

Stevens-Johnson syndrome and toxic epidermal necrolysis in Saudi Arabia: a retrospective cross-sectional multicenter study

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Abstract

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are a spectrum of life-threatening mucocutaneous conditions. Despite having a lower incidence rate than other dermatological conditions, SJS/TEN has a high mortality rate. SJS/TEN is usually caused by newly administered medications, particularly antibacterials and anticonvulsants. Little research data on SJS/TEN in Saudi Arabia has been published. We aimed to bridge this gap by reviewing and investigating the etiologies, risk factors, interventions, and outcomes of patients diagnosed with SJS/TEN. This is a retrospective cross-sectional study conducted in National Guard hospitals in Riyadh and Jeddah from January 2015 to July 2023. We reviewed all dermatology medical records diagnosed as SJS/TEN through clinical assessment and histopathology, confirmed by a dermatology consultant. Additionally, we excluded all non-Saudi patients and those referred to our center with outside reports without histopathology from the National Guard hospitals. This study included 25 patients diagnosed with the SJS/TEN spectrum between January 2015 and July 2023. Nearly two-thirds of the patients were male (n=15, 60%), and the average age was 45.96 years. Almost half of the culprit agents were antibiotics. Six of the 25 patients died (24%). Four were males, all over 50 years old, and one female was 6 years old. All these patients had TEN, except for one with SJS. Septic shock was the cause of death in 4 patients. Given the evident high risk for patients contracting this condition, prospective research and analysis to understand the correlation between SJS/TEN, mortality, and treatment are warranted.

Key words: drug reaction; Stevens-Johnsons syndrome; toxic epidermal necrolysis.

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Introduction

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are a spectrum of life-threatening mucocutaneous conditions usually due to drug-induced reactions. In SJS, the affected body surface area (BSA) percentage is less than 10%, while in TEN, the affected BSA is more than 30%. These conditions overlap when the BSA is between 10% and 30%. The exact pathogenesis underlying SJS/TEN is not yet completely understood. Some studies have suggested a cell-mediated cytotoxic reaction against keratinocytes, leading to excessive apoptosis based on the lymphocytes detected in the fluid inside the blistering lesions.¹

Estimates of the incidence of SJS/TEN range from 1.4 to 12.7 cases per million people per year.^{2,3} In a recent study including 551 patients, the calculated incidence was 5.67 per million per year.⁴ Despite having a lower incidence rate than other dermatological conditions, SJS/TEN has a high mortality rate (30%).⁵ SJS/TEN is usually caused by newly administered medications, particularly allopurinol, aromatic anticonvulsants, antibacterial sulfonamides, lamotrigine, nevirapine, and nonsteroidal anti-inflammatory drugs (NSAIDs).^{6,7} Other cofactors that can increase the risk of SJS/TEN

are human immunodeficiency virus infection, genetic factors, cancers, underlying immunologic illnesses, and physical exposure (such as ultraviolet light or radiation therapy).^{8,9}

Little research data on SJS/TEN in Saudi Arabia has been published. In a retrospective chart review conducted at King Fahad Specialist Hospital in the Qassim region between 2014 and 2019, 10 patients with TEN/SJS were reported, with a 10% mortality rate. In 5 cases, antibiotics were identified as the offending drugs, and in 3 of those cases, amoxicillin/clavulanic acid was the culprit.¹⁰ The second most common culprit medications were anticonvulsants in 3 patients. In another study, a 15% mortality rate was found in 13 patients diagnosed with TEN/SJS at King Abdullah Medical City, Makkah, between 2003 and 2010.¹¹ In five cases, trimethoprim/sulfamethoxazole was the antibiotic linked to TEN. SJS/TEN has also been reported in several other case reports from various regions of Saudi Arabia.¹²⁻¹⁴ However, data regarding SJS/TEN's incidence, clinical features, outcomes, and prognosis in Saudi Arabia are lacking. We aimed to bridge this gap by reviewing and investigating the etiologies, risk factors, interventions, and outcomes of patients diagnosed with SJS/TEN in the National Guard hospitals of Riyadh and Jeddah.

