frontiers | Research Topics

# Stevens Johnson syndrome: Past, present, and future directions

**Edited by**
Hajirah Saeed, Abdelrahman M. Elhusseiny, Maja Mockenhaupt, Swapna Shanbhag and Elizabeth Phillips

**Published in**
Frontiers in Medicine
Frontiers in Pharmacology
Frontiers in Oncology

ISSN 1664-8714
ISBN 978-2-8325-4630-7
DOI 10.3389/978-2-8325-4630-7

## About Frontiers

Frontiers is more than just an open access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

## Frontiers journal series

The Frontiers journal series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the *Frontiers journal series* operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

## Dedication to quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews. Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

## What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the *Frontiers journals series*: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area.

Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers editorial office: frontiersin.org/about/contact

# Stevens Johnson syndrome: Past, present, and future directions

**Topic editors**

Hajirah Saeed — University of Illinois Chicago, United States

Abdelrahman M. Elhusseiny — University of Arkansas for Medical Sciences, United States

Maja Mockenhaupt — University of Freiburg Medical Center, Germany

Swapna Shanbhag — L V Prasad Eye Institute, India

Elizabeth Phillips — Vanderbilt University, United States

**Citation**

Saeed, H., Elhusseiny, A. M., Mockenhaupt, M., Shanbhag, S., Phillips, E., eds. (2024). *Stevens Johnson syndrome: Past, present, and future directions*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-4630-7

# Table of contents

frontiers | Frontiers in Medicine

TYPE Editorial
PUBLISHED 07 March 2024
DOI 10.3389/fmed.2024.1383891



OPEN ACCESS

EDITED AND REVIEWED BY
Robert Gniadecki,
University of Alberta, Canada

*CORRESPONDENCE
Elizabeth J. Phillips
✉ elizabeth.j.phillips@vumc.org

RECEIVED 08 February 2024
ACCEPTED 26 February 2024
PUBLISHED 07 March 2024

CITATION
Saeed HN, Micheletti R and Phillips EJ (2024) Editorial: Stevens Johnson syndrome: past, present, and future directions.
*Front. Med.* 11:1383891.
doi: 10.3389/fmed.2024.1383891



# Editorial: Stevens Johnson syndrome: past, present, and future directions

Hajirah N. Saeed[1,2], Robert Micheletti[3] and Elizabeth J. Phillips[4,5]*

[1]Department of Ophthalmology, Illinois Eye and Ear Infirmary, University of Illinois Chicago, Chicago, IL, United States, [2]Department of Ophthalmology, Loyola University Medical Center, Maywood, IL, United States, [3]Department of Dermatology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, United States, [4]Center for Drug Safety and Immunology, Vanderbilt University Medical Center, Nashville, TN, United States, [5]Institute for Immunology and Infectious Diseases, Murdoch University, Murdoch, WA, Australia

KEYWORDS

SJS, TEN, HLA, complications, community, testing, diagnosis

Editorial on the Research Topic
Stevens Johnson syndrome: past, present, and future directions

Stevens Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) is a rare immune-mediated mucocutaneous disease with a global incidence of up to 12 cases per million population annually (1). SJS/TEN cumulative hospitalization cost is ~$128 million per year, and mortality rates can exceed 50% in the immunocompromised and elderly (2). There are still many gaps in knowledge about the pathogenesis of SJS/TEN and, hence, in the ways to optimize prevention, earlier diagnosis, targeted acute treatment and long-term management. (3).

In this Research Topic, a wide breadth of novel data and new insights is presented by researchers globally, which reflects the current collaborative work that is ongoing to eliminate the morbidity and mortality of this devastating and life-threatening disease. As a direct result of this collaboration, the SJS/TEN biennial conference was established in 2017 that promoted patient and community involvement (4). The 3rd biennial conference, SJS/TEN 2021 (Marks et al.), brought together 428 international scientists and 140 survivors and family members. The goal of the meeting was to brainstorm strategies to support the continued growth of an international SJS/TEN research network, bridging science and the community. The community workshop section of the meeting focused on eight primary themes: mental health, eye care, SJS/TEN in children, non-drug induced disease, long-term health complications, new advances in mechanisms and basic science, managing long-term scarring, considerations for skin of color, and risks of COVID-19 vaccines. This meeting has since been followed by SJS/TEN 2023 "Bringing Science to All" in August 2023 that tackled an overarching theme of overcoming geographic, social, and economic barriers and disparities, aiming to be inclusive of all populations. Many of these same contributors from the 2023 meeting who presented novel data are represented in this Research Topic.

Over the last decade, there have been considerable insights on immunotherapy and immune-checkpoint-inhibitor-therapy-induced SJS/TEN as well as novel methods to improve the diagnosis, management, and mortality risk stratification of SJS/TEN, and organ-specific pathology.

Chen et al. and Kurian et al. highlight SJS/TEN occurring in association with novel agents: the epidermal growth factor receptor tyrosine kinase inhibitor toripalimab and the α-specific PI3K inhibitor alpelisib. Kuo et al. (5) highlight the addition of severe cutaneous immune related adverse events associated with immune checkpoint inhibitors and highlight knowledge and evidence gaps related to diagnosis and treatment. The presentation can vary from SJS mimickers such as lichenoid and autoimmune bullous disorders to presentations more in keeping with traditional SJS/TEN. In their comprehensive 40 year literature review, Wang et al. identify the demographics, clinical course, and mortality risk of 379 drug culprits across four common classes associated with SJS/TEN.

While notable recent advances in SJS/TEN have made risk prediction and prevention possible for some causative factors, many challenges still exist in the scoring and documentation of the severity of SJS/TEN, which has not been standardized to be reproducible across individual cases and treatment centers. This phenotyping is a pre-requisite for engaging in further studies, particularly clinical trials, to assess the efficacy of therapeutics and other interventions. Shareef et al. examine the predictive value of a random forests classifier for mortality compared with SCORTEN, the most commonly used mortality risk prediction tool. SCORTEN requires calculation of total body surface area detached, which is subject to considerable observer error and variability. In their model, which used only routine laboratory information, the top five predictors of mortality were RBC count, total bilirubin, prothrombin time, WBC count and RBC count.

Beyond mortality prediction, however, other novel diagnostic and staging systems include medical photography to monitor progression and treatment response. Dobry et al. summarize the state of current clinical assessment and scoring tools and highlight the need for standardized approaches to measure cutaneous involvement. Lehloenya highlights the need for reproducible endpoints in clinical studies and consideration for innovative approaches such as use of biological markers, artificial intelligence, and imaging approaches (e.g., PET/CT scan) to monitor progression and therapeutic response.

In adults, >80% of SJS/TEN is caused by a small molecule drug. SJS/TEN is also marked by tissue specificity. Hence, "blood tests" and *ex vivo*/*in vitro* tests to define drug causality have been challenging. Copaescu et al. comprehensively review the current state of *in vivo* and *ex vivo*/*in vitro* diagnostic tools of potential use in severe cutaneous adverse drug reactions, including SJS/TEN, to aid diagnosis and drug causality. The sensitivity of both patch testing and *in vitro*/*ex vivo* testing in SJS/TEN was dependent on the culprit medication and was lower (<50%) for SJS/TEN than for drug reaction with eosinophilia and systemic (DRESS). Genetic testing has been posited in the past as a screening tool for the prevention of SJS/TEN or DRESS where this is a well-established association. When an HLA allele is distinct for a specific medication, genetic testing, along with patch testing and *in vitro*/*ex vivo* testing, may also aid in diagnosis.

Although there is agreement on harmonized supportive care and comprehensive ophthalmological, cutaneous, and urogynecological management in an acute critical care setting, the long-term effects of acute SJS/TEN and its management on long-term complications are largely unknown. DenAdel et al. present a retrospective chart review of 77 biopsy-supported female patients with SJS/TEN treated at a single center. They were able to measure a positive impact by protocolizing acute management that guided gynecological consultation and appropriate treatment of vulvovaginal disease.

Although there has been much progress in SJS/TEN research, many gaps exist. In addition to genetic factors, more study is needed on the social determinants of health that can drive medication utilization and impact risk in disadvantaged populations (6, 7). Further study of tissue specific responses will help define markers for earlier diagnosis and targeted treatment. A system that ensures that care does not end at hospital discharge is also crucial to providing necessary medical and psychological support and to prevent and support long-term complications such as visual impairment and blindness (8). Particularly important is documentation and a health "passport" to avoid exposure to culprit medication(s) and ensure drug safety for the future.

## Author contributions

HS: Writing – review & editing, Writing – original draft, Conceptualization. RM: Writing – review & editing, Conceptualization. EP: Writing – review & editing, Writing – original draft, Conceptualization.

## Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. EP receives support from the NIH R01HG010863, R01AI152183, U01AI154659 and the National Health and Medical Research Council of Australia. This published work was in part funded by the 1R13AR082704-01 and R13AR078623. HS receives funding from NIH K23EY028230 and U01A/154659.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note

# References


1. White ML, Chodosh J, Jang J, Dohlman C. Incidence of Stevens-Johnson syndrome and chemical burns to the eye. *Cornea*. (2015) 34:1527–33. doi: 10.1097/ICO.0000000000000646

2. Hsu DY, Brieva J, Silverberg NB, Silverberg JI. Morbidity and mortality of stevens-johnson syndrome and toxic epidermal necrolysis in United States adults. *J Invest Dermatol*. (2016) 136:1387–97. doi: 10.1016/j.jid.2016.03.023

3. Phillips EJ, Bouchard CS, Divito SJ. Stevens-Johnson syndrome and toxic epidermal necrolysis-coordinating research priorities to move the field forward. *JAMA Dermatol.* (2022) 158:607–8. doi: 10.1001/jamadermatol.2022.0484

4. White KD, Abe R, Ardern-Jones M, Beachkofsky T, Bouchard C, Carleton B, et al. SJS/TEN 2017: building multidisciplinary networks to drive science and translation. *J Allergy Clin Immunol Pract.* (2018) 6:38–69. doi: 10.1016/j.jaip.2017.11.023

5. Kuo AM, Gu S, Stoll J, Moy AP, Dusza SW, Gordon A, et al. Management of immune-related cutaneous adverse events with dupilumab. *J Immunother Cancer*. (2023) 11:e007324. doi: 10.1136/jitc-2023-007324

6. Bensken WP, Vaca GF, Williams SM, Khan OI, Jobst BC, Stange KC, et al. Disparities in adherence and emergency department utilization among people with epilepsy: a machine learning approach. *Seizure.* (2023) 110:169–76. doi: 10.1016/j.seizure.2023.06.021

7. Lu N, Rai SK, Terkeltaub R, Kim SC, Menendez ME, Choi HK. Racial disparities in the risk of Stevens-Johnson Syndrome and toxic epidermal necrolysis as urate-lowering drug adverse events in the United States. *Semin Arthritis Rheum*. (2016) 46:253–8. doi: 10.1016/j.semarthrit.2016.03.014415

8. Coromilas AJ, Divito SJ, Phillips EJ, Micheletti RG. Physical and mental health impact of Stevens-Johnson syndrome/toxic epidermal necrolysis and post-hospital discharge care: Identifying practice gaps. *JAAD Int*. (2023) 11:88–9. doi: 10.1016/j.jdin.2023.01.012

frontiers | Frontiers in Medicine

MINI REVIEW
published: 13 June 2022
doi: 10.3389/fmed.2022.898790

# High Grade Dermatologic Adverse Events Associated With Immune Checkpoint Blockade for Cancer

*Alyce M. Kuo*[1] *and Alina Markova*[1,2]*

[1] Dermatology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, United States,
[2] Department of Dermatology, Weill Cornell Medical College, New York, NY, United States

Immune checkpoint blockade (ICB) improves survival in many types of cancers including melanoma, non-small cell lung, renal cell, breast, and cervical cancers. However, many of these therapies are also associated with high grade dermatologic adverse events (DAEs), including Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN), SJS/TEN-like reactions, high grade maculopapular and psoriasiform rashes, autoimmune bullous eruptions, drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP), which may limit their tolerability and use. It is important to properly identify and treat DAEs to ICB because these DAEs may be associated with positive anti-tumor response and patients may have limited options for alternative anti-cancer therapeutics. In this review, we describe high grade DAEs to increasingly used ICB agents, which target CTLA-4 and PD-1 or its ligand, PD-L1 and enable the immune system to target cancer cells. We further differentiate life-threatening adverse reactions from mimickers and report cases of serious DAEs which have been recorded in association with ICB through the FDA Adverse Events Reporting System (FAERS), which is an archive of adverse events associated with various drugs and therapeutic biologic products reported voluntarily by consumers and healthcare professionals as well as mandatorily by manufacturers. Lastly, we summarize management recommendations for these adverse events and discuss knowledge and evidence gaps in this area.

**Keywords: toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), immune checkpoint blockade (ICB), acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), bullous pemphigoid (BP), rash, dermatologic adverse events (DAEs)**

OPEN ACCESS

***Edited by:***
*Elizabeth Phillips,*
*Vanderbilt University, United States*

***Reviewed by:***
*Sherrie Divito,*
*Brigham and Women's Hospital and Harvard Medical School, United States*

****Correspondence:***
*Alina Markova*
*markovaa@mskcc.org*

***Specialty section:***
*This article was submitted to Dermatology, a section of the journal Frontiers in Medicine*

***Received:*** *17 March 2022*
***Accepted:*** *25 May 2022*
***Published:*** *13 June 2022*

***Citation:***
*Kuo AM and Markova A (2022) High Grade Dermatologic Adverse Events Associated With Immune Checkpoint Blockade for Cancer. Front. Med. 9:898790. doi: 10.3389/fmed.2022.898790*

## INTRODUCTION

Immune checkpoint blockade (ICB) improves survival in many cancers including melanoma, non-small cell lung, renal cell, breast, and cervical cancers (1–5). However, it is also associated with dermatologic adverse events (DAEs), which may limit its tolerability and use. Although most DAEs are mild or moderate, others may be systemic and even life-threatening. High grade [Common Terminology Criteria for Adverse Events (CTCAE) grade ≥3, see **Table 1**] (6) DAEs cover a spectrum of entities, including Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN), SJS/TEN-like reactions, bullous eruptions, drug reaction with eosinophilia and systemic

**TABLE 1 |** DAE grading (Adapted from the CTCAE Version 5.0) (6).

| DAE | Grade | Description |
|---|---|---|
| SJS/TEN | 3 | Skin sloughing <10% body surface area (BSA) + associated signs (mucous membrane detachment, etc.) |
| | 4 | Skin sloughing 10–30% BSA (SJS) or ≥30% BSA (TEN) + associated signs |
| Rash maculopapular | 1 | Macules/papules covering <10% BSA ± symptoms (pruritus, burning, etc.) |
| | 2 | Macules/papules covering 10–30% BSA ± symptoms (pruritus, burning, etc.), limiting instrumental activities of daily living (ADL), or ≥30% BSA ± mild symptoms |
| | 3 | Macules/papules covering >30% BSA + moderate/severe symptoms, limiting self-care ADL |
| Bullous dermatitis | 1 | Asymptomatic, blisters covering <10% BSA |
| | 2 | Blisters covering 10–30% BSA, painful blisters, or limiting instrumental ADL |
| | 3 | Blisters covering >30% BSA, limiting self-care ADL |
| | 4 | Blisters covering >30% BSA + fluid/electrolyte abnormalities, ICU/burn unit indicated |
| | 5 | Death |
| Other skin disorders (Other DAEs) | 1 | Asymptomatic or mild symptoms |
| | 2 | Moderate; limiting ADL |
| | 3 | Severe or medically significant but not life threatening |
| | 4 | Life-threatening consequences |
| | 5 | Death |

symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP) (7). It is important to properly identify and treat DAEs to ICB because patients often have limited options for alternative anti-cancer therapeutics. In this review, we describe high grade DAEs to ICB, differentiating life-threatening DAEs from mimickers. We also report cases of serious DAEs which have been recorded in association with ICB through the FDA Adverse Events Reporting System (FAERS), which is an archive of adverse events associated with various drugs and therapeutic biologic products reported voluntarily by consumers and healthcare professionals as well as mandatorily by manufacturers.

## IMMUNE CHECKPOINT BLOCKADE

The anti-CTLA-4 monoclonal antibody ipilimumab, anti-PD-1 monoclonal antibodies cemiplimab, nivolumab, and pembrolizumab, and anti-PD-L1 monoclonal antibodies atezolizumab, avelumab, and durvalumab overcome immune checkpoints, allowing the immune system to target cancer cells. These agents are associated with many immune-related DAEs (irDAEs), which tend to develop earlier than non-cutaneous immune-related adverse events (irAEs) (8, 9). Although the most common irDAEs to ICB, such as maculopapular rash, pruritus, and lichenoid dermatoses, may be controlled with topical corticosteroids and oral anti-pruritics, high grade irDAEs may require prolonged systemic therapy and/or discontinuation of the culprit immunotherapy (10). Importantly, the development of irDAEs has been associated with better overall survival in patients treated with ICB (11).

## TRUE STEVENS-JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS

True SJS/TEN has been described in association with ICB, with classic rapid onset and progression and high mortality rates ranging from 10% for SJS to 50% for TEN (10, 12). As of March 2022, 255 cases of SJS/TEN had been reported through FAERS with pembrolizumab, 102 with ipilimumab, 224 with nivolumab, 55 with atezolizumab, 3 with avelumab, 21 with durvalumab, and 4 with cemiplimab. Diagnosis of true SJS/TEN is based on mucocutaneous involvement with supportive histopathological findings. Irregularly shaped dark, dusky macules may spread from the trunk and proximal extremities to the rest of the body. Patients may first present with a prodrome of malaise, followed by mucocutaneous pain as mucosal membranes and skin undergo necrolysis, upper respiratory symptoms, and fever, later developing systemic involvement of the liver, lungs, or gastrointestinal tract (13). Biopsy typically reveals full thickness epidermal necrosis with vacuolar interface changes, cleavage along the dermal epidermal junction, and subepidermal lymphocytes (14).

When SJS/TEN is suspected, urgent dermatologic evaluation is necessary and inpatient admission should be considered and ICB as well as other potential culprit medications should be held (15). Those with widespread mucocutaneous desquamation or life-threatening complications should be admitted to the intensive care or burn unit (16). Skin biopsies should be assessed for full-thickness epidermal necrosis, which is seen in true SJS/TEN and SJS/TEN-like reactions. Management of true SJS/TEN in patients on ICB must include supportive care and ophthalmologic, gynecologic and/or urologic consultations depending on extent and location of mucosal involvement. ICB must be discontinued once true ICB-associated SJS/TEN diagnosis is confirmed. National Comprehensive Cancer Network (NCCN) Guidelines for Management of Immunotherapy-Related Toxicities (version 1.2022) (15) provide recommendations for SJS/TEN management (without differentiating the treatment for both true SJS/TEN and SJS/TEN-like rashes) with prednisone or methylprednisolone 1–2 mg/kg/day and intravenous immune globulin (IVIg) 1 g/kg/day and/or other immunosuppressive therapies, including etanercept and cyclosporine can be considered for true SJS/TEN (15).

## STEVENS-JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS-LIKE REACTIONS

Incidence of SJS/TEN-like reactions is not known. Because cases of SJS/TEN in the FAERS database are voluntarily reported

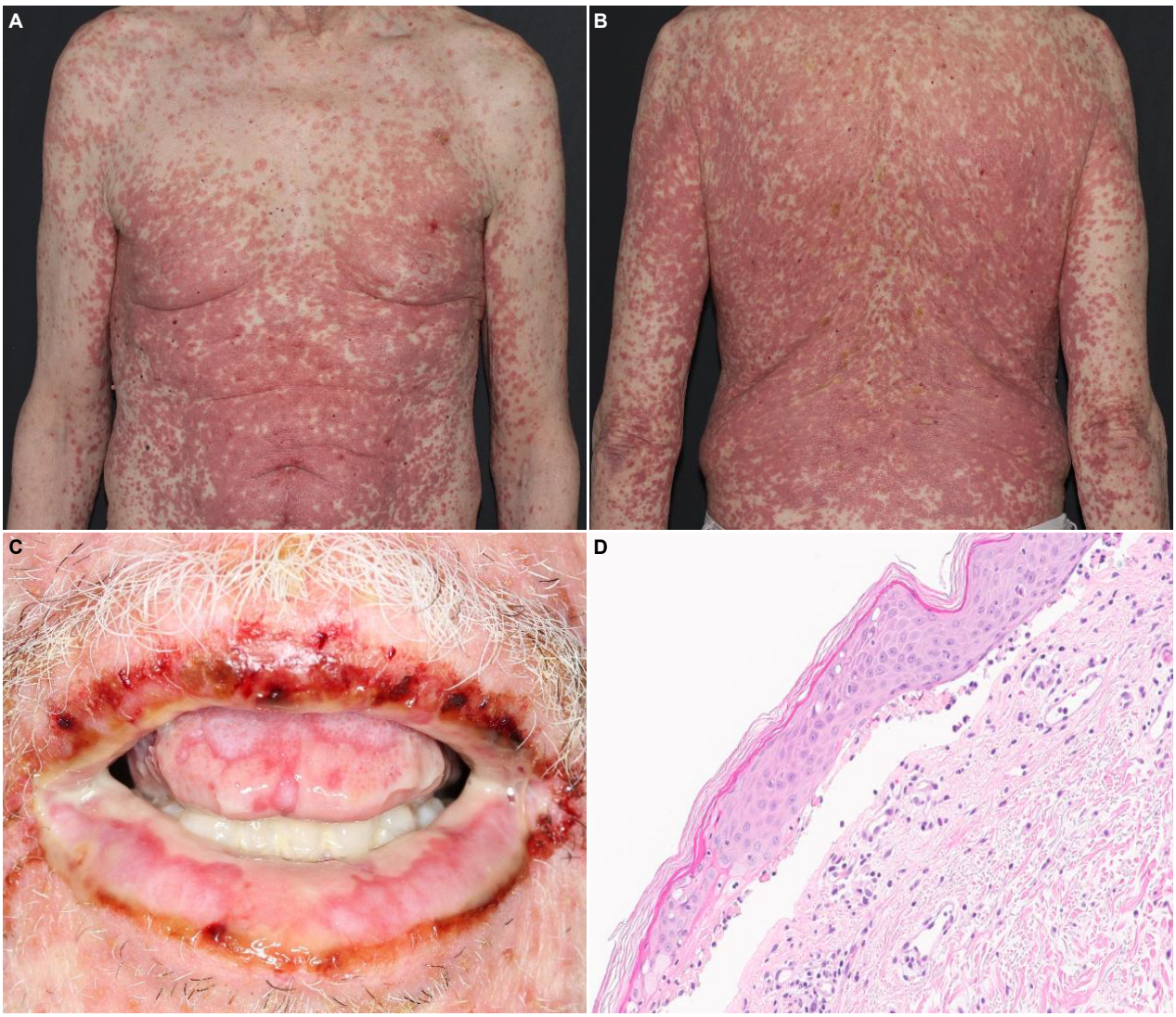


**FIGURE 1 |** SJS/TEN-like reaction with erythematous macules and papules with dusky, purpuric centers covering about 80% BSA on the **(A)** trunk and **(B)** back. **(C)** Desquamation and hemorrhagic crusts on the oral mucosa. **(D)** Histology revealing lichenoid and subepidermal vesicular dermatitis with epidermal necrosis.

and unverified, they likely include SJS/TEN-like reactions, which mimic SJS/TEN but vary in severity and clinical course. While ipilimumab has not independently been associated with SJS/TEN-like reactions, emerging evidence suggests anti-PD-1/PD-L1 therapies are associated more frequently with SJS/TEN-like reactions (**Figures 1A–C**) than true SJS/TEN (17, 18). Unlike true SJS/TEN, which presents acutely, some SJS/TEN-like reactions to anti-PD-1/PD-L1 blockade progress from mild DAEs over a few to several weeks. Initially, patients may present with a morbilliform eruption, which then turn into targetoid patches and epidermal detachment with associated mucositis. Alternatively, other SJS/TEN-like reactions occur *de novo* late in the course of treatment with anti-PD-1/PD-L1 therapy. In one series of 18 patients, 2 developed SJS/TEN-like reactions *de novo* without preceding rash more than 6 weeks after initiating treatment with anti-PD-1/PD-L1 blockade (19). These reactions develop weeks to months after initiating treatment (median: 52 days, range: 3–420 days) (14, 20). SJS/TEN-like reactions due to pembrolizumab typically occur later with a median onset of 11 weeks and average of 12.8 weeks after initiation (19). SJS/TEN-like reactions present with a more benign clinical course and favorable treatment response when compared to true SJS/TEN (18). However, concurrent use of multiple ICB agents such as ipilimumab with nivolumab can lead to earlier and more severe DAEs, as seen in one analysis of pooled safety data from 1,551 patients with advanced melanoma (21). SJS/TEN-like reactions may occur concurrently with extra-cutaneous irAEs. In a pooled analysis of three trials of 448 patients with advanced melanoma who received ipilimumab/nivolumab, the most frequently reported irAEs involved skin (64.3%) and GI (46.7%). Thirty percent of

patients developed grade 2–4 irAEs in more than one organ system (22).

Antibiotic use may precipitate SJS/TEN and SJS/TEN-like reactions to ICB. A large retrospective study of 767 patients treated with ICB at a single institution and analysis of 38,705 safety reports of patients receiving anti-PD-1/PD-L1 from FAERS found that irAE potential risks including SJS/SJS-like development was higher in patients who used antibiotics during ICB therapy compared to those who did not (23). ICB may also increase a patient's risk of developing SJS/TEN and SJS/TEN-like reactions to other agents. One series of seven patients who developed SJS-like reactions after anti-PD-1/PD-L1 with or without anti-CTLA-4 blockade found that all patients had received newly initiated drugs such as trimethoprim-sulfamethoxazole and allopurinol before DAE onset. A 2-hit hypothesis may play a part in the explanation for this association: ICB may first modulate the immune system to heighten drug sensitivity and then addition of a second drug/agent can then trigger an SJS-like reaction (18). Therefore, it is important to carefully identify the culprit agent and to differentiate SJS/TEN-like reactions from true SJS/TEN to potentially allow patients to continue therapy with ICB. Interestingly, even after discontinuation of ICB, patients are still at risk for SJS/TEN-like reactions (24, 25). This may be due to the long half-life of ICB and persistent immune activation in the setting of prolonged tumor responses, which has been observed with both anti-PD-1 and anti-CTLA-4 therapy (26).

Although SJS/TEN-like reactions resemble true SJS/TEN on histopathology (**Figure 1D**), with characteristic findings such as full-thickness epidermal necrolysis, subepidermal clefting, and interface dermatitis, severe clinical symptoms such as fever, ocular involvement, and maximal detachment are much rarer and seen in as few as 8% of patients (17).

