of TEN and SJS are not fully understood. TEN patients appear to have an increased incidence of the haplotype HLA-B12, demonstrating an inability to detoxify intermediate reactive drug metabolites [3]. SJS and TEN are characterized by massive keratinocyte apoptosis. Fas–Fas ligand-induced apoptosis in keratinocytes is one of the most thoroughly studied immune mechanisms in SJS/TEN [4].

At least 80% of TEN cases are believed to be drug-induced, whereas the proportion of SJS cases attributable to drugs is lower, with the estimates ranging from 50 to 80% [5]. The commonly associated drugs include antibacterial sulfonamides, anticonvulsant agents, NSAIDs, aminopenicillins, and quinolones [6].

Both SJS and TEN are characterized by erythematous skin and extensive detachment of the epidermis and erosions of mucous membranes [7]. The two diseases are differentiated based on the extent of skin detachment, which is limited to at least 10% of the body surface area (BSA) in SJS, 10–30% of the BSA in SJS/TEN overlap, and up to 30% of the BSA in TEN [8].

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TEN is associated with a higher mortality rate (30–35%) compared with SJS (5–15%) [9]. To assess the prognosis of patients with SJS/TEN, the severity-of-illness score of TEN (SCORTEN) was used. This scoring system takes into consideration important prognostic factors, including age, the presence of underlying malignancy, heart rate, percentage loss of BSA, blood urea nitrogen level, serum glucose level, and bicarbonate level [10].

The prevalence, etiology, clinical presentations, and outcome of SJS/TEN in Egypt have not been reported yet.

The aim of this study was to examine the prevalence, etiology, clinical presentations, and outcome of SJS/TEN among patients admitted in the Department of Dermatology, Venereology, and Andrology, Faculty of Medicine, Sohag University, Sohag, Egypt.

Patients and methods

This observational study included all patients with SJS/TEN among patients admitted in the Department of Dermatology, Venereology, and Andrology, Faculty of Medicine, Sohag University, Sohag, Egypt, from September 2013 and September 2014. It is the only tertiary medical center for admission and management of patients with SJS/TEN in Sohag government, and it contains 24 beds in public section and indeterminate number in private section. Informed consent was obtained from all patients.

According to the criteria of Bastuji-Garin *et al.* [8], the patients were diagnosed as having SJS/TEN, based on the extent of skin detachment ($\leq$10% of BSA in SJS, 10–30% of the BSA in SJS/TEN overlap, and $\geq$30% of the BSA in TEN). A complete detailed history was taken from all patients with SJS/TEN with regard to their demographics, causative offending drugs, the onset of skin eruption from drug intake, the pattern of involvement, the clinical presentations of the disease, the underlying medical diseases, and the complications. All drugs received within the previous 4 weeks from the onset of skin eruption were investigated.

All patients underwent complete general examination (pulse, blood pressure, and temperature) and local examination, including the extent of skin and mucous membrane involvement, complications, and other system affections.

All patients underwent complete laboratory investigations, including complete blood picture, erythrocyte sedimentation rate, blood glucose level, electrolyte levels, and renal and liver function tests.

SCORTEN was used to evaluate all patients within the first 24 h of admission.

On the basis of the SCORTEN score, expected mortality and expected death were calculated. The SCORTEN includes the following seven clinical variables: (a) age up to 40 years, (b) presence of malignancy, (c) tachycardia up to 120/min, (d) involvement of up to 10% of BSA, (e) serum urea level up to 28 mg/dl, (f) serum glucose level up to 252 mg/dl, and (g) bicarbonate level less than 20 mEq/l [10].

Statistical analysis

SPSS software, version 16.0 (SPSS Inc., Chicago, Illinois, USA) was used for statistical analysis. The data were descriptive statistics. The data were presented as frequencies, percentages, mean ± SD. No analytic test was used.

Results

Between September 2013 and September 2014, 500 patients were admitted in the Department of Dermatology, Venereology, and Andrology, Faculty of Medicine, Sohag University, Sohag, Egypt. Of these patients, 21 (4.2%) were diagnosed with SJS/TEN (6 men and 15 women; age: mean 30.4 years; range, 3.5–60 years; Table 1). Fourteen patients were diagnosed with SJS ($n = 14$; 66.7%), three with SJS/TEN overlap ($n = 3$; 14.3%), and four with TEN ($n = 4$, 19%; Figs 1, 2a, b and 3a, b).

