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Original Article

Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis: A 15-year Regional Burn Center Experience

Dima Obed[a,*], Mustafa Salim[b], Khaled Dastagir[a], Nicco Krezdorn[a,c], Doha Obed[a,#], Peter M. Vogt[a,#]

[a] *Department of Plastic, Aesthetic, Hand and Reconstructive Surgery, Hannover Medical School, Hannover, Germany*
[b] *Department of Human Genetics, Hannover Medical School, Hannover, Germany*
[c] *Department of Plastic and Breast Surgery, Roskilde University Hospital, Roskilde, Denmark*

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ABSTRACT

Toxic epidermal necrolysis (TEN) and Stevens–Johnson syndrome (SJS) constitute rare and potentially life-threatening dermal hypersensitivity reactions marked by epidermal necrosis and skin blistering. They present a substantial health care burden and challenge to burn units. To advance our understanding of TEN/SJS and the patient cohort at risk for mortality, we hereby report our long-term experience in the management of patients with TEN/SJS.

For this purpose, intensive care patients with TEN/SJS admitted between 2007 and 2022 to a single major burn unit in Germany were assessed. Clinical, demographic, and mortality data were collected and examined.

A total of 92 patients were included. Mortality was 46.7%, with non-survivors being significantly older, more frequently women, and having markedly higher percentages of the total body surface area (TBSA) affected. The mean age was 63 years and mean percentage of affected TBSA was 52%. The most frequent culprit drugs that caused TEN/SJS were allopurinol and metamizole, followed by various antibiotics. In 5.4% of the cases, no TEN/SJS-inducing suspect drug was identified.

* Corresponding author: Dima Obed, Department of Plastic, Aesthetic, Hand and Reconstructive Surgery, Hannover Medical School, Carl-Neuberg-Strasse 1, 30625 Hannover, Germany; Fax: +49 511 532-8864 Tel.: +49 511 532 168864
E-mail address: dima.obed@stud.mh-hannover.de (D. Obed).
DO and PMV share last authorship.

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TEN/SJS present severe adverse cutaneous reactions that are marked by high in-hospital mortality rates. Age and TBSA were associated with poor prognosis. The range of possible trigger drugs that were associated with TEN/SJS was in agreement with previous reports.

Introduction

Toxic epidermal necrolysis (TEN) and Stevens–Johnson syndrome (SJS) present severe and potentially lethal mucocutaneous disorders because of massive immune system activation that is predominantly triggered by culprit drugs or infectious agents. They present a significant public health burden owing to high morbidity and mortality. TEN and SJS are classified according to the percentage of total body surface area (TBSA) affected: SJS (<10% of TBSA), TEN/SJS overlap (10%–30% of TBSA), and TEN (>30% of TBSA). These rare conditions reportedly affect patients in all age groups with incidences of approximately 2 to 7 cases per million individuals annually.[1–3] Characteristically, they manifest with extensive mucosal and epidermal erosion and necrosis and can be observed because of keratinocyte death (Figure 1). This in turn results in considerable fluid loss, susceptibility to infection and sepsis, and organ dysfunction which may explain the high mortality rates of up to 75%.[4,5] As the dermal erosions displayed in patients with TEN/SJS appear as second degree burn wounds (Figures 2 and 3), clinical admission and treatment frequently occur within highly specialized burn units with a multidisciplinary team approach for the challenging intensive care of large blistering wounds and organ support.[6]

To date, the evidence for the effectiveness of systemic therapeutic agents is limited as the pathomechanism of TEN/SJS remains incompletely understood. Current hypotheses acknowledge the disorders as delayed-type drug hypersensitivity reactions with the onset following a typical latency of 4–28 days upon initiation of the culprit agent. The drug metabolite reaction is known to cause cytotoxicity mediated by CD8+ cytotoxic T-cells and natural killer cells which trigger keratinocyte apoptosis by numerous cytotoxic signaling modulators, including Fas/Fas ligand, granulysin, and perforin/granzyme B.[7–9] Various culprit drugs have been reported in the past, e.g., allopurinol, anticonvulsants, antiretrovirals, nonsteroidal anti-inflammatory drugs (NSAID), and several antibiotics.[10–12] The timely identification and prompt cessation of the initiating trigger remains of upmost importance.