Materials and Methods

This retrospective cross-sectional study was conducted in the National Guard hospitals in Riyadh and Jeddah in Saudi Arabia from January 2015 to July 2023. We identified 27 patients with SJS/TEN; however, 2 were excluded due to incomplete medical records. Additionally, all non-Saudi patients and those referred to our center with outside reports without histopathology from the National Guard hospitals were excluded.

We included all patients diagnosed with SJS/TEN based on clinical and histopathological reports, with the diagnosis confirmed by a dermatology consultant. The data collected included demographics and the time to SJS diagnosis, BSA, Severity-of-Illness Score for Toxic Epidermal Necrolysis (SCORTEN), culprit medication, and mortality rate. Data were entered into Excel using one Excel sheet per patient. Data analysis was performed using SPSS 24, and categorical data were calculated based on frequencies and percentages.

Results

This study included 25 patients diagnosed with SJS/TEN spectrum between January 2015 and July 2023. The mean time from developing the first lesion to the dermatology consultation was 4 days. Almost two-thirds of the patients were male (n=15, 60%), and the mean age was 45.96 years. The mean SCORTEN was 2.28 on day 1 and decreased to 2.08 on day 3. Oral mucosal involvement was observed in all patients. Blood eosinophilia was detected in 9 patients. Almost half of the culprit agents were antibiotics (n=11, 44%). Almost two-thirds of the patients had SJS (n=9, 35%), and 2 patients had Fuchs syndrome. As is evident in SJS/TEN, the patients' treatment modalities were multifaceted based on underlying severity and individual patient requirements. Etanercept and systemic steroids were the most prevalent, with a 68% treatment rate realized for each, demonstrating heavy dependence on immunosuppressive therapies for inflammatory processes inherent to SJS/TEN. What is worth mentioning regarding etanercept is that only 3 out of 17 (17%) patients who received it passed away, which further supports its efficacy in SJS/TEN cases. A significant portion of patients (56%) were treated with intravenous immunoglobulin, signifying its importance in the treatment of these acute skin reactions. Furthermore, 12% used cyclosporin, indicating the need for alternative immunomodulatory options. These treatments increase the complexity of these syndromes and emphasize the importance of adopting more advanced approaches to meet patients' needs and reduce adverse outcomes. The demographic details of the patients with SJS/TEN and Fuchs syndrome are listed in Table 1 and Figure 1. The specific culprits and latency period are listed in Table 2.

Six of the 25 patients died (24%). Four were males, all over 50 years old, and one female was 6 years old. All these patients had TEN, except for one with SJS, and the mean BSA was 33.3%. The mean SCORTEN score of deceased patients was 4, compared to 2.28 in all patients. Systemic antibiotics were the culprit agents in most of these patients. Of the 25 patients, all 3 with a history of malignancy died. Septic shock was the cause of death in 4 patients, while cardiac arrest was the cause in 2 patients. The mean time of hospital stay among deceased patients is 37.17 days, compared to 15.7 days among patients who survived. Table 3 illustrates the key demographic information of the deceased patients.

Discussion

SJS and TEN are well-known but rare acute mucocutaneous conditions. Although their prevalence is lower compared to other dermatological conditions, the mortality rate is significantly higher at 30%.¹⁵ Therefore, these conditions are classified as acute life-threatening conditions. This study aimed to investigate the epidemiology and management of SJS and TEN in a Saudi Arabian population. Research on SJS and TEN in Saudi Arabia is lacking,

Table 1. Demographics of patients with SJS/TEN.

	n	%
Sex		
Male	15	60
Female	10	40
SCORTEN (mean)		
Day 1	2.28	
Day 3	2.08	
Mucosal involvement		
Yes	25	100
No	0	0
Eosinophilia		
Yes	9	36
No	16	64
Cause		
Antibiotics	11	44
Epilepsy medications	3	12
NSAIDS	1	4
Infection	3	12
Other	8	32
Treatment		
IVIG	14	56
Etanercept	17	68
Cyclosporin	3	12
Systemic steroids	17	68
Hospital stay in days (mean)	21	

SCORTEN, Severity-of-Illness Score for Toxic Epidermal Necrolysis; NSAIDS, nonsteroidal anti-inflammatory drugs; IVIG, intravenous immunoglobulin.