In the setting of SJS/TEN-like reactions, ICB should initially be held along with other potential culprit medications. Wound care, topical emollients and high-strength topical steroids can be started (27). NCCN Guidelines for Management of Immunotherapy-Related Toxicities (version 1.2022) for SJS/TEN management (without differentiating the treatment for both true SJS/TEN and SJS/TEN-like rashes) with prednisone or methylprednisolone 1–2 mg/kg/day and IVIg 1 g/kg/day and/or other immunosuppressive therapies, including etanercept and cyclosporine can be considered for true SJS/TEN (15). While etanercept, cyclosporine, and/or IVIg are preferred for true SJS/TEN, topical and systemic steroids are typically used as first-line for SJS/TEN-like eruptions; use of cyclosporine, IVIg, and/or targeted therapies including etanercept, infliximab, tocilizumab, dupilumab may also be considered (27–29). For SJS/TEN-like eruptions, rechallenge of ICB may be considered once all skin and extracutaneous involvement resolves to grade $\leq$1, following a multidisciplinary discussion taking into consideration DAE severity, any required concurrent immunosuppressant for DAE management, prior cancer response to ICB, and alternative anti-cancer therapies (18, 30).

## HIGH-GRADE MACULOPAPULAR RASHES

Pruritic, maculopapular rashes are among the most frequent DAEs associated with ICB (10). High grade (grade 3) maculopapular rashes covering >30% of total body surface area, which develop a median of 3.6 weeks after initiation of anti-CTLA-4 blockade, have been observed in up to 4% of patients (31). There are 1,190 reported cases of serious maculopapular rashes with pembrolizumab, 1,340 with ipilimumab, 1,934 with nivolumab, 385 with atezolizumab, 32 with avelumab, 122 with durvalumab, and 36 with cemiplimab recorded in FAERS. These maculopapular rashes typically present with numerous coalescing macules and papules and most often affects the trunk and extremities (10). Biopsy reveals interface and perivascular/periadnexal lymphocytic dermatitis with or without eosinophils (32). For high grade maculopapular rashes, NCCN guidelines recommend initial management with holding ICB and applying high potency topical steroids to affected areas. Patients can be given prednisone 0.5–1 mg/kg/day and up to 2 mg/kg/day if there is no improvement. After the rash resolves to grade 1 or 0, prednisone should be tapered over 4–6 weeks and ICB may be re-challenged (15). As a targeted, steroid-sparing agent, tocilizumab, an anti-IL-6R monoclonal antibody that limits Th17 differentiation and pro-inflammatory response, may be considered for persistent maculopapular rashes (32). Dupilumab, an anti-IL-4Rα monoclonal antibody that blocks signaling in Th2 pathways implicated in eczema and itch, may be considered for eczematous DAEs and for pruritus (30, 32). Omalizumab has also been shown to relieve pruritus with increased IgE (33). Per NCCN Guidelines for Management of Immunotherapy-Related Toxicities (version 1.2022), gabapentinoids, aprepitant, and narrow-band UVB phototherapy may also be considered for persistent and severe pruritus (15).

## DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS

While classic DRESS is rare to ICB, patients commonly present with generalized maculopapular rash, fever, and concurrent extracutaneous irAEs (transaminitis, azotemia, and colitis) mimicking classic DRESS. While rarely reported in literature (34–37), FAERS has records of 24 reported cases of DRESS with pembrolizumab, 46 with ipilimumab, 89 with nivolumab, 6 with atezolizumab, 1 with avelumab, 3 with durvalumab, and 1 with cemiplimab. In classic DRESS, grade 2 eosinophilia ($\geq$1,500 $\mu L^{-1}$) is present in up to 81% of cases and grade 1 eosinophilia (700–1,499 $\mu L^{-1}$) in 14% of cases (38); however, eosinophilia is less frequently observed in irDAEs, in about 51% (32). Histopathology of the morbilliform eruption of DRESS is often non-specific and may demonstrate features such as interface dermatitis that is present in various dermatoses (16). To manage ICB-DRESS, the culprit ICB should be held initially. Due to systemic involvement, high-dose and prolonged courses of corticosteroids may be

required, with a slow 6- to 8-week taper after ICB-DRESS resolution. Anti-TNF-α, tocilizumab, and dupilumab may be considered as a steroid-sparing, precision medicine approach (16, 30, 37).

## ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS

Acute generalized exanthematous pustulosis (AGEP) is an extremely rare DAE to ICB, characterized by small sterile pustules and edematous erythema. FAERS includes 11 reported cases of AGEP with pembrolizumab, 4 with ipilimumab, 6 with nivolumab, and 8 with atezolizumab. No cases of AGEP have been recorded with avelumab, durvalumab, or cemiplimab. Diagnosis is based on clinical and histopathological findings. AGEP has an acute onset, typically within 48 h of starting a new drug, and may have spontaneous rapid resolution (16, 39, 40). Biopsy reveals subcorneal pustules and subepidermal mixed cellular infiltrates with eosinophils (39, 41). Management of AGEP includes holding ICB and a combination of topical and systemic corticosteroids (oral prednisone 0.5–1 mg/kg/day (7, 16). After multi-disciplinary discussion, ICB may be resumed once AGEP has resolved to grade $\leq$1.

## BULLOUS PEMPHIGOID, LICHEN PLANUS PEMPHIGOIDES, AND BULLOUS LICHEN PLANUS

Although rare with anti-CTLA-4 blockade, bullous disorders secondary to anti-PD-1/PD-L1 therapies have been reported with increasing frequency and may become severe. Through FAERS, 204 cases of bullous dermatitis, autoimmune blistering disease, pemphigoid, or generalized bullous fixed drug eruption have been reported with pembrolizumab. Eighty-nine cases have been reported with ipilimumab, 479 with nivolumab, 41 with atezolizumab, 5 with avelumab, 44 with durvalumab, and 16 with cemiplimab.

Bullous pemphigoid (BP) (**Figure 2**) is the most frequently reported bullous disorder relating to anti-PD-1/PD-L1 blockade, and often presents with prodromal or concurrent pruritus. BP commonly develops as a delayed DAE, appearing >4 months after starting anti-PD-1/PD-L1 blockade (10). BP associated with anti-PD-1/PD-L1 blockade appears to present in younger patients (median age 74 years, range: 50-93 years) and affects the mucosal membranes more frequently (in 38.1% of patients on anti-PD-1/PD-L1 blockade) than idiopathic BP (42). In one study, subepidermal blisters were seen in 81% and eosinophilic infiltrate in 82% of anti-PD-1/PD-L1 blockade associated BP cases on histopathology. Direct immunofluorescence was positive in 79% of cases for IgG deposition and 80% for C3 deposition at the basement membrane zone of the dermal-epidermal junction. BP180 and BP230 antibodies were elevated on serology in 61 and 13% of cases, respectively (42).

Compared to idiopathic BP, BP secondary to ICB may be more difficult to diagnose and manage (43). Serology with elevated BP180 antibodies and biopsy with direct immunofluorescence showing IgG and C3 deposition at the basement membrane zone of the dermal-epidermal junction are suggestive of BP (42). Unlike idiopathic BP which generally responds well to systemic steroid treatment, BP from ICB may be systemic steroid-refractory (44). CTCAE grade 1/2 BP in patients on ICB can be managed with high-dose topical steroids and low-dose systemic steroids. In more severe or refractory cases, systemic steroids can be increased to 0.5–1 mg/kg/day (28, 45). In one review, BP from ICB required discontinuation of ICB in 76% of cases (46). In lieu of continued systemic steroid use or for steroid-refractory cases, rituximab, intravenous immune globulin (IVIg), omalizumab, dapsone, dupilumab, or methotrexate can be considered (28, 47, 48).

Other high grade bullous disorders from ICB which have been less frequently observed include blistering lichenoid reactions, such as lichen planus pemphigoides and bullous lichen planus (49–51). Lichen planus pemphigoides presents with clinical features of both BP and lichen planus, with oral involvement in up to half of cases. Histopathological features can include lymphocyte-rich subepidermal bullae with margins exhibiting features of lichen planus including colloid bodies or focal vacuolar degeneration. As in BP, direct immunofluorescence can show IgG and C3 deposits along the basement membrane (49). In cases of bullous lichen planus associated with ICB, patients may present initially with lichenoid plaques that blister with onset time ranging from 3 to 8 months. Histopathology demonstrates lymphocytic infiltrate, as in lichen planus. Direct immunofluorescence may show non-linear IgM and C3 colloid bodies at the dermal-epidermal junction and BP180 antibodies are not expected to be elevated (51). Treatment of lichen planus pemphigoides in the setting of ICB can include topical steroids, systemic steroids, dupilumab, and rituximab, IVIg, as in BP (49). For CTCAE grade $\geq$3 lichenoid eruptions, biologics including infliximab and tocilizumab may be considered (10). For steroid-refractory bullous lichenoid DAEs, treatment with cyclosporine to inhibit T-cell activation may be used (52).

## HIGH GRADE PSORIASIFORM DERMATOLOGIC ADVERSE EVENTS

High grade psoriasiform DAEs to anti-CTLA-4 and anti-PD-1/PD-L1 blockade have been widely reported in the literature (53–56). In FAERS, 152 cases of psoriasiform DAEs have been recorded in association with pembrolizumab, 40 with ipilimumab, 243 with nivolumab, 57 with atezolizumab, 5 with avelumab, 24 with durvalumab, and 4 with cemiplimab. In one study of 21 patients, 72% had a pre-existing history of psoriasis (53). Psoriasiform DAEs subtypes included plaque (53.3%), scalp (20.0%), guttate (20.0%) psoriasis, or sebopsoriasis (6.8%) (53). Onset from ICB initiation to psoriasis development is 90.5 $\pm$ 77.7 days for new-onset psoriasis and 32.8 $\pm$ 21.8 days for flares of pre-existing psoriasis (53). In a multicenter study of 76 patients with pre-existing psoriasis and various malignancies treated with ICB, 43 (57%) patients had a psoriasis

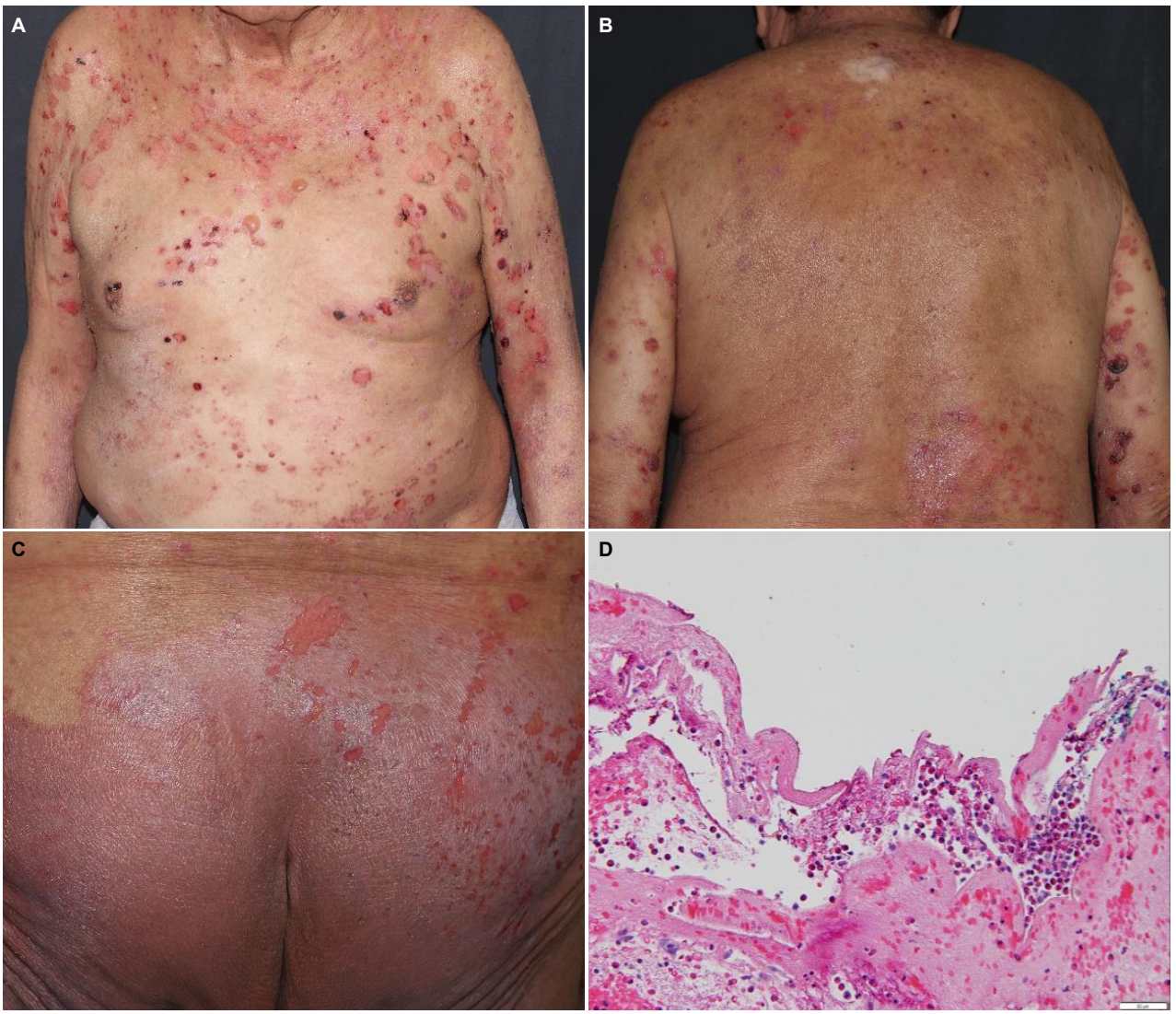


**FIGURE 2 |** Bullous pemphigoid with tense bullae and erosions on the **(A)** trunk, **(B)** back, and **(C)** buttocks. **(D)** Subepidermal vesicular dermatitis with abundant eosinophils and fibrin. Direct immunofluorescence studies revealed linear deposits of IgG, IgG4 and C3 at the basement membrane zone of the dermal-epidermal junction, focal deposits of fibrin in the reticular dermis and deposits of fibrin in the debris within the cleft.

flare after a median of 44 days after ICB initiation. Seven patients experienced grade 3–4 psoriasiform DAEs and 16 (21%) required systemic therapy. Of the 15 patients with pre-existing psoriatic arthritis prior to ICB, 6 experienced arthritis flares (56). Notably, progression-free survival was significantly longer in patients who experienced a psoriasis flare compared to those who did not (39 vs. 8.7 months, $p = 0.049$) (56). When biopsied, psoriasiform DAEs show parakeratosis, diminished granular layers, and acanthosis, with varying concomitant spongiosis (14).

Psoriasiform DAEs are thought to develop due to upregulation of Th17 lymphocytes as a result of PD-1 blockade (28). Therefore, in addition to holding ICB and using topical steroids, targeted management for psoriasiform DAEs and psoriasis flares includes anti-IL-12/23, anti-IL-23, and anti-IL-17 inhibitors, or apremilast (28, 32). **Table 2** summarizes management of the aforementioned high grade DAEs associated with ICB.

## DISCUSSION

True SJS/TEN due to ICB may be overdiagnosed (17) due to the similarity with and novelty of SJS/TEN-like reactions. Because SJS/TEN-like reactions to ICB present variably along a clinical spectrum, they have been described by various terms including: high grade lichenoid dermatosis or unclassified dermatosis (17), lichenoid mucocutaneous eruptions (57), and progressive immunotherapy-related mucocutaneous eruption (PIRME) further complicating definitive diagnosis of this pattern of reactions (18). Differentiating true SJS/TEN from DAE

**TABLE 2 |** Management of high grade DAEs.

| | ICB rechallenge | Recommendations | Level of evidence (66) |
|---|---|---|---|
| True SJS/TEN | Contraindicated | Stop ICB<br>Supportive care (hydration, electrolyte management, nutrition, etc.)<br>Dermatologic, ophthalmologic, gynecologic, and/or urologic consultations<br>Hospital, intensive care unit, or burn unit admission for widespread desquamation and life-threatening complications<br>Etanercept, cyclosporine, and/or IVIg | I (16, 27, 28, 37) |
| SJS/TEN-Like reactions | May be considered | Hold ICB<br>Dermatologic evaluation<br>Begin methylprednisolone/prednisone (1–2 mg/kg/day) and/or steroid-sparing therapies such as etanercept, cyclosporine, tocilizumab and/or IVIg | IV (17, 18) |
| Maculopapular rash | May be considered | Hold ICB<br>High potency topical corticosteroids to affected areas on body; low potency topical corticosteroids to face/folds<br>Prednisone 0.5–1 mg/kg/day<br>Consider inpatient care<br>For pruritus, consider gabapentinoids, aprepitant, dupilumab, omalizumab, or narrow-band UVB phototherapy | I (15) |
| DRESS | May be considered | Hold ICB<br>Dermatologic evaluation<br>High-dose and prolonged courses of oral or intravenous corticosteroids with slow taper<br>Addition of steroid-sparing therapies such as anti-TNF-α, tocilizumab, dupilumab | I (16, 27, 37) |
| Bullous pemphigoid and lichen planus pemphigoides | May be considered | Hold ICB until grade ≤1<br>High potency topical corticosteroids twice daily<br>Prednisone 0.5–1 mg/kg/day for grade ≥2 reactions<br>For steroid-refractory or grade ≥3 reactions consider:<br>Rituximab (375 mg/m$^2$ weekly × 4 weeks) ± IVIg (1 g/kg every 4 weeks)<br>Omalizumab (300 mg every 4 weeks)<br>Dapsone (starting dose 25 or 50 mg daily)<br>Dupilumab (600 mg loading dose, then 300 mg every other week)<br>Methotrexate (15–25 mg daily with folic acid supplementation) | I (10, 28, 47, 48) |
| Psoriasiform DAEs | May be considered | Hold ICB until grade ≤1<br>Topical corticosteroids<br>Consider targeted biologics including anti-TNF-α, anti-IL-12/23, anti-IL-23, anti-IL-17, or apremilast)<br>Consider systemic retinoids (acitretin) | I (10, 15, 56) |

mimickers is integral to a patient's cancer care, as emerging evidence suggests that although ICB challenge should not be attempted in cases of true SJS/TEN, it may be achievable after SJS/TEN-like reactions have improved (18).

Best management strategy for ICB-associated DAEs requires ongoing investigation. Evidence regarding the safety of systemic steroids for irDAE management is conflicting. Importantly, the risks and benefits of systemic corticosteroids for the management of high grade DAEs must be carefully weighed, as there is mixed evidence that systemic corticosteroid use may dampen the antitumor effects of ICB. Specifically, in patients treated with ipilimumab for melanoma, use of high-dose systemic corticosteroids was associated with significantly shorter overall survival and the time to treatment failure compared to use of low-dose corticosteroids (58). Similarly, in a study of patients treated with ICB for non-small cell lung cancer, use of systemic corticosteroids at the time of ICB initiation was significantly associated with decreased progression-free survival and overall survival (59). However, a pooled analysis of multiple phase III trials of nivolumab for advanced melanoma found no difference in objective response rates between patients who received systemic corticosteroids or other suppressive immune-modulating agents and those who did not (60).

Although steroids are currently the initial therapy for many cutaneous and extracutaneous ICB toxicities, there is increasing support for tailored approaches that account for clinical presentation and circulating biomarkers (61). In patients with DAEs associated with ICB, IL-6 has been found to be elevated in 52% of 65 patients, elafin in 30% of 43, IL-8 in 25% of 20, IgE in 24% of 101, and IFN-γ in 23% of 26 patients. Notably, serum IgE levels also correlate with DAE severity (32). In hospitalized cancer patients with high grade DAEs, elevated elafin, IL-6, and TNF-α were shown to be associated with higher all-cause mortality. As such, tocilizumab, an anti-IL-6 agent, was recently investigated and shown to be effective for management of ICB toxicities across various organ systems in 86% of 91 cancer patients without disease progression (62). Median resolution of ICB toxicity after tocilizumab initiation was 6.5 days (63). In patients with high grade DAEs associated with ICB and elevated IL-6, tocilizumab is a promising steroid-sparing agent (64). As precision medicine with targeted biologics continues to develop, future research is needed to determine its utility in the management of DAEs. In oncodermatology, continued research

to explore cytokines associated with poor outcomes in cancer patients as potentially useful therapeutic targets is important (65).

Through data from the FAERS database, we show that high grade DAEs such as SJS/TEN to immunomodulatory agents are not uncommon. We expect that as these innovative anti-cancer therapies continue to be used and as new ones develop, more patients will develop high grade DAEs. Familiarization with high grade DAEs and understanding of how to manage these will result in better outcomes through prompt management of patients with life-threatening cutaneous adverse reactions such as SJS/TEN, DRESS, and AGEP, and ability to rechallenge and continue ICB in patients with mimickers of SJS/TEN such as SJS/TEN-like reactions, bullous pemphigoid, lichenoid planus pemphigoides, and bullous lichen planus. Further research must be done not only to better delineate the high grade DAEs associated with ICB use but also to identify effective management strategies via precision medicine that do not reduce ICB efficacy.

## AUTHOR CONTRIBUTIONS

AK and AM contributed to all parts of the conception, design, and writing of the manuscript. Both authors contributed to the article and approved the submitted version.

## FUNDING

We would like to thank NIH grant P30-CA008748.

## REFERENCES


1. Rini BI, Plimack ER, Stus V, Gafanov R, Hawkins R, Nosov D, et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med.* (2019) 380:1116–27.
2. Hellmann MD, Paz-Ares L, Bernabe Caro R, Zurawski B, Kim SW, Carcereny Costa E, et al. Nivolumab plus ipilimumab in advanced non-small-cell lung cancer. *N Engl J Med.* (2019) 381:2020–31.
3. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, Lao CD, et al. Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med.* (2019) 381:1535–46. doi: 10.1056/NEJMoa1910836
4. Schmid P, Cortes J, Dent R, Pusztai L, McArthur H, Kummel S, et al. Event-free survival with pembrolizumab in early triple-negative breast cancer. *N Engl J Med.* (2022) 386:556–67. doi: 10.1056/NEJMoa2112651
5. Tewari KS, Monk BJ, Vergote I, Miller A, de Melo AC, Kim HS, et al. Survival with cemiplimab in recurrent cervical cancer. *N Engl J Med.* (2022) 386:544–55. doi: 10.1056/NEJMoa2112187
6. U.S. Department of Health and Human Services. *Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0*. Washington, DC: U.S. Department of Health and Human Services (2017).
7. Duong TA, Valeyrie-Allanore L, Wolkenstein P, Chosidow O. Severe cutaneous adverse reactions to drugs. *Lancet.* (2017) 390:1996–2011.
8. Molina GE, Allen IM, Hughes MS, Zubiri L, Lee H, Mooradian MJ, et al. Prognostic implications of co-occurring dermatologic and gastrointestinal toxicity from immune checkpoint inhibition therapy for advanced malignancies: a retrospective cohort study. *J Am Acad Dermatol.* (2020) 82:743–6. doi: 10.1016/j.jaad.2019.07.049
9. Thompson LL, Krasnow NA, Chang MS, Yoon J, Li EB, Polyakov NJ, et al. Patterns of cutaneous and noncutaneous immune-related adverse events among patients with advanced cancer. *JAMA Dermatol.* (2021) 157:577–82. doi: 10.1001/jamadermatol.2021.0326
10. Geisler AN, Phillips GS, Barrios DM, Wu J, Leung DYM, Moy AP, et al. Immune checkpoint inhibitor-related dermatologic adverse events. *J Am Acad Dermatol.* (2020) 83:1255–68.
11. Bottlaender L, Amini-Adle M, Maucort-Boulch D, Robinson P, Thomas L, Dalle S. Cutaneous adverse events: a predictor of tumour response under anti-PD-1 therapy for metastatic melanoma, a cohort analysis of 189 patients. *J Eur Acad Dermatol Venereol.* (2020) 34:2096–105. doi: 10.1111/jdv.16311
12. Chen CB, Wu MY, Ng CY, Lu CW, Wu J, Kao PH, et al. Severe cutaneous adverse reactions induced by targeted anticancer therapies and immunotherapies. *Cancer Manag Res.* (2018) 10:1259–73. doi: 10.2147/CMAR.S163391
13. Dodiuk-Gad RP, Chung WH, Valeyrie-Allanore L, Shear NH. Stevens-Johnson syndrome and toxic epidermal necrolysis: an update. *Am J Clin Dermatol.* (2015) 16:475–93.
14. Ellis SR, Vierra AT, Millsop JW, Lacouture ME, Kiuru M. Dermatologic toxicities to immune checkpoint inhibitor therapy: a review of histopathologic features. *J Am Acad Dermatol.* (2020) 83:1130–43. doi: 10.1016/j.jaad.2020.04.105
15. Thompson JA, Schneider BJ, Brahmer J, Achufusi A, Armand P, Berkenstock MK, et al. Management of immunotherapy-related toxicities, version 1.2022, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw.* (2022) 20:387–405. doi: 10.6004/jnccn.2022.0020
16. Coleman EL, Olamiju B, Leventhal JS. The life-threatening eruptions of immune checkpoint inhibitor therapy. *Clin Dermatol.* (2020) 38:94–104. doi: 10.1016/j.clindermatol.2019.10.015
17. Ingen-Housz-Oro S, Milpied B, Badrignans M, Carrera C, Elshot YS, Bensaid B, et al. Severe blistering eruptions induced by immune checkpoint inhibitors: a multicentre international study of 32 cases. *Melanoma Res.* (2022) 32:205–10. doi: 10.1097/CMR.0000000000000819
18. Molina GE, Yu Z, Foreman RK, Reynolds KL, Chen ST. Generalized bullous mucocutaneous eruption mimicking Stevens-Johnson syndrome in the setting of immune checkpoint inhibition: a multicenter case series. *J Am Acad Dermatol.* (2020) 83:1475–7. doi: 10.1016/j.jaad.2020.03.029
19. Maloney NJ, Ravi V, Cheng K, Bach DQ, Worswick S. Stevens-Johnson syndrome and toxic epidermal necrolysis-like reactions to checkpoint inhibitors: a systematic review. *Int J Dermatol.* (2020) 59:e183–8. doi: 10.1111/ijd.14811
20. Oro S, Milpied B, Carrera C, Bensaid B, Segura S, Apalla Z, et al. *Severe Blistering Drug Reactions Induced by Immune Checkpoint Inhibitors: a Retrospective International Case Series of 29 Patients. Poster Presentation EADV*. (2021). Avaliable online at: https://www.em-consulte.com/article/1484980/article/toxidermies-bulleuses-graves-induites-par-les-inhi
21. Hassel JC, Heinzerling L, Aberle J, Bahr O, Eigentler TK, Grimm MO, et al. Combined immune checkpoint blockade (anti-PD-1/anti-CTLA-4): evaluation and management of adverse drug reactions. *Cancer Treat Rev.* (2017) 57:36–49. doi: 10.1016/j.ctrv.2017.05.003
22. Sznol M, Ferrucci PF, Hogg D, Atkins MB, Wolter P, Guidoboni M, et al. Pooled analysis safety profile of nivolumab and ipilimumab combination therapy in patients with advanced melanoma. *J Clin Oncol.* (2017) 35:3815–22. doi: 10.1200/JCO.2016.72.1167
23. Jing Y, Chen X, Li K, Liu Y, Zhang Z, Chen Y, et al. Association of antibiotic treatment with immune-related adverse events in patients with cancer receiving immunotherapy. *J Immunother Cancer.* (2022) 10:e003779. doi: 10.1136/jitc-2021-003779
24. Komatsu-Fujii T, Ogawa M, Nonoyama S, Fukumoto T, Tanabe H. Recurrence of nivolumab-induced Stevens-Johnson syndrome due to tegafur/gimeracil/oteracil (TS-1(R)) after nivolumab discontinuation. *Eur J Dermatol.* (2021) 31:98–9. doi: 10.1684/ejd.2020.3957
25. Watanabe Y, Yamaguchi Y, Takamura N, Takahashi Y, Aihara M. Toxic epidermal necrolysis accompanied by several immune-related adverse events developed after discontinuation of nivolumab. *Eur J Cancer.* (2020) 131:1–4. doi: 10.1016/j.ejca.2020.02.044