The population at risk includes multimorbid older patients, immunodeficient patients, and patients with malignancies.[13,14] Additionally, genome-wide association studies have shown an association between TEN/SJS and certain human leukocyte antigen (HLA) alleles in Asian and European populations.[15,16] Herein, the demographic and clinical features of a large single-center cohort of patients with TEN/SJS admitted to our burn intensive care unit (ICU) over the course of 15 years are reported to identify risk factors for mortality and advance our understanding in the care and management of patients with TEN/SJS.

Methods

Study design and data extraction

The data for this retrospective study were collected from the records of patients admitted to the burn ICU at Hannover Medical School over a 15-year period from February 2007 to June 2022. This center presents one of the 3 major burn centers in Northern Germany with 6 ICU beds. The complete records of all patients admitted to the burn ICU were reviewed. Patients with documented diagnosis of SJS, TEN/SJS, or TEN were included without age restrictions. Diagnosis was based on recognized

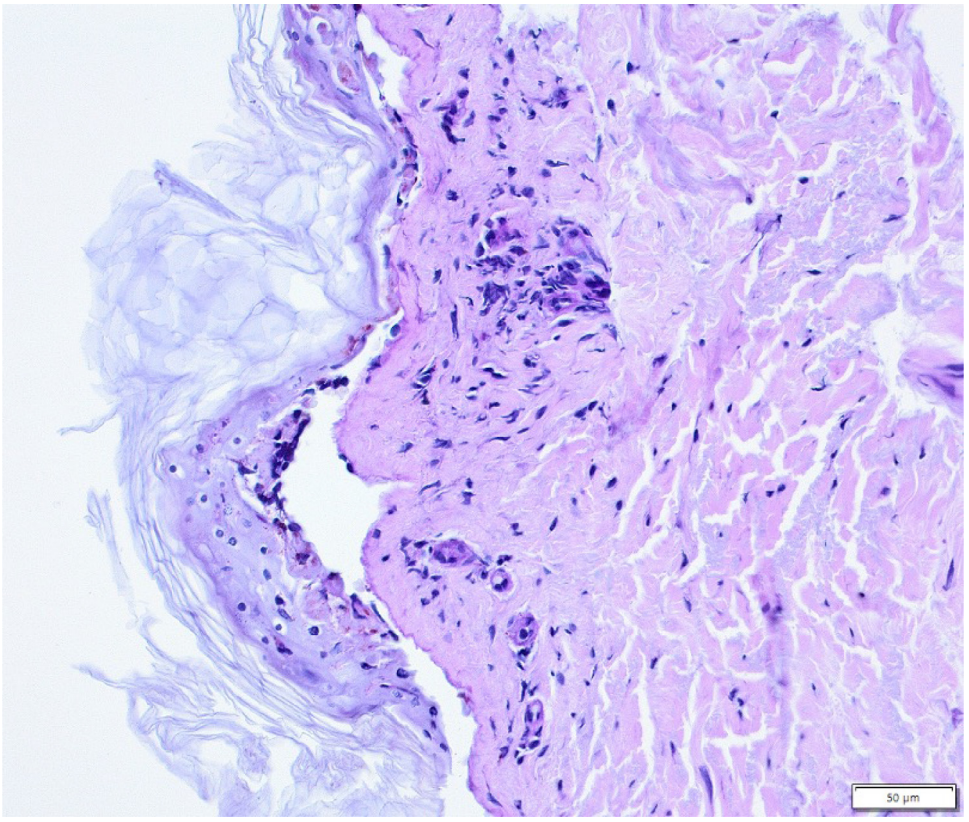

Figure 1. Histopathology of toxic epidermal necrolysis with characteristic features of epidermal necrosis, dermoepidermal detachment, and dermal inflammation (PAS) (Institute for Pathology, Hannover Medical School).