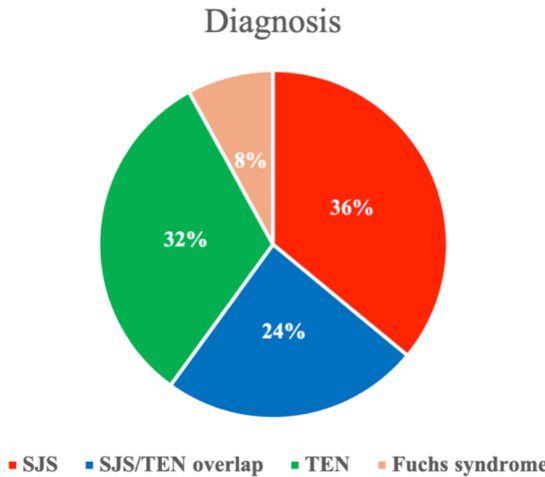


Figure 1. Pie chart showing the distribution of diagnoses.

and the data gathered for this retrospective analysis are limited. Nonetheless, the data may serve as a foundation for future research in this area of dermatology. In our analysis, we compared studies conducted in Saudi Arabia and tabulated the results extracted from these studies to facilitate comparison and understanding of the causes of SJS/TEN, as well as the subsequent related incidence and mortality rates.

Our literature review identified only two studies on SJS/TEN in Saudi Arabia. The first study included 10 patients with SJS/TEN, who had a 10% mortality rate. These data were reported in a study conducted at King Fahad Specialist Hospital in the Qassim region between 2014 and 2019. Another study, conducted at King Abdullah Medical City, Makkah, between 2003 and 2010, revealed a 15% mortality rate in the 13 identified cases of SJS/TEN. In both studies, the potential causes of SJS/TEN were identified. In the study at King Fahad Specialist Hospital, the main offending agents in 50% of the SJS/TEN patient cohort were antibiotics, with most patients affected by amoxicillin/clavulanic acid. The second most common culprit for SJS/TEN, in 30% of this cohort, was anticonvulsants. Similarly, in the study conducted at King Abdullah Medical City, 5 of the 13 patients had received

antibiotics, including trimethoprim/sulfamethoxazole, which were the main causes of SJS/TEN.

In light of existing studies from Saudi Arabia, we conducted a cross-sectional analysis that included 25 patients meeting our inclusion criteria. Our cohort comprised patients diagnosed with SJS/TEN from January 2015 to July 2023 at the National Guard hospitals in Riyadh and Jeddah. Almost two-thirds of our patients were male. Interestingly, our study revealed similar results to those of the previous studies conducted in Saudi Arabia. In almost half of our patients (44%) with SJS/TEN, antibiotics were found to be the main offenders behind their symptoms. Specifically, the main culprits for this unwanted consequence were vancomycin and amoxicillin/clavulanic acid. The mortality rate of the patients in our study was 24%, which is consistent with the global mortality rate of 30%. Six of the 25 patients died; 5 were males older than 50 years, and one was a female of 6 years old. In this patient cohort, although antibiotics were the major risk factor for SJS/TEN-related mortality, the 3 patients with a history of malignancy all died. The mortality rate of 100% in this category shows that malignancy can be classified as a high-risk factor for SJS/TEN-related deaths in our population.

Table 2. Culprits and latency period.

Culprit	n	%	Latency period (days)
Acetaminophen	1	4	1
Levofloxacin	1	4	2
Ciprofloxacin	1	4	7
Trimethoprim/sulfamethoxazole	1	4	3
Meropenem	2	8	Patient 1: 21 Patient 2: 18
Amoxicillin/clavulanic acid	3	12	Patient 1: 3 Patient 2: 2 Patient 3: not documented
Vancomycin	2	8	Patient 1: 23 Patient 2: 4
Carbamazepine	2	8	Patient 1: 17 Patient 2: 2
Levetiracetam	1	4	20
Allopurinol	1	4	60
Diclofenac	1	4	5
Piperacillin/tazobactam	1	4	7
Mycoplasma Pneumoniae	3	12	NA
Anidulafungin	1	4	14
Not specified	4	16	NA

Table 3. Demographics of deceased patients.