26. Wang LL, Patel G, Chiesa-Fuxench ZC, McGettigan S, Schuchter L, Mitchell TC, et al. Timing of onset of adverse cutaneous reactions associated with programmed cell death protein 1 inhibitor therapy. *JAMA Dermatol.* (2018) 154:1057–61. doi: 10.1001/jamadermatol.2018.1912
27. Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American society of clinical oncology clinical practice guideline. *J Clin Oncol.* (2018) 36:1714–68.
28. Muntyanu A, Netchiporouk E, Gerstein W, Gniadecki R, Litvinov IV. Cutaneous immune-related adverse events (irAEs) to immune checkpoint inhibitors: a dermatology perspective on management [formula: see text]. *J Cutan Med Surg.* (2021) 25:59–76. doi: 10.1177/1203475420943260
29. Coleman E, Ko C, Dai F, Tomayko MM, Kluger H, Leventhal JS. Inflammatory eruptions associated with immune checkpoint inhibitor therapy: a single-institution retrospective analysis with stratification of reactions by toxicity and implications for management. *J Am Acad Dermatol.* (2019) 80:990–7. doi: 10.1016/j.jaad.2018.10.062
30. Brahmer JR, Abu-Sbeih H, Ascierto PA, Brufsky J, Cappelli LC, Cortazar FB, et al. Society for immunotherapy of cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events. *J Immunother Cancer.* (2021) 9:e002435. doi: 10.1136/jitc-2021-002435
31. Weber JS, Kahler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. *J Clin Oncol.* (2012) 30:2691–7. doi: 10.1200/JCO.2012.41.6750
32. Phillips GS, Wu J, Hellmann MD, Postow MA, Rizvi NA, Freites-Martinez A, et al. Treatment outcomes of immune-related cutaneous adverse events. *J Clin Oncol.* (2019) 37:2746–58.
33. Barrios DM, Phillips GS, Geisler AN, Trelles SR, Markova A, Noor SJ, et al. IgE blockade with omalizumab reduces pruritus related to immune checkpoint inhibitors and anti-HER2 therapies. *Ann Oncol.* (2021) 32:736–45. doi: 10.1016/j.annonc.2021.02.016
34. Mirza S, Hill E, Ludlow SP, Nanjappa S. Checkpoint inhibitor-associated drug reaction with eosinophilia and systemic symptom syndrome. *Melanoma Res.* (2017) 27:271–3. doi: 10.1097/CMR.0000000000000326
35. Lu J, Thuraisingam T, Chergui M, Nguyen K. Nivolumab-associated DRESS syndrome: a case report. *JAAD Case Rep.* (2019) 5:216–8. doi: 10.1016/j.jdcr.2018.11.017
36. Ai L, Gao J, Zhao S, Li Q, Cui YH, Liu Q, et al. Nivolumab-associated DRESS in a genetic susceptible individual. *J Immunother Cancer.* (2021) 9:e002879. doi: 10.1136/jitc-2021-002879
37. Quach HT, Johnson DB, LeBoeuf NR, Zwerner JP, Dewan AK. Cutaneous adverse events caused by immune checkpoint inhibitors. *J Am Acad Dermatol.* (2021) 85:956–66. doi: 10.1016/j.jaad.2020.09.054
38. Kardaun SH, Sekula P, Valeyrie-Allanore L, Liss Y, Chu CY, Creamer D, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS): an original multisystem adverse drug reaction. Results from the prospective RegiSCAR study. *Br J Dermatol.* (2013) 169:1071–80. doi: 10.1111/bjd.12501
39. Page B, Borradori L, Beltraminelli H, Yawalkar N, Hunger RE. Acute generalized exanthematous pustulosis associated with ipilimumab and nivolumab. *J Eur Acad Dermatol Venereol.* (2018) 32:e256–7. doi: 10.1111/jdv.14282
40. Matsubara T, Uchi H, Haratake N, Takamori S, Toyozawa R, Miura N, et al. Acute generalized exanthematous pustulosis caused by the combination of pembrolizumab plus chemotherapy in a patient with squamous-cell carcinoma. *Clin Lung Cancer.* (2020) 21:e54–6. doi: 10.1016/j.cllc.2019.11.009
41. Hwang A, Iskandar A, Dasanu CA. Stevens-Johnson syndrome manifesting late in the course of pembrolizumab therapy. *J Oncol Pharm Pract.* (2019) 25:1520–2. doi: 10.1177/1078155218791314
42. Juzot C, Sibaud V, Amatore F, Mansard S, Seta V, Jeudy G, et al. Clinical, biological and histological characteristics of bullous pemphigoid associated with anti-PD-1/PD-L1 therapy: a national retrospective study. *J Eur Acad Dermatol Venereol.* (2021) 35:e511–4. doi: 10.1111/jdv.17253
43. Molina GE, Reynolds KL, Chen ST. Diagnostic and therapeutic differences between immune checkpoint inhibitor-induced and idiopathic bullous pemphigoid: a cross-sectional study. *Br J Dermatol.* (2020) 183:1126–8. doi: 10.1111/bjd.19313
44. Povilaityte E, Gellrich FF, Beissert S, Abraham S, Meier F, Gunther C. Treatment-resistant bullous pemphigoid developing during therapy with immune checkpoint inhibitors. *J Eur Acad Dermatol Venereol.* (2021) 35:e591–3. doi: 10.1111/jdv.17321
45. Apalla Z, Lallas A, Delli F, Lazaridou E, Papalampou S, Apostolidou S, et al. Management of immune checkpoint inhibitor-induced bullous pemphigoid. *J Am Acad Dermatol.* (2021) 84:540–3. doi: 10.1016/j.jaad.2020.05.045
46. Lopez AT, Khanna T, Antonov N, Audrey-Bayan C, Geskin L. A review of bullous pemphigoid associated with PD-1 and PD-L1 inhibitors. *Int J Dermatol.* (2018) 57:664–9. doi: 10.1111/ijd.13984
47. Velin M, Dugourd PM, Sanchez A, Bahadoran P, Montaudie H, Passeron T. Efficacy and safety of methotrexate, omalizumab and dupilumab for bullous pemphigoid in patients resistant or contraindicated to oral steroids. A monocentric real-life study. *J Eur Acad Dermatol Venereol.* (2022). doi: 10.1111/jdv.17999 [Epub ahead of print].
48. Zhang Y, Xu Q, Chen L, Chen J, Zhang J, Zou Y, et al. Efficacy and safety of dupilumab in moderate-to-severe bullous pemphigoid. *Front Immunol.* (2021) 12:738907. doi: 10.3389/fimmu.2021.738907
49. Boyle MM, Ashi S, Puiu T, Reimer D, Sokumbi O, Soltani K, et al. Lichen planus pemphigoides associated with PD-1 and PD-L1 inhibitors: a case series and review of the literature. *Am J Dermatopathol.* (2022) 44:360–7. doi: 10.1097/DAD.0000000000002139
50. Biolo G, Caroppo F, Salmaso R, Alaibac M. Linear bullous lichen planus associated with nivolumab. *Clin Exp Dermatol.* (2019) 44:67–8. doi: 10.1111/ced.13700
51. de Lorenzi C, Andre R, Vuilleumier A, Kaya G, Abosaleh M. Bullous lichen planus and anti-programmed cell death-1 therapy: case report and literature review. *Ann Dermatol Venereol.* (2020) 147:221–7. doi: 10.1016/j.annder.2019.07.008
52. Reschke R, Mockenhaupt M, Simon JC, Ziemer M. Severe bullous skin eruptions on checkpoint inhibitor therapy – in most cases severe bullous lichenoid drug eruptions. *J Dtsch Dermatol Ges.* (2019) 17:942–8. doi: 10.1111/ddg.13876
53. Bonigen J, Raynaud-Donzel C, Hureaux J, Kramkimel N, Blom A, Jeudy G, et al. Anti-PD1-induced psoriasis: a study of 21 patients. *J Eur Acad Dermatol Venereol.* (2017) 31:e254–7. doi: 10.1111/jdv.14011
54. Cutroneo P, Ingrasciotta Y, Isgro V, Rullo EV, Berretta M, Fiorica F, et al. Psoriasis and psoriasiform reactions secondary to immune checkpoint inhibitors. *Dermatol Ther.* (2021) 34:e14830. doi: 10.1111/dth.14830
55. Voudouri D, Nikolaou V, Laschos K, Charpidou A, Soupos N, Triantafyllopoulou I, et al. Anti-PD1/PDL1 induced psoriasis. *Curr Probl Cancer.* (2017) 41:407–12. doi: 10.1016/j.currproblcancer.2017.10.003
56. Halle BR, Betof Warner A, Zaman FY, Haydon A, Bhave P, Dewan AK, et al. Immune checkpoint inhibitors in patients with pre-existing psoriasis: safety and efficacy. *J Immunother Cancer.* (2021) 9:e003066. doi: 10.1136/jitc-2021-003066
57. Shi VJ, Rodic N, Gettinger S, Leventhal JS, Neckman JP, Girardi M, et al. Clinical and histologic features of lichenoid mucocutaneous eruptions due to anti-programmed cell death 1 and anti-programmed cell death ligand 1 immunotherapy. *JAMA Dermatol.* (2016) 152:1128–36. doi: 10.1001/jamadermatol.2016.2226
58. Faje AT, Lawrence D, Flaherty K, Freedman C, Fadden R, Rubin K, et al. High-dose glucocorticoids for the treatment of ipilimumab-induced hypophysitis is associated with reduced survival in patients with melanoma. *Cancer.* (2018) 124:3706–14. doi: 10.1002/cncr.31629
59. Arbour KC, Mezquita L, Long N, Rizvi H, Auclin E, Ni A, et al. Impact of baseline steroids on efficacy of programmed cell death-1 and programmed death-ligand 1 blockade in patients with non-small-cell lung cancer. *J Clin Oncol.* (2018) 36:2872–8.
60. Weber JS, Hodi FS, Wolchok JD, Topalian SL, Schadendorf D, Larkin J, et al. Safety profile of nivolumab monotherapy: a pooled analysis of patients with advanced melanoma. *J Clin Oncol.* (2017) 35:785–92. doi: 10.1200/JCO.2015.66.1389

61. Ferrara R, Campochiaro C, Garassino MC. Shifting from a "one size fits all" to a tailored approach for immune-related adverse events. *J Thorac Oncol.* (2021) 16:183–6. doi: 10.1016/j.jtho.2020.11.029
62. Campochiaro C, Farina N, Tomelleri A, Ferrara R, Lazzari C, De Luca G, et al. Tocilizumab for the treatment of immune-related adverse events: a systematic literature review and a multicentre case series. *Eur J Intern Med.* (2021) 93:87–94. doi: 10.1016/j.ejim.2021.07.016
63. Dimitriou F, Hogan S, Menzies AM, Dummer R, Long GV. Interleukin-6 blockade for prophylaxis and management of immune-related adverse events in cancer immunotherapy. *Eur J Cancer.* (2021) 157:214–24. doi: 10.1016/j.ejca.2021.08.031
64. Hibler BP, Markova A. Treatment of severe cutaneous adverse reaction with tocilizumab. *Br J Dermatol.* (2020) 183:785–7. doi: 10.1111/bjd.19129
65. Mori S, Hickey A, Dusza SW, Lacouture ME, Markova A. Markers of systemic involvement and death in hospitalized cancer patients with severe cutaneous adverse reactions. *J Am Acad Dermatol.* (2019) 80:608–16. doi: 10.1016/j.jaad.2018.10.039
66. OCEBM Levels of Evidence Working Group. *The Oxford 2011 Levels of Evidence.* Oxford: Oxford Centre for Evidence-Based Medicine (2011).

**Conflict of Interest:** AM received research funding from Incyte Corporation and Amryt Pharma, and royalties from UpToDate and sits on the advisory board for Alira Health, Blueprint Medicines, Janssen, and Protagonist therapeutics.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers | Frontiers in Medicine

REVIEW
published: 16 June 2022
doi: 10.3389/fmed.2022.883121

# Scoring Assessments in Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

*Allison S. Dobry*[1]*, *Sonia Himed*[2], *Margo Waters*[3] and *Benjamin H. Kaffenberger*[2,3]

[1] Department of Dermatology, University of California, San Francisco, San Francisco, CA, United States, [2] Division of Dermatology, Ohio State University Wexner Medical Center, Columbus, OH, United States, [3] Ohio State University College of Medicine, Columbus, OH, United States

Epidermal necrolysis, the unifying term for Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), is a severe cutaneous drug reaction associated with high morbidity and mortality. Given the rarity of this disease, large-scale prospective research studies are limited. Significant institutional and geographical variations in treatment practices highlight the need for standardization of clinical assessment scores and prioritization of research outcome measures in epidermal necrolysis. At the present, clinical assessment is typically simplified to total body surface area (BSA) involvement, with little focus on morphology. Validated clinical scoring systems are used as mortality prognostication tools, with SCORTEN being the best-validated tool thus far, although the ABCD-10 has also been recently introduced. These tools are imperfect in that they tend to either overestimate or underestimate mortality in certain populations and are not designed to monitor disease progression. Although mortality is often used as a primary endpoint for epidermal necrolysis studies, this outcome fails to capture more nuanced changes in skin disease such as arrest of disease progression while also lacking a validated skin-directed inclusion criterion to stratify patients based on the severity of skin disease at study entry. In addition to mortality, many studies also use BSA stabilization or time to re-epithelialization as endpoints, although these are not clearly defined morphologically, and inter- and intra-rater reliability are unclear. More specific, validated cutaneous assessment scores are necessary in order advance therapeutic options for epidermal necrolysis. In this review, we summarize the strengths and weaknesses of current clinical assessment practices in epidermal necrolysis and highlight the need for standardized research tools to monitor cutaneous involvement throughout the hospitalization.

**Keywords: SJS/TEN, scoring assessment, drug reaction, epidermal necrolysis, dermatology**

OPEN ACCESS

***Edited by:***
*Elizabeth Phillips,*
*Vanderbilt University, United States*

***Reviewed by:***
*Paola Savoia,*
*Università degli Studi del Piemonte Orientale, Italy*
*Abdulhadi Hazzaa Jfri,*
*Harvard Medical School, United States*
*Eric Tkaczyk,*
*United States Department of Veterans Affairs, United States*

***Correspondence:**
*Allison S. Dobry*
*allison.dobry@ucsf.edu*

***Specialty section:***
*This article was submitted to Dermatology, a section of the journal Frontiers in Medicine*

***Received:*** *24 February 2022*
***Accepted:*** *25 May 2022*
***Published:*** *16 June 2022*

***Citation:***
*Dobry AS, Himed S, Waters M and Kaffenberger BH (2022) Scoring Assessments in Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis. Front. Med. 9:883121. doi: 10.3389/fmed.2022.883121*

## INTRODUCTION

Epidermal necrolysis, the unifying term for Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), is a severe cutaneous drug reaction associated with high morbidity and mortality (1–3). It is considered to be the most life-threatening dermatologic disease with a mortality incidence of 15% overall, and up to 50% in the elderly (4, 5). Increasing recognition is also being given to the long-term multisystem sequelae of epidermal necrosis present in the majority

of survivors, including permanent mucosal damage, cutaneous dyspigmentation and scarring, and resultant mental illness (5). Despite its severity, epidermal necrosis has no FDA-approved therapeutics in use. Treatment, including no treatment, varies significantly by physician specialty, institutional geography, and institutional experiences. In this review, we summarize the strengths and weaknesses of current clinical assessment practices epidermal necrolysis and highlight the need for standardized research tools to monitor cutaneous involvement throughout hospitalization. More specific, validated cutaneous assessment scores are necessary to appropriately risk-stratify patients on study entry, assess skin disease change in response to treatment, and ultimately advance therapeutic options for epidermal necrolysis.

## STRENGTHS AND WEAKNESSES OF SCORTEN

### The Creation of SCORTEN and External Validation

The severity-of-illness score for TEN (SCORTEN) is a mortality prognostication tool for epidermal necrolysis (1). It was developed in 2000 by a team in France, using 165 patients to identify significant variables via a logistic regression model and 75 patients to internally validate the results (1). From this model, the researchers identified seven equally weighted parameters that are risk factors for death: age >40 years, malignancy, heart rate >120 beats per minute, initial percentage of epidermal detachment >10%, serum urea >10 mmol/L, serum glucose >14 mmol/L, and bicarbonate <20 mmol/L (score range: 0–7, **Table 1**). Collectively, these comprise the SCORTEN, which can predict risk of mortality ranging from 3.2 to 90.0%. Originally, this score was meant to be calculated once within 24 h of admission. Despite this initial intent, authors from this group later published an analysis that demonstrated SCORTEN performance on the first 5 days of hospitalization remained high (and performed even better on day 3), and thus recommended SCORTEN calculation on both days 1 and 3 (6).

In the two decades following its conception, SCORTEN has been widely used and validated in patient populations around the world. In an effort to summarize its use over the past two decades, a group of researchers performed a meta-analysis to better understand the accuracy of SCORTEN in predicting mortality (7). Overall, 64 studies were included. SCORTEN was found to be an overall good predictor of mortality but tends to underestimate mortality for values <3 and overestimate for values >3. Certain factors were associated with reduced predictive accuracy, such as mean age of patients and ending year of the study. SCORTEN tended to underestimate mortality in older cohorts of patients and overestimate mortality in more recent studies. BSA involvement may influence SCORTEN predictiveness, although the results are more varied. One study found that SCORTEN underestimated mortality for a cohort of patients with TEN (BSA > 30%) (8), but another study found SCORTEN retained good predictive ability in burn center patients (9).

### Critiques of SCORTEN and Attempts at Modified SCORTEN Models

Perhaps the most common criticism of SCORTEN is that it simplifies continuous and dynamic biologic measurements into dichotomous variables, thereby losing a significant amount of information in the process, particularly in the skin assessment which does not regard morphology or locations. Additionally, SCORTEN was originally meant to be used at a single timepoint rather than as a daily monitoring tool. Interestingly some studies have found that either delayed or sequential use of SCORTEN provides improved prognostication (6, 10). Another common concern is that defining BSA remains somewhat subjective, and may vary from one provider to another depending on how BSA involvement is estimated and whether the provider measures only desquamated skin vs. skin with bullae.

In response to this, a group of researchers designed a refined model from 369 patients in the RegiSCAR study that they termed the auxiliary score which scores both age and BSA differently (11). The auxiliary score divides age into three groups (31–55, 56–75, and ≥75 years). The score additionally uses a higher cutoff

**TABLE 1 |** Comparison of mortality prognostic tools ABCD-10 and SCORTEN.

| ABCD-10 | | SCORTEN | |
|---|---|---|---|
| Age >50 years old | 1 point | Age >40 years old | 1 point |
| Bicarbonate <20 mmol/L | 1 point | Malignancy | 1 point |
| Cancer/Malignancy | 2 points | Heart Rate >120 beats per minute | 1 point |
| Dialysis prior to admission | 3 points | Initial Epidermal Detachment BSA >10% | 1 point |
| Initial Epidermal Detachment BSA ≥10% | 1 point | Serum urea >10 mmol/L | 1 point |
| | | Serum glucose >14 mmol/L | 1 point |
| | | Bicarbonate <20 mmol/L | 1 point |
| **Score Range**: 0–8 | | **Score Range**: 0–7 | |

*A SCORTEN score of 0–1 predicts a mortality rate of 3.2%, a score of 2 as 12.1%, score of 3 as 35.3%, a score of 4 and 54.3 and a score ≥5 as 90%.*
*An ABCD-10 score of 0 predicts a mortality rate of 2.3%, a score of 1 as 5.4%, a score of 2 as 12.3%, a score of 3 as 25.5%, a score of 4 as 45.7, a score of 5 as 67.4 and a score of 6 as 83.6.*

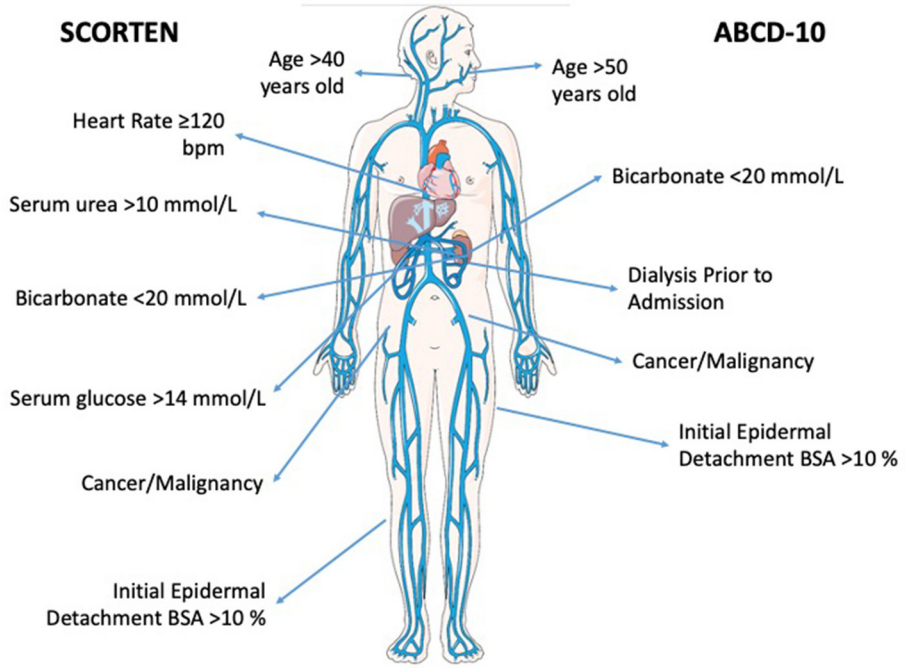


**FIGURE 1 |** Bioicon representation of the prognostic factors associated with both SCORTEN and ABCD-10 scoring systems. *Venous-circulation-body icon by Servier https://smart.servier.com/ is licensed under CC-BY 3.0 Unported https://creativecommons.org/licenses/by/3.0/*.

to differentiate between BSA involvement at >30%. Some studies have found that models that differentiate between BSA >30%, as in TEN, may have better prognostic ability (8, 10, 11). However, authors of the auxiliary score concluded that SCORTEN should remain the model of choice in the clinical setting, whereas the auxiliary score may be useful in retrospective research with missing biochemical data.

The role of other biochemical markers in predicting mortality risk has also been investigated. A group recently found that the ratio of red cell distribution width to hemoglobin (RDW/Hb) is predictive of mortality (12). They incorporated this value into the SCORTEN and named this new model the Re-SCORTEN. Overall, they found improved mortality prognostication with this revised model as compared to SCORTEN alone, but this scoring model has not yet been validated in other populations.

Despite these critiques, SCORTEN has remained the gold standard for not only predicting patient mortality, but is also frequently used in study outcomes to compare therapy efficacy by survival to expected mortality, as well as compare quality of care between institutions (13, 14).

## STRENGTHS AND WEAKNESSES OF ABCD-10

### The Creation of ABCD-10

Another recently devised mortality prognostication tool for epidermal necrolysis is ABCD-10. The ABCD-10 is calculated using the following metrics: age over 50 years (one point), bicarbonate level <20 mmol/L (one point), cancer present and active (two points), dialysis prior to admission (3 points), and epidermal detachment ≥10% body surface area on admission (one point) (**Table 1**) (13). Despite its recency in development, ABCD-10 offers many strengths when assessing patients with epidermal necrolysis. In comparison to SCORTEN, ABCD-10 takes includes patients with end stage renal disease (using prior dialysis as a proxy) and more heavily weighs cancer diagnosis (**Figure 1**). Authors of ABCD-10 discovered that undergoing dialysis prior to admission was associated with a more than 15-fold increased risk of death in comparison to those not undergoing dialysis (13). In additional studies since its inception, ABCD-10 has been validated in external cohorts as having good discriminatory capability similar to that of SCORTEN (15). With continuing advances in supportive care and intensive treatments, as well as varying treatment protocols across institutions, ABCD-10 is a great step toward improving prognostic information of epidermal necrolysis patients.

### Comparing SCORTEN vs. ABCD-10

While ABCD-10 has good discriminatory ability, multiple studies have showed that it underperforms in comparison to SCORTEN (3, 7, 15, 16). Specifically, one retrospective cohort study in Singapore found that in both patients treated with supportive care or immunomodulatory therapy, ABCD-10 underestimated mortality at lower score ranges and overestimated mortality at higher score ranges (15). Authors of another large retrospective study in the United States postulated that ABCD-10 underperformed SCORTEN due to the lower rates of dialysis and cancer in their population (3).

**TABLE 2 |** Endpoints in trials registered at ClinicalTrials.Gov for epidermal necrolysis interventions.

| ClinicalTrials.Gov ID | Intervention | Primary Outcome | Secondary Outcome(s) |
|---|---|---|---|
| NCT01696500 (17) | Intravenous immunoglobulin (IVIg) | 1. Disease evaluation score | 1. Disease evaluation score<br>2. Avulsed skin area<br>3. Erythematous area |
| NCT03585946 (18) | Cyclosporine vs. IVIg vs. etanercept vs. steroids | 1. Mortality<br>2. Time to cessation of new lesion formation<br>3. Time to re-epithelialization<br>4. Hospital length of stay | |
| NCT02987257 (19) | Cyclosporine vs. etanercept vs. placebo | 1. Time to complete re-epithelialization | 1. Time to halting of progression of SJS/TEN skin disease<br>2. Mortality<br>3. Actual mortality vs. expected mortality<br>4. Ocular involvement<br>5. Infections<br>6. Hospital length of stay<br>7. Proportion of patients with adverse events due to assigned treatment arm |
| NCT02795143 (20) | Isotretinoin vs. supportive care | 1. Number of days of hospitalization | 1. Percent of body surface area affected |
| NCT02739295 (21) | G-CSF vs. placebo | 1. Time for healing<br>2. Changes in immunohistologic typing<br>3. Neutrophilic count | 1. WBC count<br>2. WBC formula |
| NCT04651439 (22) | G-CSF vs. placebo | 1. Arrest of progression at day 5 | 1. Arrest of progression<br>2. Complete re-epidermization<br>3. 30-day survival<br>4. 1-year survival<br>5. Duration of hospitalization<br>6. Premature discontinuation of experimental treatment<br>7. Adverse events<br>8. Use of systemic corticosteroid therapy<br>9. Specialty follow-up<br>10. Quality of life evolution<br>11. Risk of developing PTSD |
| NCT04711200 (23) | Adipose derived stromal cells injected IV | 1. Safety: observation of at least one adverse effect<br>2. Efficacy: rate of complete or almost complete re-epithelialization | 1. Rate of observed and predicted death by SCORTEN<br>2. Duration of hospitalization according to historical cohort related to BSA involved<br>3. Duration of hospitalization according to historical cohort related to onset of the disease<br>4. Duration of hospitalization according to historical cohort related to SCORTEN<br>5. Duration of each mucous membranes healing<br>6. Rate of sepsis<br>7. Rate of intensive care transfer<br>8. Rate of sequelae<br>9. Th1/Th2 immune response in the peripheral blood of the patients<br>10. Evaluation of expression profile of Th1/Th2 associated chemokines and anti-inflammatory chemokines in the peripheral blood<br>11. Epidermal chimerism study on healed skin biopsy<br>12. Cutaneous re-epithelialization rate |

*Inclusion criteria included trials enrolling only patients with a diagnosis of SJS or TEN. Exclusion criteria were trials evaluating only organ specific interventions (e.g., ophthalmologic interventions) or trials that were withdrawn.*

Furthermore, some researchers have suggested that SCORTEN already adequately captures kidney disease as a co-morbidity by included serum urea and bicarbonate levels, given evidence of multicollinearity between dialysis and serum bicarbonate levels (15).