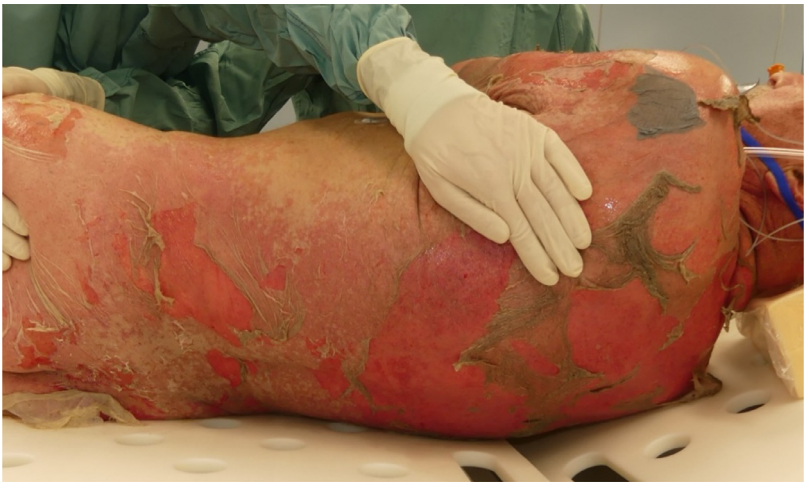

Figure 2. Clinical presentation of toxic epidermal necrolysis with diffuse desquamation and dermal denudation of the trunk and dorsum (Department of Plastic, Aesthetic and Reconstructive Surgery, Hannover Medical School).