Nineteen (90.5%) patients had underlying diseases: epilepsy in seven (33.3%) patients, headache in two (9.5%), stuttering in one (4.8%), sinusitis in two (9.5%), tonsillitis in two (9.5%), musculoskeletal diseases in three (14%), cystitis in one (4.8%), and skin burn in one (4.8%) patient (Table 1).

The most common causative drugs were carbamazepine in seven (33.3%) patients for epilepsy. Six (28.57%) patients received antibiotics + NSAIDs for sinusitis, tonsillitis, cystitis, and skin burn. Three (14.9%) patients received NSAIDs for musculoskeletal diseases. Three (14.9%) patients received lamotrigen for tension headache and stuttering. Two (9.5%) patients did not receive medications (Table 1).

The period between relevant drug intake and the onset of skin eruption in 19 patients who received medications ranged from 2 to 20 days, with a mean of 8.84 ± 5.72 days. In SJS ($n = 13$), the period ranged from 2 to 20 days, with a mean of 9.3 ± 5.6 days. In SJS/TEN overlap ($n = 2$), it ranged from 5 to 20 days, with a mean of 12.5 ± 10.6 days. In TEN ($n = 4$), it ranged from 2 to7 days with a mean of 5.5 ± 2.38 days.

Pulse and blood pressure were normal in all patients. In this study, fever on admission was found in eight (38%) patients with SJS/TEN, three of 14 (21.4%) patients with SJS, two of three (66.7%) patients with SJS/TEN overlap, and three of four (75%) patients with TEN. Fever was mild in two (9.5%) patients, moderate in four (19%), and high in two (9.5%) patients.

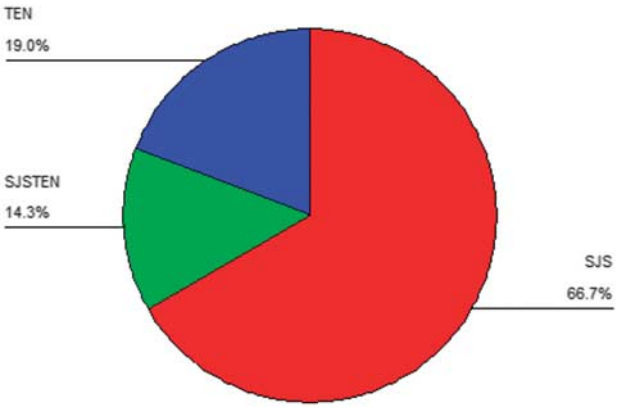
Of the patients, 20 (95.2%) presented with oral ulcerations, lip erosion, and crustations, eight (38.1%) with nasal erosion and crustations, five (23.8%) with genital erosions and crustations, 13 (62%) with eye affections such as conjunctivitis in 11 (52.4%) [seven (33.3%) with

Table 1. Clinical profiles of the 21 patients with Stevens–Johnson syndrome/toxic epidermal necrolysis