Further studies are needed to better understand the applicability of ABCD-10. Still, it is limited in its usefulness in epidermal necrolysis assessment, as it cannot be used to monitor cutaneous involvement throughout hospitalization and responsiveness to treatment.

## CLINICAL ENDPOINTS

While SCORTEN and ABCD-10 are commonly used mortality prognostication tools for epidermal necrolysis, to determine therapeutic efficacy, other clinical endpoints are needed to monitor disease response to interventions. Formal endpoints in clinical trials for patients with epidermal necrolysis have not been standardized. A query of the ClinicalTrials.Gov database for trials evaluating interventions for patients with epidermal necrolysis demonstrated high variability in primary and secondary outcomes (**Table 2**). Overall, outcomes among clinical trials and retrospective studies are generally grouped into three categories: (1) the standardized mortality ratio, (2) clinical outcomes, and (3) cutaneous response to treatment.

### The Standardized Mortality Ratio

One of the most common primary endpoints utilized in epidermal necrolysis studies is the standardized mortality ratio (SMR), defined as the ratio of observed deaths in comparison to deaths predicted by SCORTEN (13, 24–28). For example, a retrospective cohort analysis on 377 patients across multiple institutions in the United States stratified SMR by therapeutic approach, and demonstrated that combination of intravenous immunoglobulin and steroid use led to the lowest SMR of 0.52 [95% confidence interval (CI) 0.21–0.79] (27). However, the SMR for all patients in this cohort was 0.70 (95% CI 0.58–0.79), suggesting that SCORTEN as a whole overestimated mortality risk in this patient cohort. This has been reflected in other studies that use the SMR (29).

### Clinical Outcomes

Many studies commonly employ basic clinical outcomes, such as length of stay, development of sepsis, and mortality. In a systematic review of the efficacy of intravenous immunoglobulin in the treatment of epidermal necrolysis, clinical endpoints were defined as mortality rates, length of hospital stay, time to disease cessation, and time to skin healing (30). A recent European multicenter study sought to assess overall treatment approaches including supportive care only as the reference group and the treatment groups were systemic glucocorticoids, cyclosporine, intravenous immunoglobulin, and antitumor necrosis factor agents (2). This study classified outcomes as risk of infection, body surface area detachment in the acute phase, and an overall 6-week mortality rate between treatment groups (2). Furthermore, participants were also evaluated for long-term outcomes defined as the development of severe acute complications which included septicemia, acute kidney injury, pulmonary infection, or respiratory distress requiring mechanical ventilation (2). While some of these outcomes are standard clinical outcomes including complicating infections, others are more specific to the disease and lack the validation to confirm their utility such as time to disease cessation, skin healing, and body surface area detachment in the acute phase.

Disease severity is also utilized as an outcome measure, with severity measurements varying between studies. In a study assessing burn unit transfers, disease severity was classified as total body surface area as well as the Acute Physiology and Chronic Health Evaluation (APACHE) score (31). Conversely, other trials utilized their own severity illness scores by developing rating scales which combined lesion characteristics and patient general conditions (32). While these assessments are commonly used for burn and ICU patients, they are of uncertain utility as a primary outcome measure for an intervention to be beneficial.

### Cutaneous Outcome Measures

In addition to mortality and systemic disease severity as primary endpoints, cutaneous signs are an important outcome measure. The most frequently used cutaneous outcomes include time to skin re-epithelialization and body surface area stabilization from the acute phase. However, there are no standardized morphological assessments for cutaneous resolution of the acute phase and therefore, these outcomes are subject to provider bias and unclear validity. Furthermore, these cutaneous endpoints are not sensitive to special site areas such as the mucous membranes. As alluded to previously, subjectivity also arises in grading of BSA involvement. Some studies utilized a cutaneous measure of total BSA of detached and detachable skin (25, 30) that did not include strictly purpuric lesions, while another study defined cutaneous endpoints as the onset of spontaneous resolution of the acute phase (33). Clearly, more discrete skin scoring assessments and instruments are necessary to be validated for the success of future clinical studies in this disease. Further, improved cutaneous scoring assessments are critical not only as an outcome measure, but as an entry criterion for research studies to ensure balanced randomization across institutions.

## CONCLUSION

The lack of standardized endpoint measures in epidermal necrolysis is a significant barrier in the development of regulatory approved therapies. At the current time, there exists a panoply of drugs, wound care, and supportive care regimens that lack strong evidence for efficacy for treating this disease. Efforts to improve treatment options and reduce mortality require standardized clinical outcomes that are more finely tuned to risk-stratifying patients at entry, then detecting treatment response. Recently some there have been some attempts at standardization of quantitative endpoints via a survey that identified minimally clinical important differences (MCID), defined as the smallest change in a treatment outcome that a patient or clinician would identify as important and indicate a change in management (34).

Further work is required on standardizing outcome measures and validating skin assessments. We recommend the development of a consensus morphological assessment of cutaneous morphologies and locations of involvement, from which cutaneous endpoints can be reliably measured. Without these standardizations, therapeutic treatments and interventions will remain limited with a bias toward lack of intervention efficacy.

## AUTHOR CONTRIBUTIONS

AD, SH, MW, and BK contributed to the writing of the manuscript. AD and BK prepared the final manuscript. All authors contributed to the article and approved the submitted version.

## REFERENCES


1. Bastuji-Garin S, Fouchard N, Bertocchi M, Roujeau JC, Revuz J, Wolkenstein P. SCORTEN: a severity-of-illness score for toxic epidermal necrolysis. *J Invest Dermatol.* (2000) 115:149–53. doi: 10.1046/j.1523-1747.2000.00061.x
2. Kridin K, Brüggen M-C, Chua S-L, Bygum A, Walsh S, Nägeli MC, et al. Assessment of treatment approaches and outcomes in Stevens-Johnson syndrome and toxic epidermal necrolysis: insights from a pan-European multicenter study. *JAMA Dermatol.* (2021) 157:1182–90. doi: 10.1001/jamadermatol.2021.3154
3. Duplisea MJ, Roberson ML, Chrisco L, Strassle PD, Williams FN, Ziemer CM. Performance of ABCD-10 and SCORTEN mortality prediction models in a cohort of patients with Stevens-Johnson syndrome/toxic epidermal necrolysis. *J Am Acad Dermatol.* (2021) 85:873–7. doi: 10.1016/j.jaad.2021.04.082
4. Phillips EJ, Bouchard CS, Divito SJ. Stevens-johnson syndrome and toxic epidermal necrolysis-coordinating research priorities to move the field forward. *JAMA Dermatol.* (2022). doi: 10.1001/jamadermatol.2022.0484. [Epub ahead of print].
5. Chang W-C, Abe R, Anderson P, Anderson W, Ardern-Jones MR, Beachkofsky TM, et al. SJS/TEN 2019: from science to translation. *J Dermatol Sci.* (2020) 98:2–12. doi: 10.1016/j.jdermsci.2020.02.003
6. Guégan S, Bastuji-Garin S, Poszepczynska-Guigné E, Roujeau J-C, Revuz J. Performance of the SCORTEN during the first five days of hospitalization to predict the prognosis of epidermal necrolysis. *J Invest Dermatol.* (2006) 126:272–6. doi: 10.1038/sj.jid.5700068
7. Torres-Navarro I, Briz-Redón Á, Botella-Estrada R. Accuracy of SCORTEN to predict the prognosis of Stevens-Johnson syndrome/toxic epidermal necrolysis: a systematic review and meta-analysis. *J Eur Acad Dermatol Venereol.* (2020) 34:2066–77. doi: 10.1111/jdv.16137
8. Hu C-H, Chang N-J, Liu EK-W, Chuang S-S, Chung W-H, Yang J-Y. SCORTEN and impaired renal function related to mortality of toxic epidermal necrolysis syndrome patients in the Asian population. *J Eur Acad Dermatol Venereol.* (2013) 27:628–33. doi: 10.1111/j.1468-3083.2012.04502.x
9. Cartotto R, Mayich M, Nickerson D, Gomez M. SCORTEN accurately predicts mortality among toxic epidermal necrolysis patients treated in a burn center. *J Burn Care Res.* (2008) 29:141–6. doi: 10.1097/BCR.0b013e31815f3865
10. Bansal S, Garg VK, Sardana K, Sarkar R. A clinicotherapeutic analysis of Stevens-Johnson syndrome and toxic epidermal necrolysis with an emphasis on the predictive value and accuracy of SCORe of Toxic Epidermal Necrolysis. *Int J Dermatol.* (2015) 54:e18–26. doi: 10.1111/ijd.12466
11. Sekula P, Liss Y, Davidovici B, Dunant A, Roujeau J-C, Kardaun S, et al. Evaluation of SCORTEN on a cohort of patients with Stevens-Johnson syndrome and toxic epidermal necrolysis included in the RegiSCAR study. *J Burn Care Res.* (2011) 32:237–45. doi: 10.1097/BCR.0b013e31820aafbc
12. Koh HK, Fook-Chong SMC, Lee HY. Improvement of mortality prognostication in patients with epidermal necrolysis: the role of novel inflammatory markers and proposed revision of SCORTEN (Re-SCORTEN). *JAMA Dermatol.* (2021) 158:160–66. doi: 10.1001/jamadermatol.2021.5119
13. Noe MH, Rosenbach M, Hubbard RA, Mostaghimi A, Cardones AR, Chen JK, et al. Development and validation of a risk prediction model for in-hospital mortality among patients with Stevens-Johnson syndrome/toxic epidermal necrolysis-ABCD-10. *JAMA Dermatol.* (2019) 155:448–54. doi: 10.1001/jamadermatol.2019.0998
14. Nizamoglu M, Ward JA, Frew Q, Gerrish H, Martin N, Shaw A, et al. Improving mortality outcomes of Stevens Johnson syndrome/toxic epidermal necrolysis: a regional burns centre experience. *Burns J Int Soc Burn Inj.* (2018) 44:603–11. doi: 10.1016/j.burns.2017.09.015
15. Koh HK, Fook-Chong S, Lee HY. Assessment and comparison of performance of ABCD-10 and SCORTEN in prognostication of epidermal necrolysis. *JAMA Dermatol.* (2020) 156:1294–9. doi: 10.1001/jamadermatol.2020.3654
16. Suo H, Jiang B, Sun X, Dong J, Alamgir M, Guan X, et al. Comparing the accuracy of ABCD-10 and SCORTEN in predicting the in-hospital mortality of Stevens-Johnson syndrome/toxic epidermal necrolysis: a multi-institutional study from central China. *Dermatol Basel Switz.* (2021) 1–9. doi: 10.1159/000520494. [Epub ahead of print].
17. *NPB-01(Intravenous Immunoglobulin) Therapy for Patients With Stevens-Johnson Syndrome/ Toxic Epidermal Necrolysis Unresponsive to Corticosteroids. Identifier NCT01696500* (2012–2014). Available online at: https://clinicaltrials.gov/ct2/show/NCT01696500 (accessed May 2, 2022.)
18. Kroshinsky D. *A Prospective Multicenter Cohort Study Assessing Outcomes in Stevens Johnsons Syndrome and Toxic Epidermal Necrolysis*. Identifier NCT03585946 Available online at: https://clinicaltrials.gov/ct2/show/NCT03585946 (accessed May 2, 2022.)
19. Phillips EJ. *NATIENS: A Phase III Randomized Double-Blinded Placebo Controlled Study to Determine the Optimal Management and Mechanisms of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis*. Identifier NCT02987257. Available online at: https://clinicaltrials.gov/ct2/show/NCT02987257 (accessed May 2, 2022.)
20. Saavedra AP. *Evaluating the Effect of Isotretinoin in Regulatory T-Cell Function in Adverse Cutaneous Drug Eruptions (ACDEs): A Pilot Study*. Identifier NCT02795143. Available online at: https://clinicaltrials.gov/ct2/show/NCT02795143 (accessed May 2, 2022.)
21. Rousseau A. *Evaluation of G-CSF as a Treatment of Toxic Epidermal Necrolysis*. Identifier NCT02739295. Available online at: https://clinicaltrials.gov/ct2/show/NCT02739295 (accessed May 2, 2022.)
22. Ben Said B. *Evaluating the Therapeutic Efficacy of Filgrastim in Severe Bullous Drug Eruptions (Lyell and Stevens-Johnson Syndromes)*. Identifier NCT04651439. Available online at: https://clinicaltrials.gov/ct2/show/NCT04651439 (accessed May 2, 2022.)
23. Oro S. *Mesenchymal Stromal Cells Treatment in Lyell Syndrome: A Pilot Phase 1-2 Open Trial*. Identifier NCT04711200. Available online at: https://clinicaltrials.gov/ct2/show/NCT04711200 (accessed May 2, 2022.)
24. Wang C-W, Yang L-Y, Chen C-B, Ho H-C, Hung S-I, Yang C-H, et al. Randomized, controlled trial of TNF-α antagonist in CTL-mediated severe cutaneous adverse reactions. *J Clin Invest.* (2018) 128:985–96. doi: 10.1172/JCI93349
25. Bachot N, Revuz J, Roujeau J-C. Intravenous immunoglobulin treatment for Stevens-Johnson syndrome and toxic epidermal necrolysis: a prospective noncomparative study showing no benefit on mortality or progression. *Arch Dermatol.* (2003) 139:33–6. doi: 10.1001/archderm.139.1.33
26. Pushker N, Gorimanipalli B, Sharma N, Kashyap S, Bajaj MS. Mucous membrane grafting (fibrin glue vs. suture) for lid margin pathologies in Stevens-Johnson syndrome: randomized comparative study. *Eye.* (2021) 35:1985–92. doi: 10.1038/s41433-020-01203-4
27. Micheletti RG, Chiesa-Fuxench Z, Noe MH, Stephen S, Aleshin M, Agarwal A, et al. Stevens-Johnson syndrome/toxic epidermal necrolysis: a multicenter retrospective study of 377 adult patients from the United States. *J Invest Dermatol.* (2018) 138:2315–21. doi: 10.1016/j.jid.2018.04.027
28. Tsai T-Y, Huang I-H, Chao Y-C, Li H, Hsieh T-S, Wang H-H, et al. Treating toxic epidermal necrolysis with systemic immunomodulating therapies: a systematic review and network meta-analysis. *J Am Acad Dermatol.* (2021) 84:390–7. doi: 10.1016/j.jaad.2020.08.122
29. Imahara SD, Holmes JH, Heimbach DM, Engrav LE, Honari S, Klein MB, et al. SCORTEN overestimates mortality in the setting of a standardized treatment protocol. *J Burn Care Res.* (2006) 27:270–5. doi: 10.1097/01.BCR.0000216532.71360.9B
30. Huang Y-C, Li Y-C, Chen T-J. The efficacy of intravenous immunoglobulin for the treatment of toxic epidermal necrolysis: a systematic review and meta-analysis. *Br J Dermatol.* (2012) 167:424–32. doi: 10.1111/j.1365-2133.2012.10965.x
31. Harr T, French LE. Toxic epidermal necrolysis and Stevens-Johnson syndrome. *Orphanet J Rare Dis.* (2010) 5:39. doi: 10.1186/1750-1172-5-39
32. Aihara M, Kano Y, Fujita H, Kambara T, Matsukura S, Katayama I, et al. Efficacy of additional i.v. immunoglobulin to steroid therapy in Stevens-Johnson syndrome and toxic epidermal necrolysis. *J Dermatol.* (2015) 42:768–77. doi: 10.1111/1346-8138.12925
33. Kakourou T, Klontza D, Soteropoulou F, Kattamis C. Corticosteroid treatment of erythema multiforme major (Stevens-Johnson syndrome) in children. *Eur J Pediatr.* (1997) 156:90–3. doi: 10.1007/s004310050561
34. Kim WB, Worley B, Holmes J, Phillips EJ, Beecker J. Minimal clinically important differences for measures of treatment efficacy in Stevens-Johnson

syndrome and toxic epidermal necrolysis. *J Am Acad Dermatol.* (2018) 79:1150–2. doi: 10.1016/j.jaad.2018.06.002

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**Publisher's Note:** All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers | Frontiers in Medicine

BRIEF RESEARCH REPORT
published: 04 July 2022
doi: 10.3389/fmed.2022.874445

# Stevens Johnson Syndrome: Past, Present, and Future Directions Gynecologic Manifestations and Management in SJS/TEN

*Michelle A. DenAdel, Sarah E. Hendrickson and Esther Fuchs**

*Department of Obstetrics and Gynecology, University of Washington, Seattle, WA, United States*

Stevens Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are severe mucocutaneous hypersensitivity disorders characterized by sudden onset epidermal necrosis. Acute manifestations of SJS/TEN often include vulvovaginal erosions, ulcerations, vaginal discharge, bleeding, vaginal pain, dysuria, and urinary retention. If not treated, this can lead to complications such as vulvovaginal adhesions, vaginal stenosis or dryness, pain, dyspareunia, bleeding, and adenosis. Even with adequate treatment, there are lasting impacts including difficulty with vaginal exams and psychological distress. Early recognition and treatment of vulvovaginal involvement are crucial to preventing severe sequelae. Despite the potentially devastating consequences of genitourinary involvement of SJS/TEN, involvement of the mucocutaneous surfaces of the vulva and vagina is inconsistently documented, and protocols for treatment and follow-up are not well-established. The treatment of vulvovaginal involvement relies largely on expert opinion, and there is little data on the efficacy of suggested management. The goal of this review was to identify whether establishing a clinical pathway increased treatment of vulvovaginal SJS/TEN and to optimize our standardized protocol to prevent genitourinary sequelae.

**Methods:** We conducted a retrospective chart review of female patients with SJS/TEN at Harborview Medical Center, University of Washington from 2008 to 2021. Demographic and clinical data including gynecologic consultation, exam findings, treatment regimens, and outpatient follow-up were collected from the electronic medical record. We compared data before and after implementation of a clinical care pathway in 2017.

**Results:** We reviewed a total of 88 charts of women with possible SJS/TEN between 2008 and 2021. Of these 88 charts, 77 were found to have clear biopsy proven diagnosis of SJS/TEN. A total of 42 patients were found to have vulvovaginal involvement (55%) and gynecology was consulted in 43% of cases. 50% of patients ($n = 21$) with vulvovaginal involvement were recommended treatment with vaginal dilators and steroid ointment and 34% of patients with genital involvement received no treatment.
Between 2008 and May of 2017 (pre-protocol), we found 55 patients with SJS/TEN. 55% of patients ($n = 29$) had vulvovaginal involvement ($n = 26$ vulvar, $n = 21$ vaginal).

OPEN ACCESS

***Edited by:***
*Hajirah Saeed,*
*Harvard Medical School,*
*United States*

***Reviewed by:***
*Irina Khamaganova,*
*Pirogov Russian National Research Medical University, Russia*
*Abdulhadi Hazzaa Jfri,*
*Harvard Medical School,*
*United States*

****Correspondence:***
*Esther Fuchs*
*fuchses@uw.edu*

***Specialty section:***
*This article was submitted to Dermatology, a section of the journal Frontiers in Medicine*

***Received:*** *12 February 2022*
***Accepted:*** *07 June 2022*
***Published:*** *04 July 2022*

***Citation:***
*DenAdel MA, Hendrickson SE and Fuchs E (2022) Stevens Johnson Syndrome: Past, Present, and Future Directions Gynecologic Manifestations and Management in SJS/TEN. Front. Med. 9:874445. doi: 10.3389/fmed.2022.874445*

Gynecology was only consulted in 26% ($n = 14$) of patients. Of the 21 females with vaginal involvement, only 38% ($n = 8$) had dilators/vaginal molds with steroid ointment recommended. Of the 26 females with vulvar involvement, 31% ($n = 8$) had no vulvar treatment recommendations with the remaining 69% having some documentation that ranged from gauze placement only (19%) to topical lidocaine, barrier cream, antibiotic or antifungal cream/ ointment, lubricant, or topical steroid ointment (50%). Menstrual suppression was recommended in 38% ($n = 9$) of menstruating females. An antifungal medication was only prescribed in 4% of patients.

Following implementation of the clinical pathway for the treatment of SJS/TEN in 2017, 22 females with SJS/TEN were identified. 72% ($n = 16$) had documented vulvovaginal involvement ($n = 16$ vulvar, $n = 9$ vaginal). Gynecology consultations took place in 86% ($n = 19$) of patients. We identified several improvements after implementation of the protocol. Gynecology consults overall increased from 26% pre-, to 86% post-protocol. For patients with vulvovaginal involvement, consultations were completed in 93% compared to 50% prior to protocol. Of note, the finding of vulvovaginal lesions increased from 53 to 72%. Dilator use with topical steroid ointment was consistently recommended, as was antifungal use and menstrual suppression.

**Conclusion:** Having a protocol in place for treatment of female patients with SJS/TEN increased the consistency of Gynecologic consultation and the documentation and treatment of vulvovaginal SJS/TEN. We identified the need to improve clinical follow-up after discharge from the hospital, which could be arranged as multidisciplinary visits and would be a good option to assess long-term outcomes (pain, sexual activity, etc.). With regards to future directions, we are in the process of assessing long-term data on quality of life and sexual functioning. The impact of treatment in the acute setting on the development of chronic sequelae needs to be established, as does the management of long-term sequelae like vaginal dryness, pain, dyspareunia. The role of local estrogen and vaginal laser still needs to be explored. Pelvic floor physical therapy might play a significant role in rehabilitation and has yet to be studied.

**Keywords: Stevens Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), vulvovaginal sequelae, gynecologic manifestations of SJS/TEN, treatment of vulva and vagina, standardized protocol for SJS/TEN**

## INTRODUCTION

Stevens Johnson Syndrome and Toxic Epidermal Necrolysis are severe mucocutaneous reactions characterized by sudden onset epidermal necrosis. SJS/TEN is more commonly seen in women than men and is most often triggered in response to a medication (1). Mucosal surface involvement is often widespread, involving the respiratory, gastrointestinal, and genitourinary tracts (2, 3). The reported prevalence of vulvovaginal involvement in patients hospitalized with SJS/TEN is extremely variable, was previously estimated to be as high as 70% (2, 4–6) and seems to be higher with routine consultation of a specialist in Gynecology. Failure to recognize and treat vulvovaginal SJS/TEN has the potential for severe acute and chronic morbidity (4), including vulvovaginal adhesions, vaginal stenosis, vaginal dryness, pain, dyspareunia, bleeding, adenosis, and psychological distress. Even when identified and treated, available data suggest that up to one third of patients develop chronic sequelae (2). Despite the potential for severe consequences, because of the focus on critical care in the acute phases of the illness and the sensitive nature of a gynecologic exam, it is possible that pelvic exams are being deferred, and vulvovaginal SJS/TEN is likely underrecognized.

Reported genitourinary symptoms frequently include pain, swelling, and dysuria (1). The importance of a comprehensive total body examination is well-documented, including the examination of the vulvar mucosa, perineum, perianal skin, and anus. Upon examination, acute vulvovaginal SJS/TEN most often present as erosions and ulcerations. Though a speculum exam is necessary for identification of vaginal lesions, experts have suggested assuming and treating possible vaginal involvement because of the painful and potentially distressing nature of such exams (2).

Treatment of mucosal involvement in the vulva or vagina relies largely on expert opinion, as there are no prospective trials to study its treatment. Current practice typically includes the use of topical application of corticosteroids, vaginal dilator therapy,

menstrual suppression (1) and a Foley catheter with the goal of decreasing adhesion formation and agglutination, vulvar pain, and limiting metaplastic changes in affected tissue. Even when protocols exist at individual institutions, there is little data on the effectiveness of such protocols, or the degree to which they are followed (7).

Harborview Medical Center, University of Washington in Seattle, USA, is the only level one adult and pediatric trauma and burn center in Washington State and receives multistate referrals. In June of 2017, a Clinical Care Pathway for the treatment of patients with SJS/TEN was implemented. This pathway document is an institutional protocol for treating patients with SJS/TEN and provides recommendations for the evaluation and treatment of vulvovaginal involvement in SJS/TEN. It emphasizes consistent consultation of the Gynecology service with the goal of evaluating the patient and educating the patient and family regarding the treatment. The pathway document outlined several recommendations to aid the completion of a thorough gynecologic evaluation. This includes requesting notification of the Gynecology team prior to a procedure in the operating room to allow gynecological exam under anesthesia, including speculum examination to assess vaginal involvement. Treatment recommendations were protocolized. For all women or girls (who have been sexually active or who use tampons) with documented vaginal involvement, vaginal dilator therapy with concurrent use of steroid ointment was recommended to decrease risk of vaginal agglutination and adhesion formation. The protocol standardized vaginal dilator use to 20–30 min 2–3 times daily with generous application of the chosen steroid ointment (i.e., Betamethasone 0.05–0.1% or TAC 0.1% ointment). If unable to use steroid ointment, a water-based lubricant is acceptable. Ointments have fewer additives and are preferred to creams that can contain alcohol which causes a burning sensation on raw surfaces. It suggested consideration of menstrual suppression to decrease the risk of vaginal adenosis and for ease of hygiene. Vaginal antifungals were recommended to be used as needed for patients receiving long term antibiotics and to counteract the vaginal steroid which could promote fungal overgrowth. It advised that in the case of vulvar involvement only, vulvar mucous membranes should be treated similar to vaginal mucous membranes to decrease labial agglutination and scarring through application of topical steroids and manual separation of the labia two or three times daily with an impregnated gauze.

The goal of this study was to identify whether the protocol increased treatment of vulvovaginal SJS/TEN and to optimize our standardized protocol to prevent genitourinary sequelae.

## METHODS

We conducted a retrospective chart review examining the frequency and treatment of vulvovaginal involvement in female patients with SJS/TEN before and after the implementation of a pathway for treating SJS/TEN at our level one burn center in the Northwest of the United States of America. We reviewed charts from 2008 to 2021 (14 years) and identified 77 patients with biopsy proven SJS/TEN (out of a total of 88 females with SJS/TEN). Inclusion criteria were a female patient admitted to the burn unit of our institution with SJS/TEN between 2008 and 2021. Vulvovaginal involvement was established by physical exam documentation. Treatment regimens were evaluated by reviewing a combination of the discharge summary, medication list, and gynecology consult note as well as other physician and nursing documentation. Post-hospitalization outpatient gynecologic follow-up from 2017 to 2021 was reviewed within our hospital system and using electronic access to other clinic and hospital systems. Descriptive statistics were reported as % ($n$) for all categorical variables and as a mean or count for all continuous variables. Fisher exact test with significance set at $p < 0.05$ was used to compare categorical variables pre and post implementation of treatment pathway.