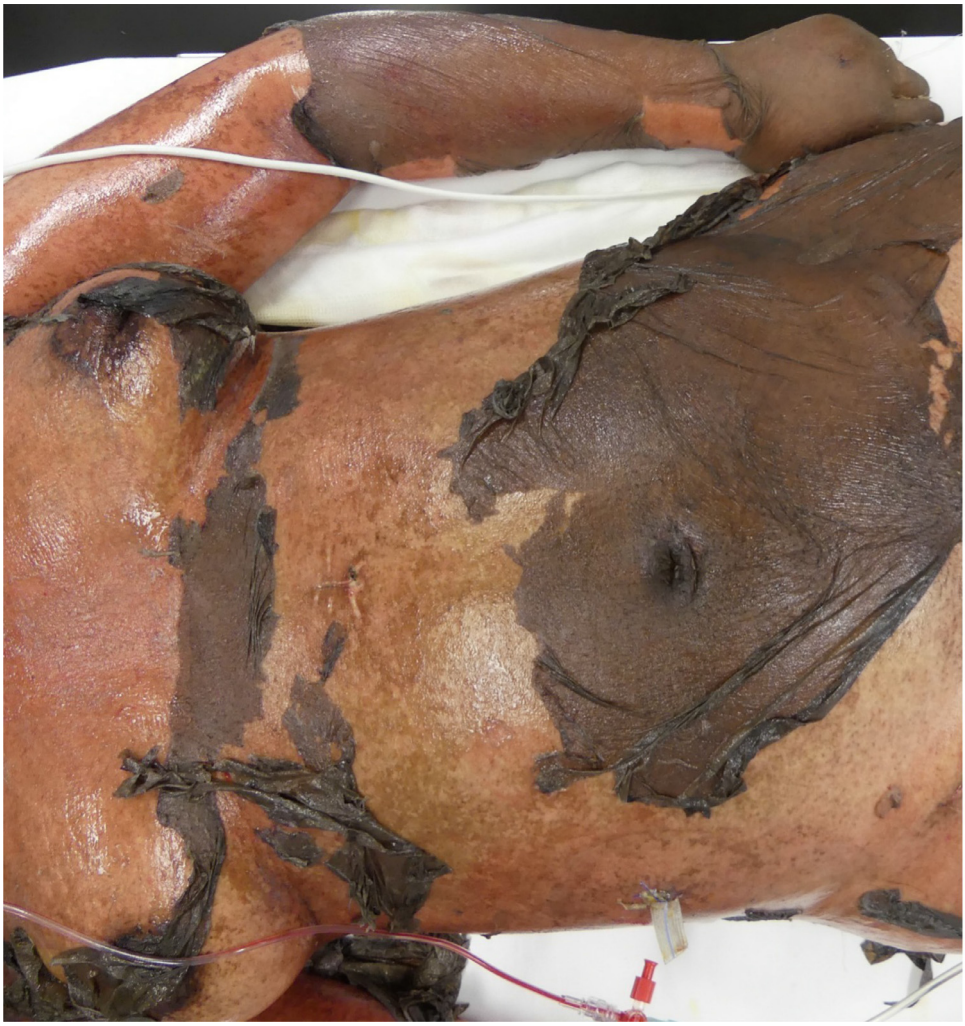

Figure 3. Clinical case of severe toxic epidermal necrolysis with extensive epithelial detachment of the trunk and extremities (Department of Plastic, Aesthetic and Reconstructive Surgery, Hannover Medical School).

criteria with supplementary histopathological confirmation.[17] The collected demographic and clinical parameters included age, gender, symptoms, TBSA, comorbidities, presence of malignancies, suspected culprit drug/suspected etiology, need for renal replacement therapy, length of stay, and in-hospital mortality. Suspected culprit drugs were identified by evaluating the history of drug administration. This research was approved by the ethics committee of Hannover Medical School.

Statistical analysis

Primarily, data were collected and processed using Microsoft Excel (Version 16, Microsoft Corporation, Redmond, WA). Data analysis and descriptive statistics were performed using GraphPad Prism 10 (GraphPad Software Inc., San Diego, CA, USA). Binomial test was used for comparative categorical analyses. T-test was used to compare $\geq$2 quantitative variables. *P*-values $<$0.05 were considered significant. All-cause in-hospital mortality was regarded as a time-dependent variable derived from the

Table 1
Demographic/clinical characteristics and outcome parameters.

Characteristics	All (n= 92)	Survivors (n=49)	Non-survivors (n= 43)	p-value
Age (years) (mean ± SD)	63.8 ± 18.8	59.3 ± 19.8	67.8 ± 15.6	**0.026**
TBSA (%) (mean ± SD)	51.7 ± 29.5	36.9 ± 15.0	69.4 ± 26.1	**<0.0001**
Gender, *n* (%)				
Female	53 (57.6)	25 (51.0)	27 (62.8)	0.78
Male	39 (42.4)	24 (49.0)	14 (32.6)	0.14
Age Group, *n* (%)				
18–29 years	6 (6.5)	5 (10.2)	1 (2.3)	0.22
30–59 years	30 (32.6)	18 (36.7)	12 (27.9)	0.36
60–79 years	32 (34.8)	17 (34.7)	15 (34.9)	0.86
≥80 years	24 (26.1)	9 (18.4)	13 (30.2)	0.40
TBSA, *n* (%)				
0-19	15 (16.3)	14 (28.6)	2 (4.7)	**0.0023**
20-49	28 (30.4)	20 (40.8)	7 (16.3)	**0.019**
50-69	12 (13.0)	7 (14.3)	5 (11.6)	0.58
>70	37 (40.2)	8 (16.3)	27 (62.8)	**0.0012**
LOS (days), mean ± SD	15.6 ± 15.0	18.9 ± 23.4	12.0 ± 14.3	0.097
Mortality, *n* (%)	43 (46.7)	0 (0)	43 (100)	-

SD: Standard deviation; TBSA: total body surface area.

time of admission to the burn unit. Kaplan–Meier curves were plotted using XLSTAT (XLSTAT, Addinsoft, NY) to determine survival probability, and statistical difference was assessed using the log rank (Mantel–Cox) test.