Criteria	Sex	Age (years)	Onset (days)	TBSA (%)	Underlying diseases	Offending drugs	SCORTEN	Hospital stay (days)	Outcome
SJS	Female	42	10	<10	Epilepsy	Carbamazepine	1	15	Recovered
SJS	Female	36	15	<10	Headache	Lamotrigen	0	18	Recovered
SJS	Female	60	7	<10	Muscloskel	NSAIDs	1	17	Recovered
SJS	Female	3.5	20	<10	Stuttering	Lamotrigen	0	16	Recovered
SJS	Female	11	7	<10	Tonsillitis	Antibiotics + NSAIDs	0	20	Recovered
SJS	Female	18	2	<10	Epilepsy	Carbamazepine	0	19	Recovered
SJS	Male	45	15	<10	Tonsillitis	Antibiotics + NSAIDs	0	22	Recovered
SJS	Female	21	0	<10	No	No	0	16	Recovered
SJS	Female	55	15	<10	Headache	Lamotrigen	1	24	Recovered
SJS	Male	9	12	<10	Epilepsy	Carbamazepine	0	19	Recovered
SJS	Male	14	3	<10	Muscloskel	NSAIDs	0	18	Recovered
SJS	Male	37	7	<10	Cystitis	Antibiotics + NSAIDs	0	16	Recovered
SJS	Male	50	3	<10	Sinusitis	Antibiotics + NSAIDs	1	15	Recovered
SJS	Male	29	5	<10	Burn	Antibiotics + NSAIDs	0	15	Recovered
SJS/TEN overlap	Female	13	5	10–30	Epilepsy	Carbamazepine	0	22	Recovered
SJS/TEN overlap	Female	21	0	10–30	No	No	1	17	Recovered
SJS/TEN overlap	Female	5	20	10–30	Epilepsy	Carbamazepine	0	17	Recovered
TEN	Female	54	2	>30	Sinusitis	Antibiotics + NSAIDs	3	25	Recovered
TEN	Female	40	6	>30	Epilepsy	Carbamazepine	2	20	Died
TEN	Female	56	7	>30	Muscloskel	NSAIDs	2	30	Died
TEN	Female	20	7	>30	Epilepsy	Carbamazepine	2	30	Recovered
Mean	–	30.4	8.84	–	–	–	–	19.6	–

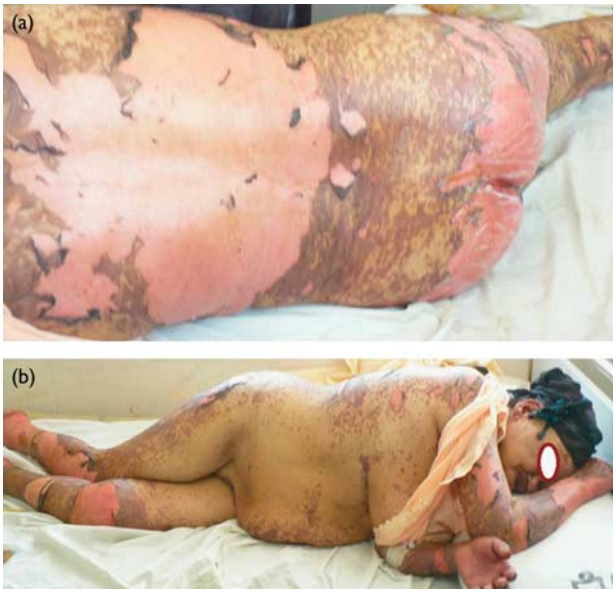
SJS, Stevens–Johnson syndrome; SCORTEN, severity-of-illness score for toxic epidermal necrolysis; TBSA, total body surface area; TEN, toxic epidermal necrolysis

Figure 1.



Diagnosis of the 21 patients with Stevens–Johnson syndrome and toxic epidermal necrolysis.

Figure 2.