Letters were sent to the patients with the goal of obtaining long term data on quality of life and sexual functioning following vulvovaginal sloughing due to TEN and SJS.

## RESULTS

From 2008 to 2021, a total of 77 female patients admitted with biopsy proven SJS/TEN were identified. A summary of patient characteristics and treatment can be found in **Table 1**. The age of patients with SJS/TEN ranged from 6 to 93 years old with a mean age of ∼45 years old. 55% of the 77 cases were classified as SJS and 43% were TEN. 55% of the patients with SJS/TEN had documented vulvar involvement ($n = 42$) and 39% had vaginal involvement ($n = 30$). A gynecology consult was obtained in 43% of patients with SJS/TEN. 49% of menstruating patients received menstrual suppression ($n = 17$), and 17% of patients were recommended an antifungal ($n = 13$).

Prior to implementation of the clinical care pathway (2008–2017), 55 patients were identified with a clear biopsy proven diagnosis of SJS/TEN. The mean age was 45 years old (6–93). 47% of patients ($n = 26$) had documented vulvovaginal involvement, 21 of which also were found to have vaginal involvement. Gynecology was consulted in 26% ($n = 14$) patients. Of the 21 females with vaginal involvement, only 38% ($n = 8$) received treatment with dilators/vaginal molds with steroid ointment. Of the 26 females with vulvar involvement, 31% ($n = 8$) received no vulvovaginal treatment. The remaining 69% had some documented treatment that ranged from gauze placement only (19%) to topical lidocaine, barrier cream, antibiotic or antifungal cream/ointment, lubricant, or topical steroid ointment (50%). Menstrual suppression was recommended in 38% ($n = 9$) of menstruating females. An antifungal medication was prescribed for 4% of patients.

Letters were sent to that patient group with the goal of obtaining long term data on quality of life and sexual functioning following vulvovaginal sloughing due to TEN and SJS. However, of the 45 letters sent (out of 55 females, 9 deceased, one location not available), only 5 patients responded and therefore feedback about long-term sequelae was insufficient.

Charts from 2017 to 2021, following implementation of the standardized protocol, were also reviewed. 22 females with

**TABLE 1 |** Demographics and clinical variables of patients with SJS/TEN from 2008 to 2021.

| Variable | % (mean or count) $n = 77$ |
|---|---|
| Age (years old) | 6–93 (45) |
| **Menstrual status** | |
| Premenstrual | 4% (3) |
| Menstruating | 45% (35) |
| post-menstrual/hysterectomy | 43% (33) |
| **Sexual activity** | |
| Yes | 17% (13) |
| No | 22% (17) |
| Not specified | 63% (48) |
| **Diagnosis** | |
| SJS | 55% (42) |
| TEN | 43% (33) |
| **Extent of vulvovaginal involvement** | |
| Vulvar involvement | 55% (42) |
| Vaginal involvement | 39% (30) |
| Gynecology consult | 43% (33) |
| Vaginal treatment recommendations (a) | 70% (21) |
| Dilator recommended | 70% (21) |
| Dilator used | 67% (20) |
| Steroid cream/ointment | 71% (30) |
| No vulvar treatment recommendations + | 19% (8) |
| Vulvar treatment recommendations (b) | 81% (34) |
| Gauze only | 19% (5) |
| Topical Steroid | 45% (19) |
| Other | 36% (15) |
| Menstrual suppression (c) | 49% (17) |
| Antifungal | 17% (13) |

*(a) recommendation for vaginal dilator of the patients with documented vaginal involvement (n = 30). (b) Vulvar treatment recommendations of the patients with vulvar involvement (n = 42). (c) menstrual suppression of menstruating patients (n = 35).*

SJS/TEN, ages 7–83 with mean age 46 years, were included. Seventy-two percentage ($n = 16$) of patients had documented vulvovaginal involvement, vulvar 72% ($n = 16$) and vaginal 41% ($n = 9$). There was no difference in rates of vulvar involvement between patients with SJS vs. TEN ($n = 8$ for both groups). The rates of vaginal involvement were also not significantly different between patients with SJS vs. TEN ($n = 5$ and 4, respectively). Gynecology consultations took place in 86% ($n = 19$) of patients and only one patient with possible vulvovaginal involvement lacked a consult, while vulvovaginal involvement in 2 females was not documented. Two patients with a gynecology consult were recommended prophylactic vulvovaginal treatment, despite lack of vulvovaginal involvement at the time of examination. One patient was recommended to use a vaginal dilator with a steroid ointment, and the other patient was recommended topical steroid both internally and externally. Both patients were recommended antifungal treatment. Recommendation for post-hospitalization follow-up with gynecology was documented in 9 out of the 20 patients (45%) that were not deceased at the time of discharge, but only 2 females had completed a documented follow-up visit within 6 months.

**TABLE 2 |** Demographics and clinical variables of patients with SJS/TEN.

| Variable | % (mean or count) | % (mean or count) |
|---|---|---|
| | Total $n = 55$ | Total $n = 22$ |
| | (a) $n = 21$ | (a) $n = 9$ |
| | (b) $n = 26$ | (b) $n = 16$ |
| | (c) $n = 24$ | (c) $n = 11$ |
| | 2008–2017 | 2017–2021 |
| Age | 45 (6–93) | 46 (7–83) |
| **Menstrual status** | | |
| Premenstrual | 4% (2) | 4.5% (1) |
| Menstruating | 49% (24) | 50% (11) |
| post-menstrual/hysterectomy | 47% (23) | 45% (10) |
| **Sexual activity** | | |
| Yes | 9% (5) | 36% (8) |
| No | 17% (9) | 36% (8) |
| Not specified | 75% (41) | 32% (7) |
| **Diagnosis** | | |
| SJS | 58% (31) | 50% (11) |
| TEN | 44% (22) | 50% (11) |
| **Extent of vulvovaginal involvement** | | |
| Vulvar involvement | 49% (26) | 72% (16) |
| Vaginal involvement | 40% (21) | 41% (9) |
| Vaginal only | 0 | 0 |
| Vaginal involvement not specified | — | 18% (4) |
| Gynecology consult | 26% (14) | 86% (19) |
| Dilator recommended (a) | 38% (8) | 59% (13) |
| Used | 38% (8) | 55% (12) |
| Steroid cream/ointment | 38% (8) | 55% (12) |
| No vulvar treatment recommendations + | 31% (8) | 6% (1) |
| Vulvar treatment recommendations (b) | 69% (18) | 100% (16) |
| Gauze only | 19% (5) | 0 |
| Topical steroid | 23% (6) | 59% (13) |
| Other | 23% (6) | 56% (9) |
| Menstrual suppression (c) | 38% (9) | 73% (8) |
| Antifungal | 4% (2) | 50% (11) |

*(a) recommendation for vaginal dilator of the patients with documented vaginal involvement (n = 21 from 2008 to 2017, n = 9 from 2017 to 2021). (b) Vulvar treatment recommendations of the patients with vulvar involvement (n = 26 from 2008 to 2017, n = 16 from 2017 to 2021). (c) menstrual suppression of menstruating patients (n = 24, n = 11).*

We are currently in the process of contacting patients that were hospitalized after 2017, with the goal of obtaining long term data on quality of life and sexual functioning.

We found several improvements after implementation of the protocol (**Table 2**). Gynecology consults increased from 26% pre- to 86% post-protocol (Fisher exam test statistic value <0.00001 at $p < 0.05$). For patients with vulvovaginal involvement, consultations were done in 93% compared to only 50% prior to protocol (Fisher exam test statistic value <0.00001 at $p < 0.05$). Documentation of vulvar involvement increased from 47% pre-protocol to 72% post-implementation (Fisher exact test statistic

value 0.048). Documented vaginal involvement remained largely unchanged, 40% pre-protocol to 41 % post-protocol. There was a significant increase in the use of vaginal dilators and steroid cream (Fisher exact test statistic value 0.0178) and in the use of an antifungal (Fisher exact test statistic value 0.0004 at $p < 0.05$). There were significant increases in treatment for patients with vulvar involvement and in the use of menstrual suppression (both $p < 0.05$). If a gynecology consult was omitted, rather no vulvovaginal exam than a negative exam was documented. Additionally, documentation of sexual activity and pregnancy status improved significantly.

## DISCUSSION

SJS/TEN is a severe mucocutaneous reaction characterized by epidermal necrosis and mucosal sloughing. The extent of mucocutaneous involvement is variable and widespread, often affecting genitourinary tracts.

In our study, from 2008 to 2021, vulvovaginal involvement was documented overall in ∼55% of SJS/TEN cases, compared to vulvovaginal involvement of up to 70% cited in the literature. Notably, when examining the patient cohorts pre and post clinical pathway implementation, the finding of vulvovaginal involvement increased from 49 to 72%. Gynecology consults also increased from 26% pre implementation to 86% post implementation. The increase in rates of vulvovaginal involvement in patients with SJS/TEN after the implementation of the clinical pathway likely represents an increase in the number of thorough pelvic evaluations, rather than an actual increase in the prevalence of the disease. Interestingly, we found no difference in the presence of vulvovaginal involvement between patients with SJS vs. TEN. Collectively these findings underscore the importance of having protocols in place with set treatment recommendations for primary teams to follow. While the severity of an individual case may not make the assessment and treatment of vulvovaginal lesions a priority, many patients with SJS/TEN will have genital involvement, and our findings suggest that severity of the disease does not correlate with the presence or absence of genital involvement and should not be a consideration in the decision of whether to do a pelvic exam.

We found a significant improvement in the percentage of patients who were treated for vulvovaginal SJS/TEN. While only 38% of patients received treatment with vaginal dilators pre-protocol, 59% received it after protocol implementation. Menstrual suppression and antifungals were also recommended more consistently following the implementation of the clinical pathway.

We were not able to gather information about the long-term outcomes of vulvovaginal involvement in the patients hospitalized prior to 2017, as the follow up was particularly low. There is still little information on how effective these treatments are in preventing adverse long-term outcomes.

With regards to future directions, we identified the need to improve clinical follow-up after discharge from the hospital which could be arranged in multidisciplinary visits and would allow the assessment of long-term symptomatic outcomes (pain, sexual activity, etc.). Of particular importance is the management of long-term sequelae like vaginal dryness, pain, dyspareunia. The role of local estrogen and vaginal laser as therapeutics still needs to be explored. Pelvic floor physical therapy might also play a key role in long-term rehabilitation. The possibility of experimental amniotic membrane application to affected vaginal walls, similar to the procedure in Ophthalmology, is promising and requires additional investigation. While our review demonstrates significant progress in the last 4 years, and highlights the importance of a clinical protocol, there is still a need for optimization of prevention and treatment of urogenital sequelae of SJS/TEN. We recommend a gynecology consult on all SJS/TEN patients seen by other services for a comprehensive assessment of genital involvement.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Washington IRB approval. Written informed consent from the participants or their legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

## AUTHOR CONTRIBUTIONS

EF, MD, and SH have contributed with data collection, data evaluation, and writing and revising of the manuscript. All authors contributed to the article and approved the submitted version.

## REFERENCES

1. Magone MT, Maiberger M, Clayton J, Pasieka H. Vulvovaginal and ocular involvement and treatment in female patients with Stevens-Johnson syndrome and toxic epidermal necrolysis: a review. *Int J Womens Dermatol.* (2021) 7:520–8. doi: 10.1016/j.ijwd.2021.08.012
2. O'Brien KF, Bradley SE, Mitchell CM, Cardis MA, Mauskar MM, Pasieka HB. Vulvovaginal manifestations in Stevens-Johnson syndrome and toxic epidermal necrolysis: prevention and treatment. *J Am Acad Dermatol.* (2021) 85:523–8. doi: 10.1016/j.jaad.2019.08.031
3. Chang WC, Abe R, Anderson P, Anderson W, Ardern-Jones MR, Beachkofsky TM, et al. SJS/TEN 2019: from science to translation [published correction appears. *J Dermatol Sci*. (2021) 104:146–7. doi: 10.1016/j.jdermsci.2020.02.003
4. Meneux E, Wolkenstein P, Haddad B, Roujeau JC, Revuz J, Paniel BJ. Vulvovaginal involvement in toxic epidermal necrolysis: a retrospective study of 40 cases. *Obstet Gynecol.* (1998) 91:283–7. doi: 10.1016/s0029-7844(97)00596-6
5. Kaser DJ, Reichman DE, Laufer MR. Prevention of vulvovaginal sequelae in stevens-johnson syndrome and toxic epidermal necrolysis. *Rev Obstet Gynecol.* (2011) 4:81–5. doi: 10.3909/riog0152

6. Crowder CA, Jeney SES, Kraus CN, Bernal N, Lane F. Vulvovaginal involvement in Stevens-Johnson syndrome and toxic epidermal necrolysis: management and techniques used to reduce gynecologic sequelae. *Int J Dermatol.* (2022) 61:158–63. doi: 10.1111/ijd.15676
7. Le HG, Saeed H, Mantagos IS, Mitchell CM, Goverman J, Chodosh J. Burn unit care of Stevens Johnson syndrome/toxic epidermal necrolysis: a survey. *Burns.* (2016) 42:830–5. doi: 10.1016/j.burns.2015.12.001

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**Publisher's Note:** All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers | Frontiers in Medicine

TYPE Systematic Review
PUBLISHED 24 August 2022
DOI 10.3389/fmed.2022.949520



OPEN ACCESS

EDITED BY
Martin Bauer,
Medical University of Vienna, Austria

REVIEWED BY
Patrick M. Brunner,
Icahn School of Medicine at Mount Sinai, United States
Johannes Griss,
Medical University of Vienna, Austria

*CORRESPONDENCE
Liqin Wang
lwang@bwh.harvard.edu

SPECIALTY SECTION
This article was submitted to Dermatology, a section of the journal Frontiers in Medicine

RECEIVED 21 May 2022
ACCEPTED 04 August 2022
PUBLISHED 24 August 2022

CITATION
Wang L, Varghese S, Bassir F, Lo Y-C, Ortega CA, Shah S, Blumenthal KG, Phillips EJ and Zhou L (2022) Stevens-Johnson syndrome and toxic epidermal necrolysis: A systematic review of PubMed/MEDLINE case reports from 1980 to 2020. *Front. Med.* 9:949520. doi: 10.3389/fmed.2022.949520



# Stevens-Johnson syndrome and toxic epidermal necrolysis: A systematic review of PubMed/MEDLINE case reports from 1980 to 2020

Liqin Wang[1]*, Sheril Varghese[1], Fatima Bassir[1], Ying-Chin Lo[1], Carlos A. Ortega[2], Sonam Shah[1,3], Kimberly G. Blumenthal[4], Elizabeth J. Phillips[5] and Li Zhou[1]

[1]Division of General Internal Medicine and Primary Care, Department of Medicine, Harvard Medical School, Brigham and Women's Hospital, Boston, MA, United States, [2]School of Medicine, Vanderbilt University, Nashville, TN, United States, [3]Harvard Medical School, Dana-Farber Cancer Institute, Boston, MA, United States, [4]Division of Rheumatology, Allergy, and Immunology, Harvard Medical School, Massachusetts General Hospital, Boston, MA, United States, [5]Division of Infectious Disease, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, United States

**Background:** Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare, life-threatening immunologic reactions. Prior studies using electronic health records, registries or reporting databases are often limited in sample size or lack clinical details. We reviewed diverse detailed case reports published over four decades.

**Methods:** Stevens-Johnson syndrome and toxic epidermal necrolysis-related case reports were identified from the MEDLINE database between 1980 and 2020. Each report was classified by severity (i.e., SJS, TEN, or SJS-TEN overlap) after being considered a "probable" or "definite" SJS/TEN case. The demographics, preconditions, culprit agents, clinical course, and mortality of the cases were analyzed across the disease severity.

**Results:** Among 1,059 "probable" or "definite" cases, there were 381 (36.0%) SJS, 602 (56.8%) TEN, and 76 (7.2%) SJS-TEN overlap cases, with a mortality rate of 6.3%, 24.4%, and 21.1%, respectively. Over one-third of cases had immunocompromised conditions preceding onset, including cancer ($n$ = 194,18.3%), autoimmune diseases ($n$ = 97, 9.2%), and human immunodeficiency virus (HIV) ($n$ = 52, 4.9%). During the acute phase of the reaction, 843 (79.5%) cases reported mucous membrane involvement and 210 (19.8%) involved visceral organs. Most cases were drug-induced ($n$ = 957, 90.3%). A total of 379 drug culprits were reported; the most frequently reported drug were antibiotics ($n$ = 285, 26.9%), followed by anticonvulsants ($n$ = 196, 18.5%), analgesics/anesthetics ($n$ = 126, 11.9%), and antineoplastics ($n$ = 120, 11.3%). 127 (12.0%) cases reported non-drug culprits, including infections ($n$ = 68, 6.4%), of which 44 were associated with a mycoplasma pneumoniae infection and radiotherapy ($n$ = 27, 2.5%).

**Conclusion:** An expansive list of potential causative agents were identified from a large set of literature-reported SJS/TEN cases, which warrant future investigation to understand risk factors and clinical manifestations of SJS/TEN in different populations.

KEYWORDS

toxic epidermal necrolysis, Stevens-Johnson syndrome, drug-related side effects and adverse reactions, case report, review literature

# Introduction

Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN), characterized by the detachment of the epidermis and mucous membrane, are rare severe cutaneous adverse reactions. SJS/TEN can be life-threatening, with mortality rates between 4.8% and 14.8% (1). Based on the degree of skin detachment, SJS/TEN can be classified into SJS, SJS-TEN overlap, and TEN (2). SJS is defined as skin involvement of <10%; TEN is defined as skin involvement of >30%; SJS-TEN overlap is defined as 10−30% skin involvement. The estimated incidences of SJS, SJS/TEN, and TEN in the United States are 9.2, 1.6, and 1.9 per million adults, respectively (1, 3).

The low incidence among patient populations has created unique challenges in elucidating the epidemiology and etiology of SJS/TEN. The optimal medical management of SJS and TEN demands prompt recognition and immediate withdrawal of the causative drugs to alter the course of the reaction and potentially evade mortality. Most prior SJS/TEN studies report findings based on small sample sizes and do not reflect the heterogeneity of the patient population affected by SJS/TEN, minimizing the generalizability of the findings (4, 5). While common causative agents are increasingly identified, little is known about uncommon and non-drug factors that are highly associated with SJS/TEN (6). For example, in two large European case-control studies, fewer than a dozen medications accounted for half of the analyzed SJS/TEN cases (7, 8). Without an exhaustive list of diverse culprits, efforts to promptly withdraw causative agents are inhibited, leading to increased morbidity and mortality.

Several studies attempted to circumvent these limitations by extracting data from electronic health records (EHRs) and large repositories (9–14). For example, Micheletti et al. (11) performed a retrospective cohort study, notably collecting data across 18 United States medical centers and identified 377 SJS/TEN cases from EHRs. Blumenthal et al. used the EHR allergy list to identify over 700 patients with SJS/TEN (11). Similar studies have taken place in Asia, identifying hundreds of patients with SJS/TEN using EHRs or registry databases (15, 16). As a result of such regional studies, it is evident that there are ethnic and regional disparities in the incidence of SJS/TEN that may arise from variation in genetics or regional medical practices (5). SJS/TEN cases have also been identified from post-marketing surveillance adverse events reporting systems; however, such cases often lack stringent SJS/TEN definitions, clinical details, and clear causal associations between drugs and adverse events (17, 18).

Considering the rarity of SJS/TEN and the challenges of collecting validated SJS/TEN cases from EHRs or registry databases, case reports from the literature can be a rich source of information to study SJS and TEN. An appreciable number of case reports have been published to highlight suspected culprit agents and effective care for SJS/TEN cases. Case reports from the literature serve to relay clinical knowledge on a case-by-case basis; they are a unique source of detailed medical information for conditions with low prevalence and undefined care. Although several studies have used case reports to study specific culprit agents (19, 20), currently, no research to our knowledge has contextualized and extrapolated significant trends across all case reports. Cognizant of the logistical barriers to evidence-based research and the need to develop a deep understanding of the etiology, optimal care, and patient outcomes of SJS/TEN, this study seeks to conduct a systematic review of case reports from the literature. By amassing data across case reports from an up-to-date database, PubMed/MEDLINE, we aim to assemble a large, diverse SJS/TEN sample set to comprehensively describe the causative agents, trends over time, differences across disease severity, and patient outcomes.

# Methods

## Data sources and collection

We queried PubMed/MEDLINE on 23 March 2021 to retrieve case reports related to SJS and TEN published between 1 January 1980 and 31 December 2020 (see **Table 1**).

Abbreviations: SJS, Stevens-Johnson syndrome; TEN, Toxic epidermal necrolysis; HIV, Human immunodeficiency virus; EHR, Electronic health records; EM, Erythema multiforme; NSAIDs, Non-steroidal anti-inflammatory drugs.

TABLE 1 PubMed/MEDLINE query to retrieve case reports related to Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).

| PubMed/MEDLINE search strategy | No. of retrieved reports |
|---|---|
| ("Case Reports"[pt] OR "Case report"[tiab]) AND (("toxic"[tiab] AND "epidermal"[tiab] AND "necrolysis"[tiab]) OR ("Steven"[tiab] AND "Johnson"[tiab]) OR ("Lyell"[tiab] AND "Syndrome") OR ("Stevens-Johnson Syndrome"[MeSH])) AND ("1980/01/01"[PDat]: "2020/12/31"[PDat]) AND ("English"[LA]) | 1982 |

The publication date was defined as the date that records were made publicly available in PubMed/MEDLINE regardless of the journal issue date of the case reports.

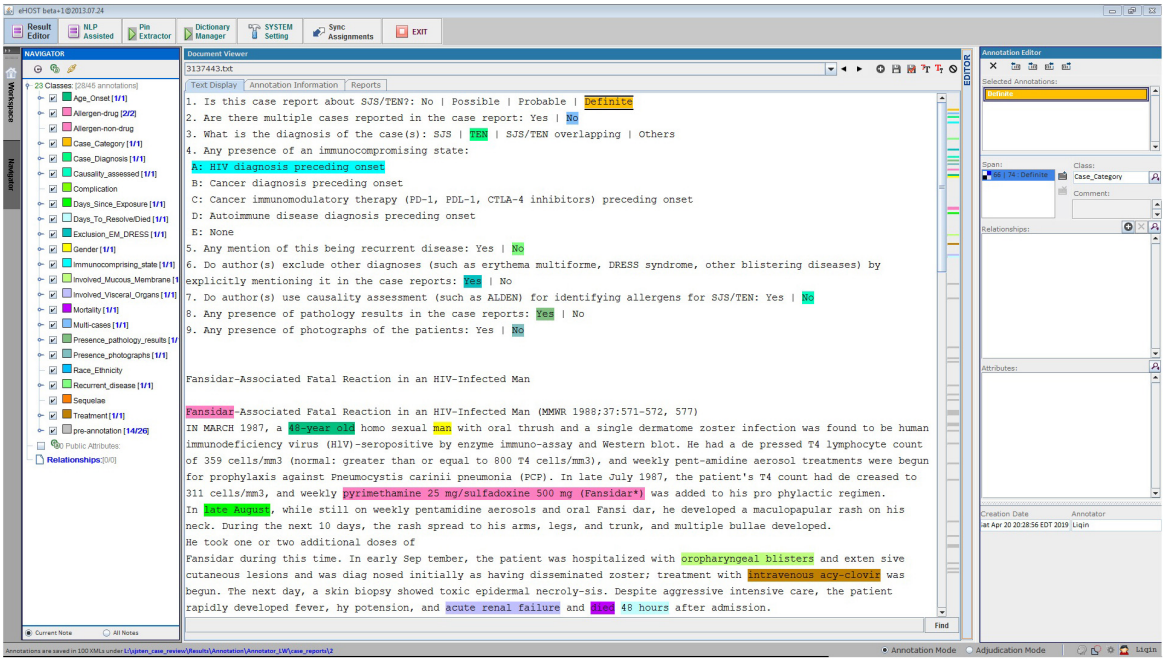


FIGURE 1
Case report annotation environment.

## Inclusion and exclusion criteria

We included case reports that were written in English with full-text available. We excluded duplicated case reports and any case reports describing more than one SJS/TEN case as the cases in those reports were often discussed in an aggregated manner and more likely to have limited clinical details. However, we included case reports that mentioned multiple cases yet only discussed one SJS/TEN case in detail. We also excluded cases that did not provide enough details about the acute phase of the reaction, such as case reports focused on SJS/TEN sequalae without describing the potential cause, the care received, or the disease progression.

## Annotation process and schema

After collecting the full-text case reports in PDF format, we converted them into text files for annotation. To facilitate manual review, we adopted an open-source annotation tool (i.e., eHOST) to support the extraction of relevant information from the case reports (Figure 1; 21). Each report was annotated by two researchers, and any conflict between the two annotators was resolved by reaching consensus or by a third reviewer. The annotation task was based on an annotation schema, with annotators identifying relevant text in the case reports and assigning the text to a class defined in the schema. We manually defined the schema to cover a broad range of topics for analysis, including age of onset, gender, race/ethnicity, preexisting conditions, involvement of visceral organs and mucous membranes during the acute phase, drug and/or non-drug culprit agents, treatments received, and mortality status.

We also developed 9 questions (see Table 2) and inserted them at the beginning of each report's text to extract additional information from the case report. The questions included whether the case report was about SJS/TEN and whether there were multiple cases examined. If the case report was related to SJS/TEN, the annotators continued to answer the remaining

TABLE 2 Questions answered by annotators for each case report.

| |
|---|
| (1) Is this case report about SJS/TEN? No \| Possible \| Probable \| Definite |
| (2) Are there multiple cases reported in the case report: Yes \| No |
| (3) What is the diagnosis of the case(s): SJS \| TEN \| SJS/TEN overlapping \| Others |
| (4). Any presence of an immunocompromising state: |
| A: HIV diagnosis preceding onset |
| B: Cancer diagnosis preceding onset |
| C: Cancer immunomodulatory therapy (PD-1, PD-L1, CTLA-4 inhibitors) preceding onset |
| D: Autoimmune disease diagnosis preceding onset |
| E: None |
| (5) Any mention of this being recurrent disease: Yes \| No |
| (6) Do author(s) exclude other diagnoses (such as erythema multiforme, DRESS syndrome, other blistering diseases) by explicitly mentioning it in the case reports: Yes \| No |
| (7) Do author(s) use causality assessment (such as ALDEN) for identifying allergens for SJS/TEN: Yes \| No |
| (8) Any presence of pathology results in the case reports: Yes \| No |
| (9) Any presence of photographs of the patients: Yes \| No |

questions regarding the severity level of the diagnosis (i.e., SJS, TEN, SJS-TEN overlap, or others), whether pathology results were reported, and whether patient photos were provided. They also judged whether there was a recurrence of SJS/TEN and if the authors used casualty assessment [e.g., algorithm of drug causality for epidermal necrolysis [ALDEN] (22)] for identifying culprit agents.