Results

Overall, 92 patients admitted to our burn ICU for TEN/SJS during the aforementioned study period were included. The detailed descriptive statistics of the patients' demographic and clinical variables are shown in Table 1.

Upon admission, all patients with TEN/SJS were treated according to the burn unit's protocol and primarily received hydrotherapy in the burn ICU. Hydrotherapeutic debridement usually involves the washing of wounds in a specifically designed bath for burn patients, followed by the removal of debris and non-vital skin tissue using warm filtered water, gauzes, and antibacterial gel lotion. This initial procedure is usually performed under general anesthesia or analgosedation upon the establishment of central venous and arterial lines. This is followed by temporary wound dressing with antimicrobial gels and fatty gauze. According to the protocol, all non-vital medications were promptly ceased and individualized fluid management was initiated. The consequent medical approach and administration of intravenous immunoglobulin and corticosteroid therapy was carried out in a multidisciplinary fashion involving plastic surgeons, intensivists, dermatologists, microbiologists, gastroenterologists, ophtalmologists, and physiotherapists according to individual needs. Throughout the hospital stay, the patients underwent daily clinical assessment and received either temporary wound dressing with antimicrobial gels and fatty gauze or hydrolytic skin substitutes consisting of a lactic acid copolymer (Suprathel®, Polymedics).

Among all patients, 4 (4.3%) had SJS, 23 (25%) had TEN/SJS overlap, and 65 (70.7%) had TEN. The mean age was 62.9 ± 20.4 years with 40.2% of all patients being ≥70 years old, and 54 (58.7%) patients were women. The mean percentage of TBSA affected was 51.7 ± 29.5%.

The most common comorbidities are depicted in Table 2. The most frequently observed medical diseases included arterial hypertension (53.3%), chronic kidney disease (31.5%), arrhythmia (22.8%), and coronary artery disease (17.4%). Furthermore, 21.7% of the patient population presented with a history of or current malignancy; 13% were active smokers; and 19 patients (20.7%) required renal replacement therapy during in-hospital stay.

In total, a mortality rate of 46.7% was noted with 43 deaths among the entire patient population (Figure 4). Non-survivors were significantly older (67.8 vs. 59.3, p=0.026) and mostly female. They

Table 2
Concomitant comorbidities.

Medical Disease, n (%)	All (n= 92)	Survivors (n=49)	Non-survivors (n= 43)	p-value
Acute kidney disease	10 (10.9)	5 (10.2)	5 (11.6)	>0.99
Arrhythmia	21 (22.8)	10 (20.4)	11 (25.6)	>0.99
Arterial hypertension	49 (53.3)	26 (53.1)	23 (53.5)	0.67
Chronic kidney disease	29 (31.5)	16 (32.7)	13 (30.2)	0.71
Chronic obstructive pulmonary disease	10 (10.9)	3 (6.1)	7 (16.3)	0.34
Coronary artery disease	16 (17.4)	10 (20.4)	6 (14.0)	0.33
Current smoker	12 (13.0)	7 (14.3)	5 (11.6)	0.58
Dementia	4 (4.3)	2 (4.1)	2 (4.7)	>0.99
Diabetes	14 (15.2)	7 (14.3)	7 (16.3)	>0.99
Glomerulonephritis	2 (2.2)	1 (2.0)	1 (2.3)	>0.99
Gout	9 (9.8)	6 (12.2)	3 (7.0)	0.51
Heart insufficiency	10 (10.9)	6 (12.2)	4 (9.3)	0.75
Lupus erythematosus	4 (4.3)	2 (4.1)	2 (4.7)	>0.99
Malignancies (history/current)	20 (21.7)	7 (14.3)	13 (30.2)	0.26
Pancreatitis	4 (4.3)	2 (4.1)	2 (4.7)	>0.99
Psoriasis	4 (4.3)	2 (4.1)	2 (4.7)	>0.99
Sjögren's syndrome	2 (2.2)	1 (2.0)	1 (2.3)	>0.99
Thyroid dysfunction	9 (9.8)	4 (8.2)	5 (11.6)	>0.99