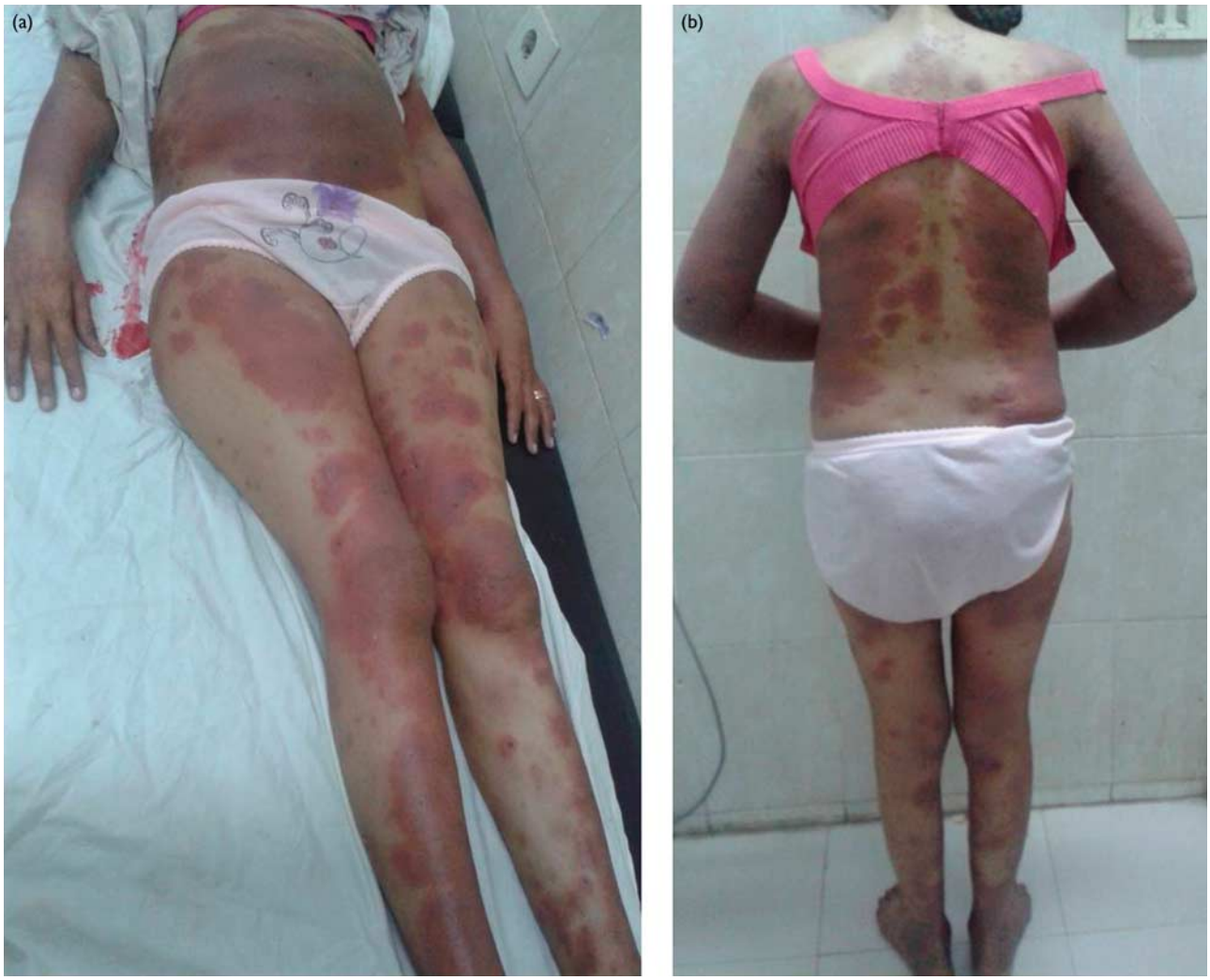
(a) The posterior view of a 56-year-old woman with toxic epidermal necrolysis. (b) The anterior view of a 56-year-old woman with toxic epidermal necrolysis.

SJS, two (9.5%) with SJS/TEN overlap, and two (9.5%) with TEN], ulcer on the inner canthus in one (4.8%) with TEN, and early papilledema in one (4.8%) with TEN (Table 2 and Fig. 4).

In laboratory investigations, hypocalcemia was found in 18 (85.7%) patients [11 of 14 (78.5%) with SJS, three of three (100%) with SJS/TEN overlap, and four of four (100%) with TEN]. Hyponatremia was found in 12 (57%) patients [six (28.5%) with SJS, two (9.5%) with SJS/TEN, and four (19%) with TEN]. Hypokalemia was found in 10 patients (47.6%) [six of 14 (42.86%) with SJS, one of three (33.3%) with SJS/TEN overlap, and three of four (75%) with TEN] (Table 3).

Anemia was found in 10 (47.6%) patients [five of 14 (35.7%) with SJS, two of three (66.6%) with SJS/TEN overlap, and three of four (75%) with TEN]. Erythrocyte sedimentation rate (first and second hours) was elevated in all patients. White blood cell and platelet counts were normal in all patients. Liver and renal function tests at the time of admission were normal in all patients. However, during hospital stay, liver function abnormality was observed in about 38% of the patients (8/21).

Figure 3.



(a) The anterior view of a 21-year-old woman with Stevens–Johnson syndrome. (b) The posterior view of a 21-year-old woman with Stevens–Johnson syndrome.

All patients received systemic steroids at a dose of 0.5 mg/kg and antibiotics (macrolides).