## Data cleaning

After applying the inclusion and exclusion criteria, we formed a final set of SJS/TEN cases to be included in the analyses. Due to variability in how information was reported, we manually mapped the annotations to standardized terms; for example, "Bactrim," "TMX-SMZ," and "co-trimoxazole" were mapped to "trimethoprim-sulfamethoxazole." Next, we determined the drug and non-drug class for individual allergens based on the First Databank drug classification and manual expert review. We converted the annotations into numerical or categorical values before including them for analysis. Ages were converted to years; if the patient's age was less than 12 months, it was coded as 0 year. Race, preconditions, and drug and non-drug allergens were manually reviewed and grouped. Mortality and mucous membrane and visceral organ involvement were converted to binary variables.

## Statistical analysis

We described patient demographics and clinical characteristics by severity (i.e., SJS, TEN, and SJS-TEN overlap). Categorical variables are presented as numbers (percentage) and continuous variables are reported as median ± inter-quartiles range. Continuous variables were compared using one-way analysis of variance (ANOVA) test for normally distributed variables or Kruskal-Wallis test for non-normally distributed variables. Categorical variables were compared using Chi-square test. *Post hoc* test was applied after a significant ANOVA, Kruskal-Wallis or Chi-square test, adjusted by Bonferroni correction. The distribution of the cases was analyzed by publication year, severity type, and allergens. Statistical analyses were completed using R software, version 4.0.4 (R Foundation for Statistical Computing).

# Results

## Identification of Stevens-Johnson syndrome and toxic epidermal necrolysis case reports from the literature

Figure 2 shows the PRISMA diagram for choosing case reports to be included in the analysis (23). The PubMed query returned a total of 1,982 case reports. We excluded 1 duplicate report, 295 reports without full text, 251 multi-case reports, and 376 reports that were irrelevant or did not contain sufficient clinical details of SJS/TEN. In total, 1,059 case reports met the inclusion criteria, which were composed of 381 (36.0%) SJS, 602 (56.8%) TEN, and 76 (7.2%) SJS-TEN overlap cases. Of included reports, 538 (50.8%) included pathology results and 700 (66.1%) contained photographs.

## Publication trends

Figure 3 shows the distribution of SJS, TEN, and SJS-TEN overlap cases by publication year. All cases were published between 1980 and 2020 with 273 (25.8%) cases published before 2000. The number of case reports peaked in 2014 with a total of 58 case reports.

## Demographics and clinical characteristics of Stevens-Johnson syndrome and toxic epidermal necrolysis cases

Table 3 shows the overall demographics and clinical characteristics of the SJS/TEN cases by severity. Approximately 52.6% ($n$ = 557) of all included cases were female. Less than half of the sample with an SJS diagnosis were female, unlike the TEN and SJS-TEN overlap samples (46.1% in SJS, 56.1% in TEN, and 56.6% in SJS-TEN overlap, $p$-Value = 0.007). The majority of cases ($n$ = 795, 75.1%) did not report race or ethnicity.

Out of all 1,059 cases, 194 patients had a cancer diagnosis, 35 patients were receiving cancer immunomodulatory

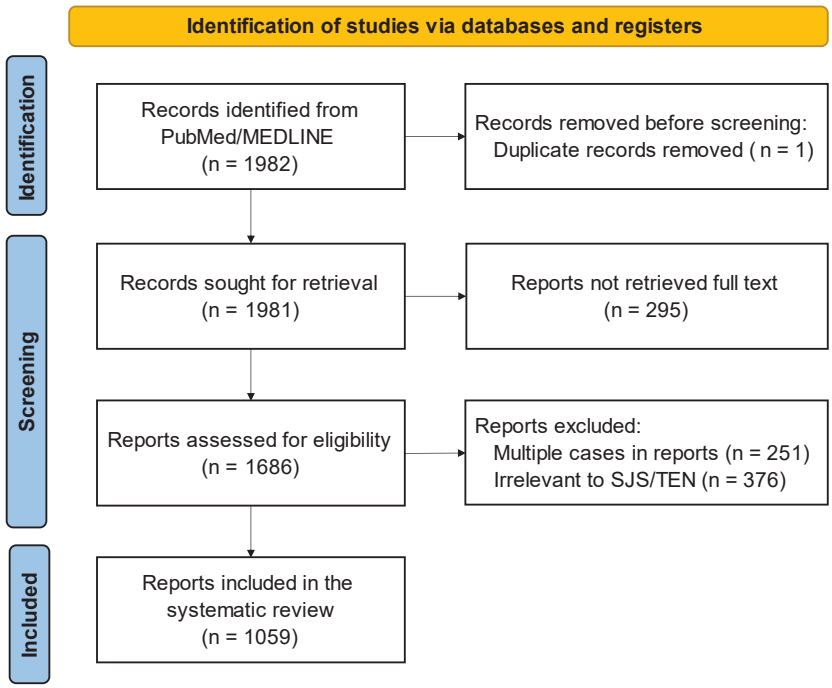


FIGURE 2
PRISMA flow diagram for choosing Steven Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) case reports for analysis.

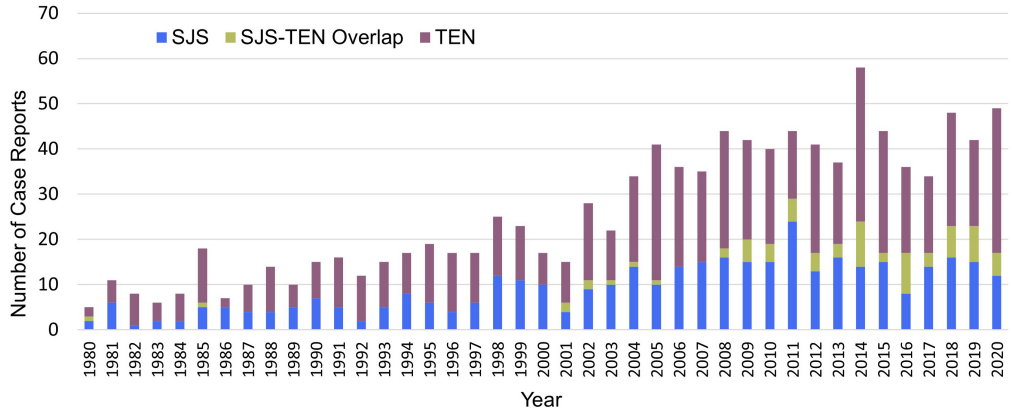


FIGURE 3
Distribution of Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and SJS-TEN overlap case reports from PubMed/MEDLINE by publication year.

therapy (PD-1, PD-L1, CTLA-4 inhibitors), 97 patients had an autoimmune disease diagnosis (i.e., systemic lupus erythematosus, rheumatoid arthritis, psoriasis), and 52 patients presented with an HIV diagnosis preceding onset. About 20% and 16% of patients diagnosed with TEN and SJS, respectively, were diagnosed with cancer. 2.0% of TEN cases and 2.6% of SJS cases were receiving cancer therapy at the time of their SJS/TEN diagnoses. Altogether, 7−10% of cases in all groups were documented to have at least one autoimmune disease.

Among all the SJS/TEN cases, infections were the most common preconditions prior to SJS/TEN onset ($n$ = 201, 19.0%). The presentation of infections is highest among SJS cases (21.8%) compared to TEN (17.1%) and SJS-TEN overlap (11.8%) cases. This pattern applies to respiratory tract infections and mycoplasma pneumonia infections, while the later one also shows a significant difference across the three-severity groups ($p$-Value $< 0.001$). Other less common preconditions include epilepsy/seizure disorders ($n$ = 102, 9.6%), hypertension

($n$ = 92, 8.7%), cardiovascular conditions ($n$ = 54, 5.1%), diabetes ($n$ = 54, 5.1%), musculoskeletal conditions ($n$ = 52, 4.9%), and endocrine/hormonal conditions ($n$ = 50, 4.7%).

We also extracted data from the case reports regarding the acute phase of SJS/TEN. The majority of cases ($n$ = 842, 79.5%) reported involvement of mucosal membranes, including the oropharynx, conjunctiva, genitalia, and/or anus. The SJS-TEN overlap cases reported the highest percentage of patients with mucosal membrane involvement (92.1%), while TEN cases, the severest of the three diagnoses, reported the lowest rate of mucous membrane involvement (73.0%). 210 (19.8%) cases reported that visceral organs were impacted throughout the diagnosis. Fewer patients in the SJS cohort experienced involvement of visceral organs relative to both SJS-TEN overlap and TEN cases alone (14.7% vs. 23.7% vs. 22.6%, $p$-Value = 0.007).

Approximately 18% ($n$ = 187) of patients diagnosed with SJS/TEN did not survive. Case reports with a TEN diagnosis reported the highest mortality relative to patients diagnosed with SJS-TEN overlap syndrome and SJS (TE*N* = 24.4%, SJS-TEN overlap = 21.1%, SJS = 6.3%, $p$-Value $< 0.001$).

## Causative agents of Stevens-Johnson syndrome and toxic epidermal necrolysis cases

Of all cases, 957 (90.3%) implicated medications as the cause of the diagnoses. 781 (73.7%) cases reported a single medication as the culprit. More TEN and SJS-TEN overlap cases were caused by drug allergens compared to SJS cases (93.7% for TEN, 97.4% for SJS-TEN overlap, and 83.7% for SJS). 127 (12.0%) cases implicated non-drug culprit agents, of which 46 were concurrently exposed to drug agents. 16 (1.5%) cases did not report the cause of the reaction.

Table 4 shows the number of SJS/TEN cases caused by drug and non-drug culprits across the spectrum of severity. A total of 379 drugs were associated with the SJS/TEN cases, more than half of which ($n$ = 226, 59.6%) were associated with only one case. Phenytoin, trimethoprim-sulfamethoxazole, carbamazepine, lamotrigine, allopurinol, acetaminophen, amoxicillin, ibuprofen, phenobarbital, and vancomycin were the most reported drugs, each associated with over twenty SJS/TEN cases. The most frequently suspected drug class was antibiotics ($n$ = 285, 26.9%), which includes sulfonamides ($n$ = 108, 10.2%), penicillins ($n$ = 60, 5.7%), and quinolones ($n$ = 35, 3.3%) (Table 4). Antibiotics were reported as the causative agent in TEN cases (30.1%) slightly more than in SJS (22.1%) and SJS-TEN overlap (26.3%) cases primarily due to sulfonamides. Quinolones were reported to cause the fewest number of SJS cases (1.6%) relative to TEN (4.2%) and SJS-TEN overlap (5.2%) cases. Anticonvulsants, including phenytoin, carbamazepine, lamotrigine, and valproate, are also associated with a significant number of SJS/TEN cases ($n$ = 196, 18.5%) and were reported to cause a greater amount of TEN (19.4%) and SJS-TEN overlap (25.0%) cases compared to SJS cases (15.7%). Analgesics/anesthetics were also commonly reported, with a total of 126 (11.9%) cases, 93 of which were associated with non-steroidal anti-inflammatory drugs (NSAIDs). Antineoplastics were reported in 120 (11.3%) SJS/TEN cases. Detailed medications under each category as well as the number of associated SJS/TEN cases are reported in Table 5.

Of all SJS/TEN cases, the most common non-drug culprits were infections ($n$ = 68, 6.4%), which were reported more frequently to cause SJS (13.4%) compared to TEN (2.5%) and SJS-TEN overlap (2.6%) ($p$-Value $< 0.001$). Mycoplasma pneumonia infections ($n$ = 44, 4.2%) were highest in SJS cases (13.4%) compared to TEN (2.5%) and SJS-TEN overlap cases (2.6%). The second most common non-drug agent implicated in SJS/TEN was radiotherapy, which was reported in 27 SJS/TEN cases; however, many of these cases ($n$ = 25) also reported a drug as a causative agent, including anticonvulsants ($n$ = 13), antineoplastics ($n$ = 4) and chemotherapy rescue drugs ($n$ = 3). Chemical substances [e.g., arsenic (24, 25), insecticide (26, 27)] were also reported to cause SJS/TEN. Detailed non-drug culprits as well as the number of associated SJS/TEN cases are reported in Table 6.

## Publication trends of the culprit agents

Figure 4 shows the distribution of drug culprits causing SJS/TEN over time. In particular, Figure 4A shows the distribution of the drug categories, while the distribution of cases caused by specific antibiotics, anticonvulsants, NSAIDs, and antineoplastics over time can be found in Figure 4B.

# Discussion

In the present study, we retrieved a large set of SJS/TEN cases reported in the literature. We described the demographics and clinical characteristics of the cases across the spectrum of severity and identified a variety of drug and non-drug culprits as well as their frequency of being reported over the years. By examining a significant number of SJS/TEN cases from case reports, our investigation overcomes several research limitations and minimizes logistical challenges. Despite the time-consuming nature of annotating over 1,000 case reports, exhaustive manual data extraction ensured the quality of the extracted data. Because it is difficult to conduct robust evidence-based studies and clinical trials that examine the etiology for a rare condition such as SJS/TEN, our review allowed for a broad analysis of clinical cases that were rich with detail. Like current research utilizing EHR or registry data, our

TABLE 3 Demographics and clinical characteristics of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) cases from PubMed/MEDLINE.

| Characteristics | Total ($n$ = 1,059) | SJS ($n$ = 381) | SJS-TEN Overlap ($n$ = 76) | TEN ($n$ = 602) | $P$-value[a] |
|---|---|---|---|---|---|
| Age of onset[b] (y), median (IQR) | 38 (19.75—59) | **32 (15—54)** | 39 (23—58) | **41 (23—60.75)** | <0.001 |
| Gender, female[b] | 557 (52.6) | **176 (46.3)** | 43 (56.6) | **338 (56.1)** | 0.007 |
| Race[b] | | | | | 0.832 |
| White | 105 (9.9) | 34 (8.9) | 8 (10.5) | 63 (10.5) | |
| Asian | 87 (8.2) | 28 (7.3) | 8 (10.5) | 51 (8.5) | |
| Black | 54 (5.1) | 22 (5.8) | 4 (5.3) | 28 (4.7) | |
| Hispanic | 11 (1.0) | 5 (1.3) | 2 (2.6) | 4 (0.7) | |
| Others[c] | 7 (0.7) | 3 (0.8) | 0 (0.0) | 4 (0.7) | |
| Immunocompromised status | | | | | |
| Cancer | 194 (18.3) | 61 (16.0) | 11 (14.5) | 122 (20.3) | 0.163 |
| Cancer immunomodulatory therapy (PD-1, PD-L1, CTLA-4 inhibitor) | 35 (3.3) | 16 (4.2) | 2 (2.6) | 17 (2.8) | 0.473 |
| Autoimmune disease | 97 (9.2) | 28 (7.3) | 8 (10.5) | 61 (10.1) | 0.31 |
| HIV/AIDS | 52 (4.9) | 22 (5.8) | 1 (1.3) | 29 (4.8) | 0.256 |
| Pre-conditions | | | | | |
| Infections | 201 (19.0) | 83 (21.8) | 9 (11.8) | 103 (17.1) | 0.056 |
| Respiratory tract infections | 102 (9.6) | 48 (12.6) | 4 (5.3) | 50 (8.3) | 0.034 |
| Mycoplasma pneumoniae infections | 23 (2.2) | **20 (5.2)** | 1 (1.3) | **2 (0.3)** | <0.001 |
| Epilepsy/seizure disorders | 102 (9.6) | 37 (9.7) | 10 (13.2) | 55 (9.1) | 0.533 |
| Hypertension | 92 (8.7) | 29 (7.6) | 6 (7.9) | 57 (9.5) | 0.636 |
| Cardiovascular/vascular conditions | 54 (5.1) | 15 (3.9) | 7 (9.2) | 32 (5.3) | 0.149 |
| Diabetes | 54 (5.1) | 17 (4.4) | 4 (5.3) | 33 (5.5) | 0.814 |
| Musculoskeletal conditions | 52 (4.9) | 18 (4.7) | 2 (2.6) | 32 (5.3) | 0.693 |
| Endocrine/hormonal conditions | 50 (4.7) | 20 (5.2) | 3 (3.9) | 27 (4.5) | 0.849 |
| Psychological conditions | 38 (3.6) | 13 (3.4) | 4 (5.3) | 21 (3.5) | 0.656 |
| Renal conditions | 34 (3.2) | 12 (3.1) | 1 (1.3) | 21 (3.5) | 0.73 |
| Substance use | 28 (2.6) | 9 (2.4) | 2 (2.6) | 17 (2.8) | 0.954 |
| Gastrointestinal conditions | 22 (2.1) | 3 (0.8) | 1 (1.3) | 18 (3.0) | 0.053 |
| Respiratory conditions (e.g., chronic obstructive pulmonary disease) | 20 (1.9) | 10 (2.6) | 1 (1.3) | 9 (1.5) | 0.388 |
| Other[d] | 27 (2.5) | 8 (2.1) | 2 (2.6) | 17 (2.8) | — |
| Clinical characteristics during the acute phase | | | | | |
| Involvement of mucous membrane | 842 (79.5) | **333 (87.4)** | **70 (92.1)** | **439 (72.9)** | <0.001 |
| Involvement of visceral organs | 210 (19.8) | **56 (14.7)** | 18 (23.7) | 136 (22.6) | 0.007 |
| Mortality | 187 (17.6) | **24 (6.3)** | 16 (21.1) | **147 (24.4)** | <0.001 |
| Medications listed as causative agents, No. (%) | 956 (90.3) | **319 (83.7)** | 74 (97.4) | **563 (93.5)** | <0.001 |
| 1[e] | 781 (73.7) | 266 (69.8) | 63 (82.9) | 451 (74.9) | 0.36 |
| 2 | 111 (10.5) | 38 (10.0) | 9 (11.8) | 64 (10.6) | |
| 3 | 39 (3.7) | 9 (2.6) | 1 (1.3) | 29 (4.8) | |
| 4 | 16 (1.5) | 5 (1.3) | 1 (1.3) | 10 (1.7) | |
| 5 or more | 10 (0.9) | 1 (0.3) | 0 (0) | 9 (1.5) | |
| Non-drug listed as causative agents, No. (%) | 127 (12.0) | **71 (18.6)** | 6 (7.9) | **50 (8.3)** | <0.001 |
| Non-drug causative agents only | 81 (7.6) | 52 (13.6) | 2 (2.6) | 27 (4.5) | — |
| 1 | 73 (6.9) | 48 (12.6) | 2 (2.6) | 23 (3.8) | |
| 2 or more | 8 (0.8) | 4 (1.0) | 0 (0) | 4 (0.7) | |
| Combined with drug causative agents | 46 (4.3) | 19 (5.0) | 4 (5.3) | 23 (3.8) | |

IQR, interquartile range; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome.

For continuous variables, the number (percentage) in bold indicates a significant difference between the cells detected by Dunn's *post hoc* test. For categorical variables, the number (percentage) in bold indicates a significant adjusted residual for that cell (meaning that there were significantly more or fewer cases than what would be expected by chance).

[a] *P*-values were provided based on Kruskal-Wallis test for the continuous variable (age of onset) and Chi-square test for categorical variables.

[b] The number of missing cases (age of onset = 7; gender = 3; race = 795).

[c] Includes native American, Pacific Islander, mixed race.

[d] Includes skin/cutaneous ($n$ = 9), hereditary ($n$ = 8), and neurological conditions ($n$ = 10).

[e] The numbers were calculated based on the annotated medications. Due to the variation of medications, this numbers can be under-counted.

TABLE 4 Drug and non-drug allergens reported to cause SJS or TEN among reported cases from the literature.

| Allergen[a] | Total ($n$ = 1,059) | SJS ($n$ = 381) | SJS-TEN Overlap ($n$ = 76) | TEN ($n$ = 602) | $P$-value[b] |
|---|---|---|---|---|---|
| Drug Allergen | | | | | |
| *Antibiotics* | 285 (26.9) | 84 (22.1) | 20 (26.3) | 181 (30.1) | 0.022 |
| Sulfonamides | 108 (10.2) | 26 (6.8) | 5 (6.6) | 77 (12.8) | – |
| Penicillins | 60 (5.7) | 21 (5.5) | 6 (7.9) | 33 (5.5) | – |
| Quinolones | 35 (3.3) | 6 (1.6) | 4 (5.2) | 25 (4.2) | – |
| Macrolides | 25 (2.4) | 12 (3.2) | 1 (1.3) | 12 (2.0) | – |
| Vancomycin | 21 (2.0) | 2 (0.5) | 2 (2.6) | 17 (2.8) | – |
| Tetracycline | 11 (1.0) | 4 (1.1) | 1 (1.3) | 6 (1.0) | – |
| Other antibiotics[a] | 72 (6.8) | 19 (5.0) | 5 (6.6) | 48 (8.0) | – |
| Anticonvulsants | 196 (18.5) | 60 (15.7) | 19 (25.0) | 117 (19.4) | 0.111 |
| Phenytoin | 62 (5.7) | 16 (4.2) | 3 (3.9) | 43 (7.1) | – |
| Carbamazepine | 54 (5.1) | 15 (3.9) | 8 (10.5) | 31 (5.1) | – |
| Lamotrigine | 49 (4.6) | 20 (5.2) | 2 (2.6) | 27 (4.5) | – |
| Valproate | 16 (1.5) | 8 (2.1) | 2 (2.6) | 6 (1.0) | – |
| Other anticonvulsants | 32 (3.0) | 10 (2.6) | 5 (6.6) | 17 (2.8) | – |
| Analgesics/anesthetics | 126 (11.9) | 34 (8.9) | 14 (18.4) | 78 (13.0) | 0.031 |
| NSAIDs | 93 (8.8) | 24 (6.3) | 9 (11.8) | 60 (10.0) | – |
| Ibuprofen | 23 (2.2) | 6 (1.6) | 5 (6.6) | 12 (2.0) | – |
| Acetaminophen | 24 (2.3) | 5 (1.3) | 3 (3.9) | 16 (2.7) | – |
| Analgesic/antipyretics, non-salicylate | 37 (3.5) | 10 (2.6) | 6 (7.9) | 21 (3.5) | – |
| Other | 5 (0.3) | 1 (0.3) | 1 (1.3) | 3 (0.5) | – |
| Antineoplastics | 119 (11.2) | 42 (11.0) | 10 (13.2) | 67 (11.1) | 0.858 |
| Systemic enzyme inhibitors (e.g., imatinib) | 24 (2.3) | 16 (4.2) | 1 (1.3) | 7 (1.2) | – |
| Antimetabolites (e.g., methotrexate) | 19 (1.8) | 3 (0.8) | 3 (3.9) | 13 (2.2) | – |
| Alkylating agents (e.g., cyclophosphamide) | 15 (1.4) | 3 (0.8) | 1 (1.3) | 11 (1.8) | – |
| Immunotherapy checkpoint inhibitor combination (nivolumab) | 12 (1.1) | 4 (1.0) | 0 (0) | 8 (1.3) | – |
| Immunomodulator agents (e.g., lenalidomide) | 11 (1.0) | 6 (1.6) | 1 (1.3) | 4 (0.7) | – |
| Other antineoplastics | 50 (4.7) | 12 (3.1) | 4 (5.3) | 34 (5.6) | – |
| Antiarthritics | 48 (4.5) | 14 (3.7) | 6 (7.9) | 28 (4.7) | 0.265 |
| Xanthine oxidase inhibitors (allopurinol) | 45 (4.2) | 14 (3.7) | 6 (7.9) | 25 (4.2) | – |
| Antivirals | 34 (3.2) | 14 (3.7) | 3 (3.9) | 17 (2.8) | 0.71 |
| HIV-specific antivirals (e.g., nevirapine) | 25 (2.4) | 12 (3.1) | 0 (0) | 13 (2.2) | – |
| Gastrointestinal drugs (e.g., sulfasalazine) | 34 (3.2) | 8 (2.1) | 2 (2.6) | 24 (4.0) | 0.251 |
| Psychotherapeutic drugs | 25 (2.4) | 12 (3.1) | 1 (1.3) | 12 (2.0) | 0.419 |
| Antidepressant | 11 (1.0) | 6 (1.6) | 0 (0) | 5 (0.8) | – |
| Anti-Infectives | 24 (2.3) | 12 (3.1) | 0 (0) | 12 (2.0) | 0.191 |
| Antimalarial drugs | 20 (1.9) | 11 (2.9) | 0 (0) | 9 (1.5) | – |
| Antifungals | 20 (1.9) | 7 (1.8) | 0 (0) | 13 (2.2) | 0.426 |
| Cardiovascular drugs | 27 (2.5) | 8 (2.1) | 0 (0) | 19 (3.2) | 0.203 |
| Diuretics | 17 (1.6) | 7 (1.8) | 1 (1.3) | 9 (1.5) | 0.897 |
| Vitamin/herb | 15 (1.4) | 8 (2.1) | 0 (0) | 7 (1.2) | 0.267 |
| Hormones | 14 (1.3) | 5 (1.3) | 0 (0) | 9 (1.5) | 0.561 |
| Glucocorticoids | 11 (1.0) | 3 (0.8) | 0 (0) | 8 (1.3) | – |
| Biologicals/vaccine | 10 (0.9) | 6 (1.6) | 1 (1.3) | 3 (0.5) | 0.222 |
| Diagnostic (contrast medium) | 10 (0.9) | 3 (0.8) | 2 (2.6) | 5 (0.8) | 0.287 |
| Chemotherapy rescue/antidote agents | 8 (0.8) | 3 (0.8) | 0 (0) | 5 (0.8) | 0.73 |
| Antithrombotic agents | 8 (0.8) | 2 (0.5) | 0 (0) | 6 (1.0) | 0.518 |
| Cough/cold preparations | 6 (0.6) | 2 (0.5) | 0 (0) | 4 (0.7) | 0.761 |

*(Continued)*

TABLE 4 (Continued)

| Allergen[a] | Total ($n$ = 1,059) | SJS ($n$ = 381) | SJS-TEN Overlap ($n$ = 76) | TEN ($n$ = 602) | $P$-value[b] |
|---|---|---|---|---|---|
| Immunosuppressants | 6 (0.6) | 5 (1.3) | 0 (0) | 1 (0.2) | 0.052 |
| Non-drug Allergen | | | | | |
| Infection | 68 (6.4) | **51 (13.4)** | 2 (2.6) | **15 (2.5)** | <0.001 |
| Mycoplasma pneumonia infection | 44 (4.2) | 38 (10.0) | 2 (2.6) | 4 (0.7) | – |
| Radiotherapy | 27 (2.5) | 11 (2.9) | 2 (2.6) | 14 (2.3) | 0.861 |
| Chemical substance | 9 (0.8) | 5 (1.3) | 1 (1.3) | 3 (0.5) | 0.36 |
| Others | 25 (2.4) | 4 (2.6) | 1 (1.3) | 20 (3.3) | – |

NSAIDs, non-steroidal anti-inflammatory drugs; HIV, human immunodeficiency virus.
The number (percentage) in bold indicates a significant adjusted residual for that cell (meaning that there were significantly more or fewer cases than what would be expected by chance).
[a]The detailed allergen included in each category could be found in the Tables 5, 6.
[b]$P$-values were provided based on Chi-square test for categorical variables.

data characterizes common causes across many patients and highlights potential agents that have yet to be studied at large, such as herbal medications.