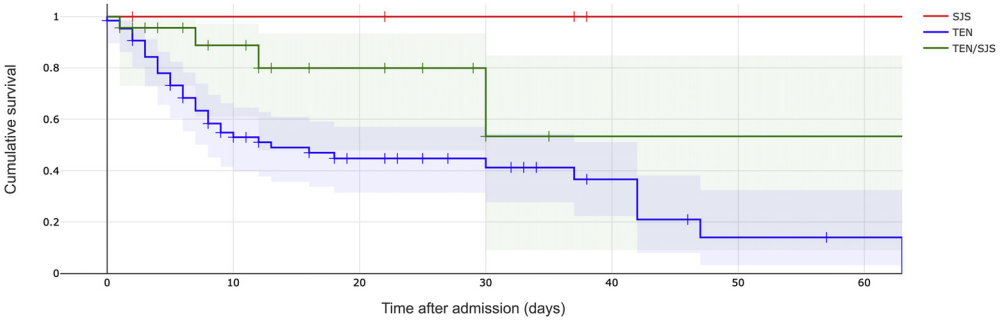

Figure 4. Kaplan–Meier survival analysis of the overall in-hospital survival following admission to the burn ICU.

presented with significantly higher skin blistering severity, depicted by the higher TBSA (69.4% vs. 36.9%, p <0.001). Notably, patients with ≥50% TBSA affected displayed a mortality rate of 72%. Non-survivors considerably suffered more frequently from concomitant comorbidities; however, without statistical significance. Death occurred on an average on the 12th day following admission with the most common causes of death being sepsis, multiple organ failure, and acute respiratory distress syndrome.

An overview of the most frequent and probable culprit drugs is given in Table 3. Overall, 105 probable culprit drugs were found in the entire study population. The most suspected drugs that caused TEN/SJS were allopurinol (14.1%), metamizole (14.1%), piperacillin/tazobactam (10.9%), ciprofloxacin (9.8%), and vancomycin (8.7%). Among 5 patients (5.4%), no TEN/SJS-inducing suspect drug could be identified. These TEN/SJS cases were attributable to systemic lupus erythematosus (SLE) (3 cases), mycoplasma pneumonia infection (1 case), and paraneoplastic syndrome (1 case).

Discussion

TEN/SJS are some of the few dermatological conditions that require urgent care and constitute a medical emergency. In recent years, considerable progress has been made in understanding immunogenomics, pathomechanism, and possible treatment modalities. Nonetheless, evidence-based guidelines on the clinical and therapeutic management of patients with TEN/SJS remain sparse. Hence, timely diagnosis and prompt discontinuation of suspected trigger agents are crucial to halt the pro-

Table 3
Most probable culprit drugs suspected of inducing TEN/SJS.