The mean hospitalization duration for the 21 patients with SJS and TEN was 15–30 days, with a mean of 19.6 ± 4.5 days. Disease duration was 15–24 (mean 17.8 ± 2.7) days, 15–24 (mean 18. 37 ± 2.9) days, and 20–30 (26.3 ± 4.8) days in patients with SJS ($n = 14$), SJS/TEN overlap ($n = 3$), and TEN ($n = 4$), respectively.

SCORTEN scores of 0 or 1, 2, and 3 were seen in 17 (81%), three (14.3%), and one (4.8%) patients with SJS ($n = 14$), SJS/TEN overlap ($n = 3$), and TEN ($n = 4$), respectively (Table 4).

As regards systemic complications, respiratory tract infections were found in two (9.5%) patients, in one with SJS/TEN and the other with TEN.

Nineteen (90.5%) patients recovered, but two (50%) patients with TEN ($n = 4$) died from electrolyte disturbance.

Discussion

This study found that the incidence of SJS/TEN was 4.2% ($n = 21$) in relation to all admitted cases ($n = 500$). The annual incidence of SJS/TEN in the general population of Southern Taiwan was 2.8 cases per million individuals according to a retrospective study [11]. In particular, the annual incidences of SJS and TEN were ~1–7 cases and 0.4–1.2 cases per million people, respectively [12–14].

Fourteen ($n = 14$; 66.7%) patients were diagnosed with SJS, three with SJS/TEN overlap ($n = 3$; 14.3%), and four ($n = 4$; 19%) with TEN in this study.

The mean age of the patients was 30.4 ± 18.4 years with marked female predominance (female-to-male ratio 2.5 : 1). This observation was consistent with earlier studies that showed that women are two times more susceptible to SJS/TEN compared with men [15,16] In contrast, another study found that men and women were equally affected [17].

Table 2. Mucous membrane affections of 21 patients with Stevens–Johnson syndrome/toxic epidermal necrolysis

Types of mucous membrane affection	*n* (%)
Oral ulcerations	
Yes	20 (95.2)
No	1 (4.8)
Lip erosion and crustations	
Yes	20 (95.2)
No	1 (4.8)
Nasal erosion and crustations	
Yes	8 (38.1)
No	13 (61.9)
Eye affections	
Yes	13 (62)
No	8 (38)
Conjunctivitis	11 (52.4)
Ulcer on inner canthus	1 (4.8)
Early papilledema	1 (4.8)
Genital erosion and crustations	
Yes	5 (23.8)
No	16 (76.2)

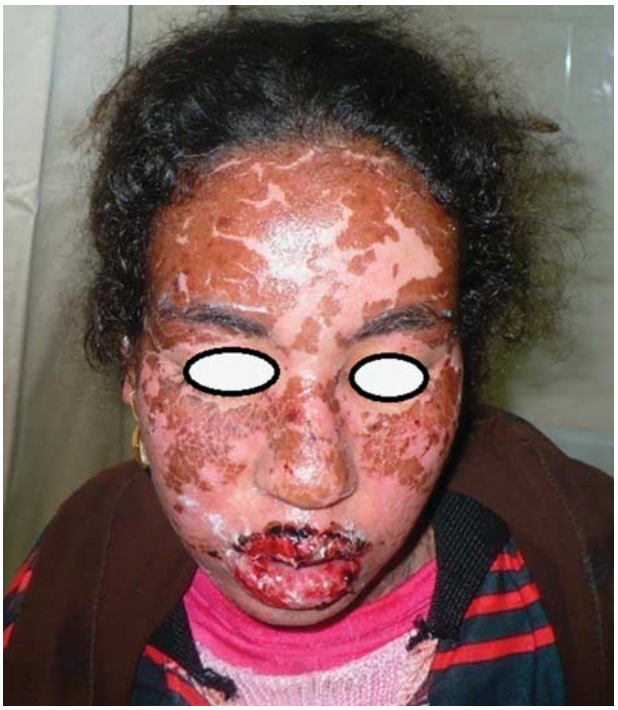
The strong female predominance observed in the SJS cases in the present study and other studies suggests sex-specific predisposing factors. Estrogen deficiency has been found to be a predisposing factor for SJS. This was supported by the fact that in most of the patients the disease was expressed in the premenopausal period of life of women [18]. Studies in normal mice have shown that estrogen suppresses the development of SJS, whereas ovariectomy leads to a condition that mimics SJS [19]. In the present study, 46.6% of the female patients (7/15) were older than 35 years. This female predominance can be explained by estrogen level.