## Publication trends

Overall, the number of published SJS and TEN case reports increased over the past forty years, peaking in 2014. Consistent with other study populations, over half of the cases were female (8, 9, 28). Contrary to the incidence reported in other study populations in this field (1, 9, 29, 30), there were more cases concerning TEN than cases of SJS or SJS-TEN overlap. Although the incidence of TEN is three to four times less than SJS (1, 29), the larger proportion of TEN case reports likely reflects a publication bias for cases with higher clinical severity and complexity. TEN cases reported lower rates of mucous membrane involvement than SJS and SJS-TEN overlap cases, which may be due to a greater degree of skin detachment or underreporting. Also, over 20% of TEN and SJS-TEN overlap cases reported involvement of visceral organs, such as lungs, liver, and kidney, indicating the fatality of the disease and long-term sequalae. With over 600 case reports solely focused on TEN, case reports are an abundant source of information to explore TEN etiology, diagnosis, and treatment.

Publishing trends of the culprit agents reveal that medications classified as antibiotics, anticonvulsants, and analgesics/anesthetics are the dominant culprit agents throughout time. Among these categories, there are several medications that have been repeatedly cited to trigger SJS/TEN. For antibiotics, sulfonamides and penicillins are frequently reported causative agents. Since the 2000s, there has been an increasing number of cases identifying quinolones and vancomycin as the causative agents. Among anticonvulsants, phenytoin is a common causative agent throughout the study period, but from 2015 to 2020, there appears to be a decline in cases citing phenytoin relative to other anticonvulsants. Carbamazepine and lamotrigine, the next most common anticonvulsant culprit agents, have more cases that triggered SJS/TEN after the 2000s. Antineoplastic-induced cases are skewed to the more recent half of the study period with the vast majority reported after the start of the 2000s. This upward publication trend in antineoplastics parallels the notable increase in the incidence of cancer internationally as well as the growing oncology literature during the study period (31). For all sub-categories, including systemic enzyme inhibitors and antimetabolites, nearly all cases were published after 2000. NSAIDs, specifically ibuprofen, similarly mirror the trend seen in antineoplastics; however, NSAIDs have triggered fewer reported cases of SJS/TEN in general. At large, these fluctuations in publishing trends may be indicative of changes in prescribing practices, incidences of various health conditions, and reporting biases.

## Drug culprits associated with Stevens-Johnson syndrome and toxic epidermal necrolysis

An overwhelming amount of research demonstrates that drugs are the primary causal agents, accounting for nearly 90% of SJS/TEN cases (7). This is consistent with the finding of the present study. We have compiled a comprehensive list of 379 drug culprit agents reported to be associated with SJS and TEN, which is more than most published SJS/TEN studies. Other studies, including Hsu et al. (1) did not study a similarly exhaustive list of medications despite their large sample sizes. The commonly reported medications (e.g., phenytoin, trimethoprim-sulfamethoxazole, carbamazepine) correspond to the list of highly suspected drugs associated with SJS/TEN in preexisting literature (6–8, 12, 32). Among all the drug classes, antibiotics, in particular sulfonamides, were reported to cause the highest number of TEN cases, and analgesics/anesthetics accounted for a higher proportion of SJS-TEN overlap cases. The

TABLE 5 Drug category, drug type, and allergen with case count.

| Drug Category | Drug Type | Specific Allergen (Number of SJS/TEN Cases)[a] |
|---|---|---|
| Antibiotics | Sulfonamides | Trimethoprim/sulfamethoxazole (54), sulfonamides (9), cephalexin (7), ceftriaxone (5), cefotaxime (5), sulfadiazine (5), Sulfamethoxazole (3), sulfadoxine (3), ceftazidime (3), cefuroxime (2), sulfacetamide (2), cefazolin (2), sulfa drugs (1), cefepime (1), cefozopran (1), cefsulodin (1), ceftizoxime (1), cefixime (1), cephradine (1), maxipime (1), sulfa antibiotic therapy (1), sulfapyridine (1), sulfisoxazole (1), cefamandole (1), cefaclor (1), cefotiam hydrochloride (1) |
| | Penicillins | Amoxicillin (24), ampicillin (12), penicillin (8), amoxicillin/clavulanic acid (7), piperacillin/tazobactam (5), oxacillin (2), cloxacillin (2), flucloxacillin (2), amoxycillin (1), ampicillin/sulbactam (1), coamoxiclav (1) |
| | Quinolones | Ciprofloxacin (11), levofloxacin (10), moxifloxacin (4), norfloxacin (3), ofloxacin (3), lomefloxacin (1), sparfloxacin (1), tosufloxacin (1), trovafloxacin (1) |
| | Macrolides | Azithromycin (13), erythromycin (7), clarithromycin (3), roxithromycin (2) |
| | Vancomycin | Vancomycin (21) |
| | Tetracycline | Doxycycline (7), tetracycline (2), tigecycline (1), minocycline (1) |
| | Other antibiotics | Antibiotics therapy (7), trimethoprim (7), thalidomide (7), meropenem (6), teicoplanin (5), rifampin (4), gentamicin (3), amikacin (3), cephalosporin (3), nitrofurantoin (3), tobramycin (3), clindamycin (3), aztreonam (2), metronidazole (2), ethambutol (2), rifaximin (2), lincomycin (2), mupirocin (1), anti-tuberculosis medication (1), antibiotics (1), bacitracin (1), cephem (1), chloramphenicol (1), cilastatin (1), cycloserine (1), dapsone (1), ertapenem (1), furazolidone (1), imipenem (1), oral medication for an upper respiratory tract infection (1), pristinamycin (1), pyrazinamide (1), rifabutin (1), streptomycin (1), telithromycin (1) |
| Anticonvulsants | | Phenytoin (61), carbamazepine (54), lamotrigine (49), valproate (15), oxcarbazepine (7), levetiracetam (5), zonisamide (4), antiepileptic drugs (3), clobazam (3), lacosamide (1), anticonvulsant (1), cannabidiol (1), felbamate (1), gabapentin (1), anticonvulsants (1), nitrazepam (1), phenylhydantoin (1), rufinamide (1), tetrazepam (1), trazepam (1), valproic acid (1) |
| Analgesics/ anesthetics | Anagelsics/antipyretics/ non-salicylates | Acetaminophen (36), phenacetin (1), dipyrone (1) |
| | NSAIDs | Ibuprofen (23), etoricoxib (6), acetylsalicylic acid (6), diclofenac (5), non-steroidal anti-inflammatory drug (5), naproxen (5), benoxaprofen (4), mefenamic acid (4), anti, inflammatory drug (3), celecoxib (3), metamizole (3), nimesulide (3), salicylamide (2), diacerein (2), piroxicam (2), ketoprofen (2), oxaprozin (2), indomethacin (2), fenbufen (1), isoxicam (1), loxoprofen (1), Mesalazine (1), methampyrone (1), diflunisal (1), oxyphenbutazone (1), rofecoxib (1), salicylates (1), sulindac (1), valdecoxib (1), diclofenac/serratiopeptidase (1), aceclofenac (1), etofenamate (1), Etodolac (1) |
| | Other analgesics/anesthetics | Analgesics (1), codeine (1), mepivacaine (1), isopropylantipyrin/arylisopropylacetoureid/phenacetinum (1), acetaminophen/oxycodone (1) |
| Antineoplastics | Alkylating agents | Cyclophosphamide (4), temozolomide (4), chlorambucil (3), cisplatin (1), carboplatin (1), ifosfamide (1), mechlorethamine (1) |
| | Antimetabolites | Methotrexate (13), gemcitabine (2), pemetrexed (2), capecitabine (1), cytosine arabinoside (1) |
| | Immunomodulator agents | Lenalidomide (9), everolimus (1), levamisole (1) |
| | Immunotherapy checkpoint inhibitor combination | Nivolumab (12) |
| | Systemic enzyme inhibitors | Imatinib (9), osimertinib (3), afatinib (2), sunitinib (2), sorafenib (2), ribociclib (2), vandetanib (1), bortezomib (1), gefitinib (1), Masitinib (1) |
| | Other antineoplastics | Vemurafenib (8), pembrolizumab (6), mogamulizumab (6), docetaxel (3), cetuximab (3), fulvestrant (2), Ipilimumab (2), vincristine (2), premetrexed/cisplatin (2), letrozole (2), etoposide (2), ofatumumab (1), paclitaxel (1), pd1 inhibitor (1), atezolizumab (1), peplomycin (1), procarbazine (1), rituximab (1), rituximab/bendamustine (1), tamoxifen (1), actinomycin (1), vinorelbine (1), cobimetinib (1), dactinomycin (1), brentuximab vedotin (1), denileukin diftitox (1), enfortumab vedotin (1), etoposide/cisplatin (1), l-asparaginase (1), bleomycin (1) |

*(Continued)*

TABLE 5 (Continued)

| Drug Category | Drug Type | Specific Allergen (Number of SJS/TEN Cases)[a] |
|---|---|---|
| Antiarthritics | Xanthine oxidase inhibitors | Allopurinol (45) |
| | Other antiarthritics | Leflunomide (2), penicillamine (1) |
| Antivirals | HIV-specific antivirals | Nevirapine (17), abacavir (2), efavirenz (2), stavudine (2), zidovudine (2), indinavir (1), darunavir (1), emtricitabine/tenofovir (1), nelfinavir (1) |
| | Other antivirals | Lamivudine (4), acyclovir (4), oseltamivir (3), adefovir (1), 18 drugs for encephalitis (1) |
| Gastrointestinal drugs | | Sulfasalazine (10), omeprazole (5), ranitidine (5), lansoprazole (3), famotidine (2), hyoscyamine (1), cimetidine (1), dimenhydrinate (1), donnatal (1), glycerin (1), h2 antagonist (1), lactulose (1), pantoprazole (1), prochlorperazine (1), promethazine (1), rabeprazole (1), scopolamine (1) |
| Psychotherapeutic drugs | Antidepressant | Fluoxetine (2), mirtazapine (2), amoxapine (1), fluvoxamine (1), venlafaxine (1), duloxetine (1), paroxetine (1), sertraline (1), bupropion (1) |
| | Other psychotherapeutic drugs | Chlorpromazine (3), lithium (2), paliperidone (1), armodafinil (1), benzodiazepines (1), chlordiazepoxide (1), chlormezanone (1), haloperidol (1), modafinil (1), oxazepam (1), thioridazine (1) |
| Anti-infectives | Antimalarial drugs | Sulfadoxine/pyrimethamine (11), chloroquine phosphate (7), pyrimethamine (3), mefloquine (2), hydroxychloroquine (1), proguanil (1) |
| | Other anti-infectives | Atovaquone (2), ivermectin (2), pentamidine (1) |
| Antifungals | | Fluconazole (8), voriconazole (3), terbinafine (3), griseofulvin (2), caspofungin (1), amphotericin B (1), itraconazole (1), nystatin (1) |
| Cardiovascular drugs | | Captopril (3), minoxidil (3), carvedilol (2), hydralazine (2), vasoprotectors (1), rosuvastatin (1), atropine sulfate (1), irbesartan (1), nitroprusside (1), phenylephrine (1), ramipril (1), atorvastatin (1), sildenafil (1), timolol (1), vasodilators (1), amiodarone (2), amlodipine (2), nitroglycerin (1), diltiazem (1), dronedarone (1), isosorbide dinitrate (1) |
| Diuretics | | Furosemide (4), methazolamide (4), acetazolamide (2), hydrochlorothiazide (2), indapamide (2), metolazone (2), bumetanide (1), spironolactone (1) |
| Vitamin/herb | | Herbal medication (7), ayurvedic medication (3), ophiopogonis tuber (1), pyritinol (1), supradyn (1), vitamin b complex (1), traditional Chinese medicine (1), golden health blood purifying tablets (1), moringa oleifera (1) |
| Hormones | Glucocorticoids | Dexamethasone (7), prednisolone (3), betamethasone (1) |
| | Other hormones | Danazol (1), gemeprost (1), human chorionic gonadotropin (1), medroxyprogesterone acetate (1), cabergoline (1), clomiphene (1) |
| Biologicals/vaccine | | Vaccine (2), influenza vaccine (2), measles vaccine (1), anthrax (1), hantavirus vaccine (1), MPR vaccine (1), rabies vaccination (1), smallpox vaccine (1), tetanus vaccines (1), varicella-zoster virus vaccine (1), yellow fever vaccine (1) |
| Diagnostic (contrast medium) | | Contrast medium (9), diatrizoate meglumine-diatrizoate sodium (1), cardiac catheterization dye (1) |
| Chemotherapy rescue/antidote agents | | Amifostine (5), mesna (1), leucovorin (1), folinic acid (1) |
| Antithrombotic agents | Anticoagulants | Warfarin (3), warfarin potassium (1), heparin (1), dabigatran (1) |
| | Antiplatelet drugs | Acetylsalicylic acid/dipyridamole (1), clopidogrel (1), ticlopidine hydrochloride (1) |
| Cough/cold preparations | | Tipepidine (2), phenylpropanolamine (2), pseudoephedrine (2), guaifenesin (1), guaifenesin/pseudoephedrine (1) |
| Immunosuppressants | | Mizoribine (2), tacrolimus (1), azathioprine (1), tocilizumab (1), mycophenolate mofetil (1) |
| Others | | Teriflunomide (1), phenobarbital (22), strontium ranelate (3), ritodrine (3), propylthiouracil (2), adalimumab (2), tranexamic acid (2), glyburide (1), albuterol (1), alfuzosin (1), amphetamine (1), astemizole (1), bromisovalum (1), butalbital (1), carbocisteine (1), cetirizine (1), cocaine (1), contraceptive pills (1), cromoglycate (1), dimercapto-propane sulfonate (1), disulfiram (1), dorzolamide (1), etidronate (1), etretinate (1), fexofenadine (1), glipizide (1), glyphosate (1), immunoglobulin (1), iron protein succinylate (1), lactose (1), latanoprost (1), mancozeb (1), methamphetamine (1), methimazole (1), mifepristone (1), pirenzepine hydrochloride (1), promethazine methylene disalicylate (1), repaglinide (1), suramin (1), titanium silicate (1), some medications (1) |

TMP-SMZ, trimethoprim/sulfamethoxazole; NSAIDs, non-steroidal anti-inflammatory drug; MPR, morbilli-parotitis-rubella; SJS/TEN, Stevens-Johnson syndrome and/or toxic epidermal necrolysis.

[a]The case count is reflecting the number of unique cases while some of the cases could have more than one allergen annotations.

TABLE 6 Non-drug allergen category and non-drug allergen with case count.

| Non-Drug Allergen Category | Allergen Type | Specific Allergen (Number of SJS/TEN Cases)[a] |
|---|---|---|
| Infection | Mycoplasma pneumonia infection | *M. pneumoniae* (2), mycoplasma pneumonia infection (40), pneumonia infection (3), upper respiratory infection (2) |
| | Other infection | Brucella melitensis (1), cytomegalovirus infection (1), dengue virus (1), enterovirus (1), Epstein-Barr virus infection (1), herpes simplex virus (4), influenza B infection (2), mucor infection (1), parvovirus infection (1), pneumonia infection (2), psittacosis (1), respiratory infection (2), staphylococcus septicemia (1), upper respiratory infection (1), varicella-zoster virus (1), varicella infection (1), viral hepatitis type a (1), viral illness (2), yersinia enterocolitica infection (1) |
| Radiotherapy | | Brain radiotherapy (13), cranial radiotherapy (2), radiotherapy (14) |
| Chemical substance | Chemical compound | Gangliosides (1), s,s-dimethyl cyanocarbonimidodithioate (1), trichloroethylene (1), arsenic (2), Iodine (1), mercury (1), carbamate insecticide (2), organophosphate insecticide (1) |
| Others | Disease | HIV (1), Hodgkin's disease (cancer) (1), lupus (1), non-Hodgkin lymphoma (1) |
| | Others | Acrylonitrile-butadiene-styrene (1), alpha-PVP (1), anhydrous caffeine (1), black widow spider bite (1), burn (1), caffeine (1), cellulose acetate (1), cologne (1), cosmetic cream (1), interleukin-2 (1), oil lamp (1), phototoxic allergy (1), polyvinyl chloride (1), printing inks (1), spirulina (1), sun exposure (1), tanning salon (1), UV-cured inks (1), pregnancy (2), pregnancy (2), bone marrow transplantation (2), stem cell transplantation (2) |

SJS/TEN, Stevens-Johnson syndrome and/or toxic epidermal necrolysis; HIV, human immunodeficiency virus.
[a]The case count is reflecting the number of unique cases while some of the cases could have more than one allergen annotations.

remaining drug classes had no obvious differences in terms of the percentages among SJS, TEN, and SJS-TEN overlap cases.

Investigating immunosuppressive conditions and preconditions may reveal whether these conditions or related treatments amplify the risk of SJS/TEN. Risk factors, such as cancer, autoimmune disease, and infection, appear to be associated with SJS/TEN diagnosis in this study and prior research (1, 33, 34). Nearly a fifth of all cases reported having cancer prior to being diagnosed with SJS/TEN. Additionally, antineoplastics are one of the most frequently prescribed medications stated to cause SJS/TEN. Imatinib, methotrexate, lenalidomide, and nivolumab were among the most common antineoplastic agents listed as a causative drug. The increasing SJS/TEN cases among cancer patients suggests that the diseased cancer state and anticancer medication regimens may cause patients to be susceptible to severe cutaneous adverse reactions.

To a lesser extent, epilepsy and seizure disorders are a notable comorbidity, affecting nearly one in every ten cases. The high prevalence of epileptic disorders partially explains the significant number of anticonvulsants induced cases. At the same time, patients diagnosed with cancer who are treated with radiotherapy are often also treated with multiple medications, including anticonvulsants to preemptively abate seizures. While the occurrence of SJS/TEN in patients undergoing radiotherapy is rare, this condition has been frequently recognized in patients who are taking anticonvulsant drugs [i.e., phenytoin (35–46), carbamazepine (47), or antineoplastics (43, 48, 49)] while receiving cranial radiation.

In addition to cancer and epileptic disorders, approximately 5% of cases had a preexisting HIV infection, an established risk factor for SJS/TEN (1, 3, 11). Other studies noted a similar rate of 5—7% HIV cases among SJS/TEN cases, which is often higher than the controls for studies with a control group (7, 8). Data from the Nationwide Inpatient Sample from 2009 to 2012 also confirms that HIV/AIDs is one of the most common primary diagnoses for patients diagnosed with SJS/TEN (1). As Mockenhaupt et al. (8) suggest, HIV-associated cases have not significantly fluctuated over time as HIV incidence has stabilized. Still, as standard treatment has evolved, the causative agents associated with SJS/TEN have also changed. Of note, there is a preponderance of nevirapine-associated SJS/TEN cases in patients with HIV, accounting for 39% of all cases with HIV/AIDs. Additionally, nearly 12% of patients with HIV received trimethoprim-sulfamethoxazole, a common cause of adverse reactions in HIV patients (50) and one of the leading causes of SJS/TEN alone.

Beyond studying SJS/TEN through preconditions and risk factors, the compilation of case reports facilitated the identification of unique medication categories that are not often studied in relation to SJS/TEN including herbal medications and vaccines. Herbal medications/vitamins and vaccines are implicated as culprit agents in nearly 2% of cases. These drug categories are not frequently cited to cause SJS/TEN; however, in the case of herbal medications, the lack of cases may be due to underreporting in populations that are more likely to use herbal medications and not as likely to interface with allopathic medicine regularly. One study noted that 34% of

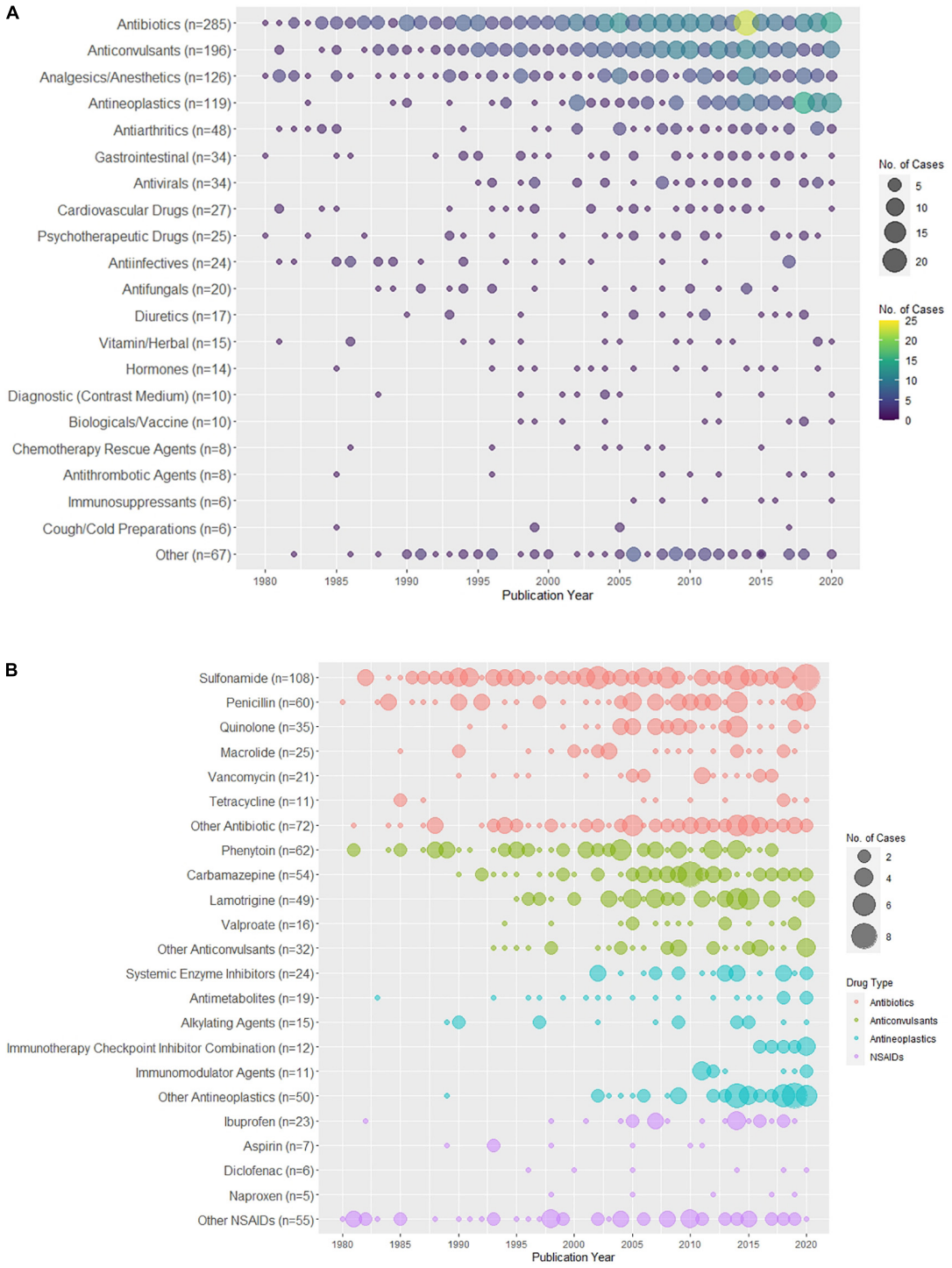


FIGURE 4
Distribution of drug culprits over the years. **(A)** Distribution of the drug categories of the culprit drugs associated with SJS/TEN over the years. **(B)** Distribution of the culprit drugs of top four common drug categories (antibiotics, anticonvulsants, antineoplastics, non-steroidal anti-inflammatory drugs [NSAIDs]) associated with SJS/TEN over the years.

people diagnosed with TEN in a burn center in Bangladesh took herbal medications and did not recall the medication name or its ingredients (51). Further analysis revealed that illiteracy and lack of financial resources influenced their use of herbal medications. The vague understanding of which herbal medications triggers SJS/TEN indicates that there are many

unknowns associated with these medications and their true risk of causing SJS/TEN.

Unlike herbal medications, significant research has been performed to guarantee the overall safety of vaccines (52), yet common vaccines have also been linked to SJS/TEN, including the vaccines for influenza (53), smallpox, anthrax and tetanus (54), measles (55), the varicella-zoster virus (56), morbilli-parotitis-rubella (57), yellow fever (58), and rabies (59). Recently, COVID-19 vaccines were also reported to cause SJS/TEN (60, 61). Despite this potential risk, standard vaccines are not highly suspected to cause these reactions considering they account for 0.9% of cases. Moreover, relative to the sheer number of vaccines distributed annually, patients with vaccine-induced SJS/TEN represent a very small percentage of all vaccine recipients (62). However, these cases are difficult to validate as some probable cases were ill prior to receiving the vaccine or concomitantly taking other medications. All the same, it cannot be ruled out that SJS/TEN is a rare but possible adverse reaction for a small percentage of vaccine recipients.

Because many medical treatments involve multiple medications, it is difficult to determine whether a specific medication alone caused SJS/TEN without controlling for concomitant therapies (63). Approximately 16.6% of all cases were exposed to more than one medication at the time of the diagnosis and in those cases, it may be difficult to understand the influence of drug interactions. A medication that demonstrates the confounding effect of multiple drug therapies is the anticonvulsant valproate. Valproate was identified to cause 1.5% of SJS/TEN cases, suggesting it is a probable culprit agent that may trigger SJS/TEN. Yet 75% of patients receiving valproate were receiving other medications, particularly other anticonvulsants. Prior research reveals that valproate extends the half-life of lamotrigine such that lamotrigine persists in the body longer (64). Thus, while valproate alone has little to no significant risk of SJS/TEN, it increases the likelihood of an adverse reaction like SJS/TEN when interacting with specific medications (8, 64). With respect to cases involving antineoplastics, it is common to prescribe other medications in addition to antineoplastics, including anticonvulsants or antibiotics, which are also strongly associated with an SJS/TEN diagnosis. Several of the cases reporting more than one causative agent are patients with cancer, suggesting that patients with cancer may be at greater risk due to receiving a combination of highly suspected culprit agents that may interact and heighten the risk of SJS/TEN (39, 42, 43, 65).

## Non-medication culprits associated with Stevens-Johnson syndrome and toxic epidermal necrolysis

Non-drug allergens are reportedly associated with SJS/TEN in 12% of cases in the present study, among which, more than half implicated infections. Three-quarters of the cases with infections as the culprit agent triggered an SJS diagnosis, indicating a strong association between SJS and infections. This link has also been confirmed in other studies (1, 66). Dissimilarly, a vast majority of TEN cases are associated with a medication culprit agent (67). Within our data, 19% of all cases had an infection as a preexisting condition, and at least 2% were confirmed mycoplasma pneumoniae infections. Likewise, infections, specifically mycoplasma pneumoniae infections, were also classified as a non-drug allergen for about 6.4% and 4.2% of all cases, respectively. This discrepancy between how many reports identified the infection as a precondition or as a causative agent indicates that the exact causal mechanism of infections remains unknown (1). It is possible that the antibiotics or other medication used to treat the infection were the true causative agents. However, there are several case reports that did not identify any potential medication that could serve as a causative agent (68–70). Additionally, some research groups have suggested that mycoplasma pneumoniae is more likely to trigger erythema multiforme (EM) and not SJS/TEN. While EM was previously regarded to fall along the same spectrum of severe cutaneous reactions, EM and severe cutaneous reactions such as SJS/TEN have separate diagnostic criteria at present (71). Ultimately, the relationship between infections and SJS/TEN requires further exploration, and understanding the shared characteristics of cases with non-drug allergens will be invaluable in identifying potential risk factors for SJS/TEN or similar severe cutaneous reactions beyond common causative medications.