Drug, n (%)	All (n=105)	Survivors (n=50)	Non-survivors (n= 55)	p-value
Antibiotics				
Amoxicillin/clavulanic acid	1 (1.1)	0 (0.0)	1 (2.3)	>0.99
Cefaclor	1 (1.1)	1 (2.0)	0 (0.0)	>0.99
Cefazolin	2 (2.2)	2 (4.1)	0 (0.0)	0.5
Ceftriaxone	5 (5.4)	1 (2.0)	4 (9.3)	0.38
Cefuroxime	2 (2.2)	1 (2.0)	1 (2.3)	>0.99
Ciprofloxacin	9 (9.8)	2 (4.1)	7 (16.3)	0.18
Clindamycin	4 (4.3)	3 (6.1)	1 (2.3)	0.63
Cotrimoxazole	5 (5.4)	4 (8.2)	1 (2.3)	0.38
Doxycycline	1 (1.1)	1 (2.0)	0 (0.0)	>0.99
Meropenem	7 (7.6)	1 (2.0)	6 (14.0)	0.13
Metronidazole	3 (3.3)	1 (2.0)	2 (4.7)	>0.99
Moxifloxacin	1 (1.1)	1 (2.0)	0 (0.0)	>0.99
Piperacillin/Tazobactam	10 (10.9)	4 (8.2)	6 (14.0)	0.75
Sultamicillin	3 (3.3)	1 (2.0)	2 (4.7)	>0.99
Vancomycin	8 (8.7)	2 (4.1)	6 (14.0)	0.29
Pain medication				
Coxibs	1 (1.1)	1 (2.0)	0 (0.0)	>0.99
Metamizole	13 (14.1)	7 (14.3)	6 (14.0)	>0.99
Paracetamol	4 (1.1)	1 (2.0)	0 (0.0)	>0.99
Others				
Allopurinol	13 (14.1)	10 (20.4)	3 (7.0)	0.092
Carbamazepine	2 (2.2)	1 (2.0)	1 (2.3)	>0.99
Contrast media	1 (1.1)	1 (2.0)	0 (0.0)	>0.99
Corticosteroids	3 (3.3)	2 (4.1)	1 (2.3)	>0.99
Fulvestrant	1 (1.1)	0 (0.0)	1 (2.3)	>0.99
Glibenclamide	1 (1.1)	1 (2.0)	0 (0.0)	>0.99
Palbociclib	1 (1.1)	0 (0.0)	1 (2.3)	>0.99
Pembrolizumab	1 (1.1)	0 (0.0)	1 (2.3)	>0.99
Rituximab	1 (1.1)	0 (0.0)	1 (2.3)	>0.99
Spironolactone	1 (1.1)	1 (2.0)	0 (0.0)	>0.99

gression of the condition. The suspected culprit drugs found to cause TEN/SJS in our study cohort was consistent with findings of earlier studies, which repeatedly found anticonvulsants, allopurinol, and antibiotics to be significant disease triggers.[18–20] Allopurinol and metamizole were found to be the leading culprit drugs in our study population over the course of 15 years. Allopurinol, a drug commonly recommended in hyperuricemia and gout, is known to be a potent inducer of severe cutaneous adverse drug reactions. Our finding is consistent with those of previous reports that identified allopurinol as a leading trigger of TEN/SJS in the Asian and European populations.[21,22] The high incidence of allopurinol-induced TEN/SJS may reflect the widespread administration of this medication in older patients with hyperuricemia and gouty arthritis. In the past, allopurinol-attributable TEN/SJS was also observed more frequently in populations displaying high frequency of the HLA-B*5801 allele (i.e., Asian), which may further explain the large case numbers in the literature.[23]

Another leading culprit drug found in this study was metamizole, a non-opioid analgesic and cyclooxygenase inhibitor. Metamizole presents a well-known trigger of allergic and non-allergic hypersensitivity reactions.[24] It has been effectively withdrawn from the markets in Australia, the United Kingdom, and the United States of America because of the potential risk of agranulocytosis. Nonetheless, it is available and widely used in various European, Asian, and South American countries.[25] Several reports have been published in the past on metamizole-induced TNE/SJS.[26–28] Our cases highlight the significance of clinical vigilance and awareness of metamizole-triggered TEN/SJS when administering the drug.

No probable drug trigger was found in 5 patients in our study. The absence of a causative agent is a frequent and interesting observation in multiple studies, alluding to other potential pathomechanisms besides drug metabolite exposure. Various other causes have been considered as possible disease triggers such as paraneoplastic entities, bacterial infections, and auto-immune diseases.[3,7,29] In this study,