In this study, 90.5% of the SJS/TEN cases were apparently drug related. The most commonly implicated drugs were anticonvulsants (48.2%). Among the anticonvulsants, carbamazepine and lamotrigen were the causative agents in 33.3 and 14.9% of the cases, respectively. Meanwhile, NSAIDS and antibiotics (aminopenicillins and ciproflaxacin) caused 42.9 and 28.6% of cases, the latter percentage including six patients who received NSAID and antibiotics in the present study.

This study is in agreement with many other studies that showed that anticonvulsants were the most common culprit agents implicated [20–23]. Retrospective studies in Southeast Asia also reported that the major culprit drugs were carbamazepine (17%), allopurinol (15%), β-lactam antibiotics (13%), sulfonamide antibiotics (12%), phenytoin (9%), NSAIDs (8%), lamotrigene (2%), and phenobarbitol (1%) [24].

A unique and strong association between HLA, drug hypersensitivity, and ethnic background was discovered by Tassaneeyakul *et al.* [25], who showed a strong association between the HLA-B*1502, SJS, and carbamazepine in Han Chinese. Another study by Huang *et al.* [26] confirmed the susceptibility of individuals with HLA-B*1502 to carbamazepine in a Thai population. The authors found that phenytoin, lamotrigine, and oxcarbazepine, which possess an aromatic ring similar to that of carbamazepine, share a common risk allele. They suggested that aromatic antiepileptic drugs should be avoided in the B*1502 carrier and caution should also be exercised for lamotrigine.

Figure 4.



Affection of the oral mucous membrane and the face of a 20-year-old woman with toxic epidermal necrolysis.

These results were different from the results obtained in another study by Yeung *et al.* [27] who reported that allopurinol was the most frequently responsible drug in 31% of patients, followed by anticonvulsants (13%). Another study showed that the most common causative agents were NSAIDs (54.5%), followed by allopurinol, prednisolone, and carbamazepine [28].

In this study, the mean duration of drug exposure before the onset of symptoms was 2–20 days, with a mean of 8.84 ± 5.72 days. Our study showed a mean period of drug exposure of 7.7 days for antibiotics and a slightly longer duration of 11.2 days for anticonvulsants. Yim *et al.* [28] reported shorter time for appearance of skin lesions, with a mean of 4.27 days. Two studies reported a slightly longer duration between drug intake and onset of symptoms as the mean was 14 and 15 days, respectively [17,27].

For many drugs, the risks for SJS and TEN were highest during the first weeks of use, particularly for antibiotics, as shown by Tan and Tay [17]. For most high-risk drugs that were intended for long-term use, the risk of developing SJS and TEN were elevated during the initial 2 months of use [29].

Fever has been found to be a commonly reported prodromal symptom, with variations among SJS patients and occurs in almost 100% of TEN patients. The highest body temperature could reach 40°C in drug hypersensi-

Table 3. Electrolyte disturbance in the 21 patients with Stevens–Johnson syndrome/toxic epidermal necrolysis

Electrolyte disturbances	Total ($n=21$)	SJS ($n=14$)	SJS/TEN overlap ($n=3$)	TEN ($n=4$)
Hypocalcemia	18 (85.7)	11 (52.3)	3 (14.3)	4 (19)
Hyponatremia	12 (57)	6 (28.5)	2 (9.5)	4 (19)
Hyopkalemia	10 (47.6)	6 (28.5)	1 (4.8)	3 (14.3)

Values are expressed as *n* (%).
SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

Table 4. Severity-of-illness score for toxic epidermal necrolysis scores of the 21 patients with Stevens–Johnson syndrome/toxic epidermal necrolysis

SCORTEN scores	Total ($n=21$)	SJS ($n=14$)	SJS/TEN overlap ($n=3$)	TEN ($n=4$)
0–1	17 (81)	14 (66.7)	3 (14.3)	0
2	3 (14.3)	0	0	3 (14.3)
3	1 (4.8)	0	0	1 (4.8)
4	0	0	0	0
≥ 5	0	0	0	0

Values are expressed as *n* (%).
SJS, Stevens–Johnson syndrome; SCORTEN, severity-of-illness score for toxic epidermal necrolysis; TEN, toxic epidermal necrolysis.

tivity syndrome but usually subsides within a few days [30].