Sex	Age	Trigger	SCORTEN	BSA	Cause of death	Systemic medication	Comorbidities
M	81	Meropenem	6	40	Septic shock	IVIG, etanercept	HTN, ESRD, hypothyroidism, colon cancer, RCC
F	6	Carbamazepine	2	20	Cardiac arrest	IVIG, etanercept, SCS	ESRD, epilepsy
F	65	Meropenem	5	60	Septic shock	IVIG, etanercept	DLBCL, RA, DM, HTN, CKD
M	74	Tazocin	3	10	Cardiac arrest	IVIG	Hypothyroidism, ESRD, CVA
M	53	Anidulafungin	4	35	Septic shock	IVIG, SCS	Prostate cancer
M	53	Not specified	4	35	Septic shock	IVIG, SCS	Pilocytic astrocytoma

SCORTEN, Severity-of-Illness Score for Toxic Epidermal Necrolysis; IVIG, intravenous immunoglobulin; HTN, hypertension; ESRD, end-stage renal disease; RCC, renal cell carcinoma; SCS, systemic corticosteroids; DLBCL, diffuse large B cell lymphoma; RA, rheumatoid arthritis; DM, diabetes mellitus; CKD, chronic kidney disease; CVA, cerebral vascular accident.

Furthermore, most of the patients who died in this study were revealed to have septic shock as their main cause of death. The rest of the cohort affected by SJS/TEN died due to cardiac arrest. Most of the patient deaths in this study were the result of a history of TEN. Only one death was of a patient with a background of SJS. In line with the available research regarding TEN/SJS-related outcomes, our study confirms the published research on the Saudi Arabian population with SJS and TEN. Based on this evidence, antibiotics induced SJS/TEN reveal a high mortality rate in those treated with this class of drugs.

Due to the low incidence and the lack of research in Saudi Arabia about SJS/TEN, the cohorts in these studies were very small. However, the small sample size does not significantly skew the relationship between the treatments and the outcomes measured, in comparison with studies conducted globally. In our study, the mortality rate of SJS/TEN was 24%, which is consistent with studies done in Europe, which showed 34-38% mortality in drug-induced SJS/TEN.¹⁶

Additionally, global studies have noted the effects of antibiotics and anticonvulsants as the main threat for SJS/TEN, which was also the primary focus of our cross-sectional review.¹⁷

Conclusions

SJS/TEN is a life-threatening dermatological condition that has a high risk of mortality. The relationship of SJS/TEN with a high risk of mortality is consistent, even in the Saudi Arabian population. Furthermore, it is evident that antibiotics are the major culprits for these syndromes, followed by anticonvulsants. The sample sizes in the Saudi Arabian studies, including this study, are relatively small due to a lack of proper reporting of these health conditions. However, the results show a pattern of risk that has already been assessed globally. Given the evident high risk for patients contracting this condition, prospective research and analysis to understand the correlation between SJS/TEN, mortality, and treatment are warranted. Future research, especially in Saudi Arabia, will contribute to the understanding of the genetic, geographical, and environmental factors that influence the course of SJS/TEN. Furthermore, the data gathered from these studies may help formulate evidence-based treatment protocols and policy changes to current practices in this region.

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Contributions: Rayan Alkhodair: study conception and design, results analysis and interpretation; Yazeed Alowairdhi: study conception and design, data collection, results analysis and interpretation, manuscript preparation and drafting; Abdulrahman Alfawzan: analysis conception and design, results analysis and interpretation, manuscript preparation and drafting; Ali Alghamdi: data collection, manuscript preparation and drafting. All authors reviewed the results and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest: the authors have no conflict of interest to declare.

Ethics approval and consent to participate: this study, numbered NRC23R/117/02, was approved by the IRB office at King Abdullah International Medical Research Center (KAIMRC), No. IRB/0652/23, on 12/03/2023. Written consent to participate was obtained from all study participants.

Availability of data and materials: the datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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