3 patients presented with TEN/SJS attributable to SLE. SLE-associated TEN/SJS has been described in the literature with authors coining the term lupus-associated TEN.[30] The frequent multiple comorbidities and polypharmacotherapy in patients with SLE complicates TEN/SJS diagnosis, as SLE may manifest with various forms of bullous exanthema and because the current body of evidence remains sparse in that field. We also observed one patient who experienced TEN as an extrapulmonary complication of *Mycoplasma pneumoniae* infection. A few reports on *M. pneumonia* infection-associated TEN/SJS have been published in the past, particularly presenting non-adult cases with and without prior drug metabolite exposure.[31–33]

Furthermore, TEN/SJS were found to occur more frequently in women than men which is consistent with the findings of previous studies.[5,34,35] Nonetheless, a significant association between sex and mortality could not be observed. Our study revealed a positive correlation of increasing age and higher TBSA affection with mortality. A possible explanation for the more frequent incidence in older patients may be the greater exposure to culprit drugs and higher incidence of relevant comorbidities that might affect the systemic pharmacological impact of the given drugs.

The mortality rate in our cohort was considerably high when compared to the rates in previous reports. A possible explanation may be the cohort's comparably high mean age of 64 years and significant mean TBSA affection of 52%, which have both shown association with poor prognosis. Also, the rate of the accompanying malignancy or history of malignancy was higher in our collective than in previously published reports.[36] A significantly increased risk of TEN/SJS in patients with malignancies has repeatedly been described, particularly in patients with hematologic cancers.[37]

Further, a considerable heterogeneity among the analyzed patient collective could be assumed, given that the study period displayed a relatively large range from 2007 to 2022. We hypothesize that better clinical understanding of TEN/SJS pathophysiology has brought advancements in therapeutic regimens including wound dressing/care, infection prevention, and fluid management. Moreover, progress in intensive care management and therapeutic measures such as nutritional support may have assisted in reducing TEN/SJS-related mortality over the course of the years.

Conclusion

Some findings in this study present considerable relevance to the understanding and care of these challenging diseases. Allopurinol and metamizole were found to be the most frequently responsible culprit drugs, echoing the extensive use of the drugs in the general population. They were followed by the antibiotics piperacillin/tazobactam, ciprofloxacin, and vancomycin. Clinical vigilance is therefore recommended when administering these anti-infective agents. TEN/SJS mostly occurred in women, and older patients with high percentages of TBSA affected particularly experienced increased risk for mortality, highlighting the importance of increased multidisciplinary efforts in treating this vulnerable patient collective.

Limitations

Some limitations exist with regard to our results. Our burn center is one of the few major burn centers and a large referral center in the region, thereby, the disease severity in our patient collective may be skewed. Treatments that used by external practitioners and hospitals were not considered in the analysis. All results are based on the retrospective data from a single-center and a relatively small patient cohort; therefore, they may only in part reflect the epidemiological characteristics of patients with TEN/SJS in Germany which may limit the generalizability of the results. Another limitation is the lack of a standardized protocol for the implementation of intravenous immunoglobulin and corticosteroid therapy in these patients. Thus, adaptation of national and international registries of hospitalized patients with TEN/SJS is encouraged.

Conflicts of interest

The authors declare that they have no conflict of interest.

Ethical approval

Ethical Approval was given by Hannover Medical School (Nr. 10806_BO_K_2023).

Authorship and Author's Responsibility

Dima Obed: conception and design, acquisition of data, analysis and interpretation of data, drafting the article, critical revision of article, final approval, agreement to be accountable for all aspects of the work. **Mustafa Salim:** analysis and interpretation of data, critical revision of article, final approval, agreement to be accountable for all aspects of the work. **Khaled Dastagir:** critical revision of article, final approval, agreement to be accountable for all aspects of the work. **Nicco Krezdorn:** critical revision of article, final approval, agreement to be accountable for all aspects of the work. **Doha Obed:** conception and design, analysis and interpretation of data, critical revision of article, final approval, agreement to be accountable for all aspects of the work. **Peter M. Vogt:** critical revision of article, final approval, agreement to be accountable for all aspects of the work

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Consent for photo publication

Consent for photo publication void of identifying information was retrieved along participation in research.

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