In this study, fever on admission was found in many patients with SJS/TEN.

Fever in patients with SJS/TEN has been found to be related to the drug themselves or the release of some pyogenes from the necrotic epidermis rather than the infection itself [30]. Thus, prophylactic antibiotics are generally not recommended in the literature [31]. However, another study suggested that prophylactic antibiotics may decrease the mortality rate by lowering the infectious threat in SJS and TEN patients [32].

Involvement of the buccal, genital, and/or ocular mucosa (erythema and erosions) occurs in more than 90% of patients with SJS/TEN [33].

In this study, the oral, nasal, genital, and/or ocular mucosa affections were found in most of the patients with SJS/TEN.

Routine ophthalmic consultation with lubrication, steroids, and antibiotic eye drops was well established in our department.

Many studies showed that ocular involvement at the onset of disease was frequent and can range from acute conjunctivitis, eyelid edema, erythema, crusts, and ocular discharge to conjunctival membrane or pseudomembrane formation or corneal erosion, and, in severe cases, to cicatrizing lesions, symblepharon, fornix foreshortening, and corneal ulceration [34,35].

At the time of admission, liver function test results were normal in all patients. During hospital stay, liver function abnormalities were observed in about 38% (8/21) of the patients. This finding concurs with that from the study of Huang *et al*. [11] who reported liver function abnormalities in 50% of patients with SJS and TEN.

Drug-mediated hepatitis is an idiosyncratic toxicity in which unusual drug metabolites and immune-mediated hepatocyte injury are the main pathogenetic mechanisms [36].

Liver function abnormalities did not correlate with disease severity or hospitalization duration in our observation; this finding matched with that of Huang *et al*. [11].

It is reasonable to say that transaminase level is influenced by many factors such as inflammatory reactions, fatty liver, and underlying virus hepatitis status. This observation is compatible with that previously documented based on the severe-of-illness score system (SCORTEN), in which liver functions were found to be a poor predictor of disease severity in cases of SJS-TEN [37].

The present study showed that the mean duration of hospital care to complete skin healing was 9–21 days, with a mean of 14.1 days, and the mean hospitalization duration was 15–30 days, with a mean of 19.6 days. These results concur with those from the study of Kim *et al*. [38] who reported a hospital stay of 19.7 days. Another study reported a slightly longer stay of 20.6 days [39]; two studies reported slightly shorter mean hospital stay durations of 17 and 16.9 days [27,40].

In contrast, Yim *et al*. [28] reported that treatment of their patients in a burn intensive care unit shortened the time to complete reepithelialization to 9 days and shortened the mean hospital stay to 14.66 days.

Many studies reported that the mortality rate in SJS/TEN patients ranged from 5 to 40% [11,22,41]. The present study recorded a high mortality rate of 50% for the TEN patients and 9.5% for the SJS/TEN patients. Similar to the present study results, the results obtained by Mockenhaupt [7] showed that the mortality was almost 10% for patients with SJS, ~30% for patients with

SJS/TEN overlap, and almost 50% for patients with TEN. For SJS, SJS/TEN overlap, and TEN the overall mortality rate was almost 25%.

Huang *et al.* [11] reported a mortality of 20% for TEN (2/10) and 0% for SJS in their retrospective study. Gravante *et al.* [42] reported a higher mortality rate of 34% in SJS/TEN patients (11/32).

The causes of death in the present study were electrolyte disturbances, as in the study of Haung *et al.* [11]. This finding contradicts another study that found that septicemia was an important mortality factor [42].

This study had many limitations, including its small sample size and the need for a genetic analysis to explain HLA association.

Conclusion

Prevention and early detection are critical to treat this disease. Differences in disease severity and morbidity mainly influenced the course and outcome. The most common causative drugs in the present study were carbamazepine, NSAIDs, and antibiotics, and thus these should be considered by physicians.

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Conflicts of interest

There are no conflicts of interest.

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