## Limitations of using case reports from literature to study Stevens-Johnson syndrome and toxic epidermal necrolysis

In general, algorithms that assessed drug causality were rarely reported in the case reports. Therefore, in many cases, the actual causative agent may be a probable but not definite cause for SJS/TEN. Similarly, there is uncertainty surrounding the true causative agents in several studies using EHR or registry database data (4, 9, 72). In addition to multiple drug interactions (7, 73, 74), increased dosage of a medication may also trigger SJS/TEN (8, 75). It is also unclear how many SJS/TEN cases are truly caused by non-drug allergens, considering 7.6% of cases solely implicate non-drug allergens. Furthermore, validating diagnoses of SJS/TEN can be challenging (39), and the definition of SJS/TEN has changed over time. This might result in the inclusion of some EM cases in our analysis inadvertently due to the author's assessment, particularly with cases reported prior to 2000 when the diagnostic criteria were less defined (2, 76). Due to the retrospective nature of our study, we could not re-evaluate the case diagnosis, and only about

half of the SJS/TEN case reports indicated confirmation from pathology results.

By design, data collected from case reports are not generalizable nor can we make causal inferences from case reports, unlike other evidence-based study designs. Although our study reviewed a large number of SJS/TEN cases, there was no way to form a control group for comparison to identify differences that result from an SJS/TEN diagnosis. Also, while our data captures comprehensive patient information, our compiled data cannot be used to infer the epidemiology of SJS/TEN. With publication biases, some cases are more likely to be reported than others, impacting the generalizability of our findings.

Studies that rely on database or registry data may be more capable of overcoming certain reporting biases. For instance, Fukasawa et al. (16) used a large-scale employee claims database that includes longitudinal inpatient, outpatient, and pharmacy information for all employees receiving national coverage to approximate the true and relative risk of SJS/TEN in the Japanese population (77). However, selection bias may still be involved from excluding cases that arise from uncommon medications or causes that are not recorded in the database (9, 62). Also, not all studies take precautions to validate cases or define a control population (9). Despite lacking a control group and being subject to publication biases, significant results from our data remain consistent with data extracted from large-scale databases and registries.

Additionally, missing data due to a lack of standardized criteria that promoted complete, detailed reports made it difficult to detect associations between patient characteristics and SJS/TEN. Such variable level of detail in each case report complicated the annotation and analysis process. For instance, a majority of cases did not report race or ethnicity, inhibiting us from uncovering associations between race and incidence of SJS/TEN diagnosis for certain medications (6, 34, 78). Also, case reports used different terms to refer to the same medication. Because case reports are published according to differing journal-specific standards (79), a broader quality metric does not exist to ensure high quality data reporting. Still, nearly half of all included cases contained pathology results, and approximately 66% contained photographs as reference, indicating that reports have the potential to be very comprehensive and provide invaluable clinical insight. Establishing a quality measure can help ensure the clinical utility of case reports and may minimize publication bias.

Despite these shortcomings, case reports are a rich source of detail regarding the etiology, clinical courses, and potential treatments of SJS/TEN. The information extracted from case reports can shape clinical guidelines for providing care for prospective SJS/TEN patients and, ultimately, enhance our medical understanding these reactions.

## Conclusion

Our study assembled a large, unique set of SJS/TEN cases from the literature and provided an extensive list of potential causative agents associated with SJS/TEN. By identifying differences across the disease spectrum and trends across individual case reports, this research builds a more holistic understanding of SJS/TEN, extracting information from seminal research in the field and validating trends observed in prior studies. For future research, it is necessary to understand the distinct impact of individual medications on SJS/TEN progression and how culprit agents differ in various populations. The sheer abundance of case reports and the level of detail therein will likely support efforts to address these next steps in SJS/TEN research.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Author contributions

LW had full access to all the data in this study, took responsibility for the integrity of the data and the accuracy of the data analysis, and did the concept and design. LW, SV, FB, Y-CL, CO, and SS did the acquisition, analysis, or interpretation of data. LW and SV drafted the manuscript and performed the statistical analysis. KB, EP, and LZ obtained the funding. LW and LZ contributed to the administrative, technical, or material support. LW, KB, EP, and LZ supervised the data. All authors critically revised the manuscript for important intellectual content.

## Funding

LW, SV, FB, Y-CL, KB, EP, and LZ were partly supported by the NIH-NIAID R01AI150295.

## Acknowledgments

We thank all the people who have contributed to the annotation of the full text, including Adrian Wong, Yen Po Chin, Olivia Kern, and Diane Seger for helping with the medication classification.

## Conflict of interest

LW receives research funding from the Alzheimer's Association unrelated to this work. KB reports receiving grants from the NIH, AHRQ, and Massachusetts General Hospital (Transformative Scholars Award, COVID-19 Junior Investigator Initiative, Executive Committee on Research); Royalties from UpToDate; and personal fees from Weekley Schulte Valdes, Piedmont Liability Trust, and Vasios, Kelly, and Strollo, outside the submitted work. LZ receives research funding from the NIH and IBM Watson Health.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

## References


1. Hsu DY, Brieva J, Silverberg NB, Silverberg JI. Morbidity and mortality of Stevens-Johnson syndrome and toxic epidermal necrolysis in united states adults. *J Invest Dermatol.* (2016) 136:1387–97. doi: 10.1016/j.jid.2016.03.023

2. Bastuji-Garin S, Rzany B, Stern RS, Shear NH, Naldi L, Roujeau JC. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. *Arch Dermatol.* (1993) 129:92–6. doi: 10.1001/archderm.129.1.92

3. Lerch M, Mainetti C, Terziroli Beretta-Piccoli B, Harr T. Current perspectives on Stevens-Johnson syndrome and toxic epidermal necrolysis. *Clin Rev Allergy Immunol.* (2018) 54:147–76. doi: 10.1007/s12016-017-8654-z

4. White KD, Abe R, Ardern-Jones M, Beachkofsky T, Bouchard C, Carleton B, et al. SJS/TEN 2017: Building multidisciplinary networks to drive science and translation. *J Allergy Clin Immunol Pract.* (2018) 6:38–69. doi: 10.1016/j.jaip.2017.11.028

5. Chang WC, Abe R, Anderson P, Anderson W, Ardern-Jones MR, Beachkofsky TM, et al. SJS/TEN 2019: From science to translation. *J Dermatol Sci.* (2020) 98:2–12.

6. Hasegawa A, Abe R. Recent advances in managing and understanding Stevens-Johnson syndrome and toxic epidermal necrolysis. *F1000Res.* (2020) 9:F1000FacultyRev–612. doi: 10.12688/f1000research.24748.1

7. Roujeau JC, Kelly JP, Naldi L, Rzany B, Stern RS, Anderson T, et al. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *N Engl J Med.* (1995) 333:1600–7. doi: 10.1056/NEJM199512143332404

8. Mockenhaupt M, Viboud C, Dunant A, Naldi L, Halevy S, Bouwes Bavinck JN, et al. Stevens-Johnson syndrome and toxic epidermal necrolysis: Assessment of medication risks with emphasis on recently marketed drugs. The EuroSCAR-study. *J Invest Dermatol.* (2008) 128:35–44. doi: 10.1038/sj.jid.5701033

9. Blumenthal KG, Wickner PG, Lau JJ, Zhou L. Stevens-Johnson syndrome and toxic epidermal necrolysis: A cross-sectional analysis of patients in an integrated allergy repository of a large health care system. *J Allergy Clin Immunol Pract.* (2015) 3:277–280.e1. doi: 10.1016/j.jaip.2014.10.002

10. Davis RL, Gallagher MA, Asgari MM, Eide MJ, Margolis DJ, Macy E, et al. Identification of Stevens-Johnson syndrome and toxic epidermal necrolysis in electronic health record databases. *Pharmacoepidemiol Drug Saf.* (2015) 24:684–92. doi: 10.1002/pds.3778

11. Micheletti RG, Chiesa-Fuxench Z, Noe MH, Stephen S, Aleshin M, Agarwal A, et al. Stevens-Johnson syndrome/toxic epidermal necrolysis: A multicenter retrospective study of 377 adult patients from the united states. *J Invest Dermatol.* (2018) 138:2315–21. doi: 10.1016/j.jid.2018.04.027

12. de Bustros P, Baldea A, Sanford A, Joyce C, Adams W, Bouchard C. Review of culprit drugs associated with patients admitted to the burn unit with the diagnosis of Stevens-Johnson syndrome and toxic epidermal necrolysis syndrome. *Burns.* (2021) S0305-4179(21)00220-5. doi: 10.1016/j.burns.2021.08.009 [Epub ahead of print].

13. Ou-Yang C, Agustianty S, Wang HC. Developing a data mining approach to investigate association between physician prescription and patient outcome – a study on re-hospitalization in Stevens-Johnson syndrome. *Comput Methods Programs Biomed.* (2013) 112:84–91. doi: 10.1016/j.cmpb.2013.07.004

14. Ma DH, Tsai TY, Pan LY, Chen SY, Hsiao CH, Yeh LK, et al. Clinical aspects of Stevens-Johnson syndrome/toxic epidermal necrolysis with severe ocular complications in Taiwan. *Front Med (Lausanne).* (2021) 8:661891. doi: 10.3389/fmed.2021.661891

15. Park CS, Kang DY, Kang MG, Kim S, Ye YM, Kim SH, et al. Severe cutaneous adverse reactions to antiepileptic drugs: A nationwide registry-based study in Korea. *Allergy Asthma Immunol Res.* (2019) 11:709–22. doi: 10.4168/aair.2019.11.5.709

16. Fukasawa T, Takahashi H, Kameyama N, Fukuda R, Furuhata S, Tanemura N, et al. Development of an electronic medical record-based algorithm to identify patients with Stevens-Johnson syndrome and toxic epidermal necrolysis in Japan. *PLoS One.* (2019) 14:e0221130. doi: 10.1371/journal.pone.0221130

17. Borrelli EP, Lee EY, Descoteaux AM, Kogut SJ, Caffrey AR. Stevens-Johnson syndrome and toxic epidermal necrolysis with antiepileptic drugs: An analysis of the US Food and drug administration adverse event reporting system. *Epilepsia.* (2018) 59:2318–24. doi: 10.1111/epi.14591

18. Abe J, Mataki K, Umetsu R, Ueda N, Kato Y, Nakayama Y, et al. Stevens-Johnson syndrome and toxic epidermal necrolysis: The food and drug administration adverse event reporting system, 2004-2013. *Allergol Int.* (2015) 64:277–9. doi: 10.1016/j.alit.2015.01.002

19. Milosavljevic MN, Pejcic AV, Milosavljevic JZ. A review of published cases of Stevens-Johnson syndrome and toxic epidermal necrolysis associated with the use of acetaminophen. *Cutan Ocul Toxicol.* (2021) 40:280–92. doi: 10.1080/15569527.2021.1942896

20. Pejcic AV. Stevens-Johnson syndrome and toxic epidermal necrolysis associated with the use of macrolide antibiotics: A review of published cases. *Int J Dermatol.* (2021) 60:12–24. doi: 10.1111/ijd.15144

21. South BR, Mowery D, Suo Y, Leng J, Ferrández Ó, Meystre SM, et al. Evaluating the effects of machine pre-annotation and an interactive annotation interface on manual de-identification of clinical text. *J Biomed Inform.* (2014) 50:162–72. doi: 10.1016/j.jbi.2014.05.002

22. Sassolas B, Haddad C, Mockenhaupt M, Dunant A, Liss Y, Bork K, et al. ALDEN, an algorithm for assessment of drug causality in Stevens-Johnson syndrome and toxic epidermal necrolysis: Comparison with case-control analysis. *Clin Pharmacol Ther.* (2010) 88:60–8. doi: 10.1038/clpt.2009.252

23. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ.* (2021) 372:n71. doi: 10.1136/bmj.n71

24. Vassileva S, Berova N, Dourmishev A. Stevens-Johnson syndrome caused by arsenic. *Int J Dermatol.* (1990) 29:381–2. doi: 10.1111/j.1365-4362.1990.tb04771.x

25. Wu ML, Deng JF. Toxic epidermal necrolysis after extensive dermal use of realgar-containing (arsenic sulfide) herbal ointment. *Clin Toxicol (Phila).* (2013) 51:801–3. doi: 10.3109/15563650.2013.831100

26. Roca B, Tomás G, Climent A. Stevens-Johnson syndrome after exposure to a pesticide in a patient with AIDS. *Ir Med J.* (1999) 92:374.

27. Lim JH, Kim HS, Kim HO, Park YM. Stevens-Johnson syndrome following occupational exposure to carbamate insecticide. *J Dermatol.* (2010) 37:182–4. doi: 10.1111/j.1346-8138.2009.00784.x

28. Zhang AJ, Nygaard RM, Endorf FW, Hylwa SA. Stevens-Johnson syndrome and toxic epidermal necrolysis: Retrospective review of 10-year experience. *Int J Dermatol.* (2019) 58:1069–77. doi: 10.1111/ijd.14409

29. Yang MS, Lee JY, Kim J, Kim GW, Kim BK, Kim JY, et al. Incidence of Stevens-Johnson syndrome and toxic epidermal necrolysis: A nationwide population-based study using national health insurance database in Korea. *PLoS One.* (2016) 11:e0165933. doi: 10.1371/journal.pone.0165933

30. Diphoorn J, Cazzaniga S, Gamba C, Schroeder J, Citterio A, Rivolta AL, et al. Incidence, causative factors and mortality rates of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) in northern Italy: Data from the REACT registry. *Pharmacoepidemiol Drug Saf.* (2016) 25:196–203. doi: 10.1002/pds.3937

31. Global Burden of Disease Cancer Collaboration, Fitzmaurice C, Akinyemiju TF, Al Lami FH, Alam T, Alizadeh-Navaei R, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 1990 to 2016: A systematic analysis for the global burden of disease Study. *JAMA Oncol.* (2018) 4:1553–68. doi: 10.1200/JCO.2018.36.15_suppl.1568

32. Kongpan T, Mahasirimongkol S, Konyoung P, Kanjanawart S, Chumworathayi P, Wichukchinda N, et al. Candidate HLA genes for prediction of co-trimoxazole-induced severe cutaneous reactions. *Pharmacogenet Genomics.* (2015) 25:402–11. doi: 10.1097/FPC.0000000000000153

33. Charlton OA, Harris V, Phan K, Mewton E, Jackson C, Cooper A. Toxic epidermal necrolysis and Steven-Johnson syndrome: A comprehensive review. *Adv Wound Care (New Rochelle).* (2020) 9:426–39. doi: 10.1089/wound.2019.0977

34. Harr T, French LE. Toxic epidermal necrolysis and Stevens-Johnson syndrome. *Orphanet J Rare Dis.* (2010) 5:39. doi: 10.1186/1750-1172-5-39

35. Delattre JY, Safai B, Posner JB. Erythema multiforme and Stevens-Johnson syndrome in patients receiving cranial irradiation and phenytoin. *Neurology.* (1988) 38:194–8. doi: 10.1212/WNL.38.2.194

36. Rowe JE, Pina J, Sau P, Samlaska C, James W. Toxic epidermal necrolysis associated with diphenylhydantoin and cranial irradiation. *Int J Dermatol.* (1991) 30:747–9. doi: 10.1111/j.1365-4362.1991.tb02629.x

37. Cockey GH, Amann ST, Reents SB, Lynch JW Jr. Stevens-Johnson syndrome resulting from whole-brain radiation and phenytoin. *Am J Clin Oncol.* (1996) 19:32–4. doi: 10.1097/00000421-199602000-00007

38. Frangogiannis NG, Boridy I, Mazhar M, Mathews R, Gangopadhyay S, Cate T. Cyclophosphamide in the treatment of toxic epidermal necrolysis. *South Med J.* (1996) 89:1001–3. doi: 10.1097/00007611-199610000-00015

39. Micali G, Linthicum K, Han N, West DP. Increased risk of erythema multiforme major with combination anticonvulsant and radiation therapies. *Pharmacotherapy.* (1999) 19:223–7. doi: 10.1592/phco.19.3.223.30917

40. Eralp Y, Aydiner A, Taş F, Saip P, Topuz E. Stevens-Johnson syndrome in a patient receiving anticonvulsant therapy during cranial irradiation. *Am J Clin Oncol.* (2001) 24:347–50. doi: 10.1097/00000421-200108000-00005

41. Aguiar D, Pazo R, Durán I, Terrasa J, Arrivi A, Manzano H, et al. Toxic epidermal necrolysis in patients receiving anticonvulsants and cranial irradiation: A risk to consider. *J Neurooncol.* (2004) 66:345–50. doi: 10.1023/B:NEON.0000014538.31561.bc

42. Oner Dincbas F, Yörük S, Demirkesen C, Uzel O, Koca S. Toxic epidermal necrolysis after cranial radiotherapy and phenytoin treatment. *Onkologie.* (2004) 27:389–92. doi: 10.1159/000079094

43. Levitt MR, Benedict WJ, Barton K, Melian E, Gamelli RL, Vandevender D, et al. Management of scalp toxic epidermal necrolysis and cranial osteomyelitis with serratus anterior myocutaneous pedicle flap: A case report. *J Burn Care Res.* (2007) 28:524–9. doi: 10.1097/BCR.0B013E318053DA97

44. Goyal S, Biswas A, Puri T, Mohanti BK. Stevens-Johnson syndrome following concurrent phenytoin and holocranial radiotherapy. *Acta Oncol.* (2010) 49:259–60. doi: 10.3109/02841860903246581

45. Fidan E, Fidan M, Ozdemir F, Kavgaci H, Aydin F. Phenytoin- and cranial radiotherapy-induced toxic epidermal necrolysis treated with combination therapy: Systemic steroid and intravenous immunoglobulin. *Med Oncol.* (2012) 29:686–9. doi: 10.1007/s12032-011-9864-5

46. Keklik F, Özkan MC, Yenipazar GK, Yaman B, Saydam G, Şahin F. Toxic epidermal necrolysis associated with radiotherapy and phenytoin in a patient with non-Hodking's lymphoma: A case report. *Rep Pract Oncol Radiother.* (2016) 21:81–3. doi: 10.1016/j.rpor.2015.09.002

47. Hoang-Xuan K, Delattre JY, Poisson M. Stevens-Johnson syndrome in a patient receiving cranial irradiation and carbamazepine. *Neurology.* (1990) 40:1144–5. doi: 10.1212/WNL.40.7.1144

48. Sarma N. Stevens-Johnson syndrome and toxic epidermal necrolysis overlap due to oral temozolomide and cranial radiotherapy. *Am J Clin Dermatol.* (2009) 10:264–7. doi: 10.2165/00128071-200910040-00007

49. Sommers KR, Kong KM, Bui DT, Fruehauf JP, Holcombe RF. Stevens-Johnson syndrome/toxic epidermal necrolysis in a patient receiving concurrent radiation and gemcitabine. *Anticancer Drugs.* (2003) 14:659–62. doi: 10.1097/00001813-200309000-00012

50. Meyer C, Behm N, Brown E, Copeland NK, Sklar MJ. An adverse drug reaction to trimethoprim-sulfamethoxazole revealing primary HIV: A case report and literature review. *Case Rep Infect Dis.* (2015) 2015:691010. doi: 10.1155/2015/691010

51. Kumar Das K, Khondokar S, Rahman A, Chakraborty A. Unidentified drugs in traditional medications causing toxic epidermal necrolysis: A developing country experience. *Int J Dermatol.* (2014) 53:510–5. doi: 10.1111/ijd.12253

52. Dudley MZ, Halsey NA, Omer SB, Orenstein WA, O'Leary ST, Limaye RJ, et al. The state of vaccine safety science: Systematic reviews of the evidence. *Lancet Infect Dis.* (2020) 20:e80–9. doi: 10.1016/S1473-3099(20)30130-4

53. Oda T, Sawada Y, Okada E, Yamaguchi T, Ohmori S, Haruyama S, et al. Stevens-Johnson syndrome after influenza vaccine injection. *J Investig Allergol Clin Immunol.* (2017) 27:274–5. doi: 10.18176/jiaci.0169

54. Chopra A, Drage LA, Hanson EM, Touchet NL. Stevens-Johnson syndrome after immunization with smallpox, anthrax, and tetanus vaccines. *Mayo Clin Proc.* (2004) 79:1193–6. doi: 10.1016/S0025-6196(11)62605-0

55. Hazir T, Saleem M, Abbas KA. Stevens-Johnson syndrome following measles vaccination. *J Pak Med Assoc.* (1997) 47:264–5.

56. Christou EM, Wargon O. Stevens-Johnson syndrome after varicella vaccination. *Med J Aust.* (2012) 196:240–1. doi: 10.5694/mja11.11484

57. Dobrosavljevic D, Milinkovic MV, Nikolic MM. Toxic epidermal necrolysis following morbilli-parotitis-rubella vaccination. *J Eur Acad Dermatol Venereol.* (1999) 13:59–61. doi: 10.1111/j.1468-3083.1999.tb00846.x

58. Flora TB, Alves CAXM, Barucci FMP, Mattos CB. Toxic epidermal necrolysis after yellow fever vaccination. *An Bras Dermatol.* (2018) 93:942–3. doi: 10.1590/abd1806-4841.20188237

59. Ma L, Du X, Dong Y, Peng L, Han X, Lyu J, et al. First case of Stevens-Johnson syndrome after rabies vaccination. *Br J Clin Pharmacol.* (2018) 84:803–5. doi: 10.1111/bcp.13512

60. Elboraey MO, Essa E. Stevens-Johnson syndrome post second dose of Pfizer COVID-19 vaccine: A case report. *Oral Surg Oral Med Oral Pathol Oral Radiol.* (2021) 132:e139–42. doi: 10.1016/j.oooo.2021.06.019

61. Bakir M, Almeshal H, Alturki R, Obaid S, Almazroo A. Toxic epidermal necrolysis post COVID-19 vaccination – first reported case. *Cureus.* (2021) 13:e17215. doi: 10.7759/cureus.17215

62. Ball R, Ball LK, Wise RP, Braun MM, Beeler JA, Salive ME. Stevens-Johnson syndrome and toxic epidermal necrolysis after vaccination: Reports to the vaccine adverse event reporting system. *Pediatr Infect Dis J.* (2001) 20:219–23. doi: 10.1097/00006454-200102000-00022

63. Rosen AC, Balagula Y, Raisch DW, Garg V, Nardone B, Larsen N, et al. Life-threatening dermatologic adverse events in oncology. *Anticancer Drugs.* (2014) 25:225–34. doi: 10.1097/CAD.0000000000000032

64. Nanau RM, Neuman MG. Adverse drug reactions induced by valproic acid. *Clin Biochem.* (2013) 46:1323–38. doi: 10.1016/j.clinbiochem.2013.06.012

65. Hafiji J, Orpin S, Roberts C, Heagerty A, Lewis H. Radiotherapy: A protective role for toxic epidermal necrolysis? *Br J Dermatol.* (2010) 162:1139–41. doi: 10.1111/j.1365-2133.2010.09651.x

66. Dodiuk-Gad RP, Chung WH, Valeyrie-Allanore L, Shear NH. Stevens-Johnson syndrome and toxic epidermal necrolysis: An update. *Am J Clin Dermatol.* (2015) 16:475–93. doi: 10.1007/s40257-015-0158-0

67. Knowles S, Shear NH. Clinical risk management of Stevens-Johnson syndrome/toxic epidermal necrolysis spectrum. *Dermatol Ther.* (2009) 22:441–51. doi: 10.1111/j.1529-8019.2009.01260.x

68. Alshafi KM, Ironton R. Unusual presentation of mycoplasma pneumoniae infection. *Lancet.* (1991) 338:1519–20. doi: 10.1016/0140-6736(91)92331-U

69. Amin R, Smit E, Shaikh G, Rawling P, Alexander E. Mycoplasma respiratory tract infection complicated by Stevens-Johnson syndrome and surgical emphysema. *Acta Paediatr.* (2007) 96:472. doi: 10.1111/j.1651-2227.2007.00088.x

70. Vanfleteren I, Van Gysel D, De Brandt C. Stevens-Johnson syndrome: A diagnostic challenge in the absence of skin lesions. *Pediatr Dermatol.* (2003) 20:52–6. doi: 10.1046/j.1525-1470.2003.03012.x

71. Frantz R, Huang S, Are A, Motaparthi K. Stevens-Johnson syndrome and toxic epidermal necrolysis: A review of diagnosis and management. *Medicina (Kaunas).* (2021) 57:895. doi: 10.3390/medicina57090895

72. Strom BL, Carson JL, Halpern AC, Schinnar R, Snyder ES, Stolley PD, et al. Using a claims database to investigate drug-induced Stevens-Johnson syndrome. *Stat Med.* (1991) 10:565–76. doi: 10.1002/sim.4780100408

73. Bellón T, Lerma V, González-Valle O, González Herrada C, de Abajo FJ. Vemurafenib-induced toxic epidermal necrolysis: Possible cross-reactivity with other sulfonamide compounds. *Br J Dermatol.* (2016) 174:621–4. doi: 10.1111/bjd.14201

74. Wadelius M, Karlsson T, Wadelius C, Rane A. Lamotrigine and toxic epidermal necrolysis. *Lancet.* (1996) 348:1041. doi: 10.1016/S0140-6736(05)64979-3

75. Barreiro P, Soriano V, Casas E, Estrada V, Téllez MJ, Hoetelmans R, et al. Prevention of nevirapine-associated exanthema using slow dose escalation and/or corticosteroids. *AIDS.* (2000) 14:2153–7. doi: 10.1097/00002030-200009290-00012

76. Roujeau JC. The spectrum of Stevens-Johnson syndrome and toxic epidermal necrolysis: A clinical classification. *J Invest Dermatol.* (1994) 102:28S–30S. doi: 10.1111/1523-1747.ep12388434

77. Fukasawa T, Takahashi H, Takahashi K, Tanemura N, Amagai M, Urushihara H. Risk of Stevens-Johnson syndrome and toxic epidermal necrolysis associated with anticonvulsants in a Japanese population: Matched case-control and cohort studies. *Allergol Int.* (2021) 70:335–42. doi: 10.1016/j.alit.2021.01.004

78. Chen P, Lin JJ, Lu CS, Ong CT, Hsieh PF, Yang CC, et al. Carbamazepine-induced toxic effects and HLA-B*1502 screening in Taiwan. *N Engl J Med.* (2011) 364:1126–33. doi: 10.1056/NEJMoa1009717

79. Calvache JA, Vera-Montoya M, Ordoñez D, Hernandez AV, Altman D, Moher D. Completeness of reporting of case reports in high-impact medical journals. *Eur J Clin Invest.* (2020) 50:e13215. doi: 10.1111/eci.13215

frontiers | Frontiers in Medicine

TYPE Perspective
PUBLISHED 12 September 2022
DOI 10.3389/fmed.2022.901401



OPEN ACCESS

EDITED BY
Hajirah Saeed,
Massachusetts Eye and Ear Infirmary and Harvard Medical School, United States

REVIEWED BY
Priscila Giavedoni,
Hospital Clinic of Barcelona, Spain

*CORRESPONDENCE
Rannakoe J. Lehloenya
rannakoe.lehloenya@uct.ac.za

SPECIALTY SECTION
This article was submitted to Dermatology, a section of the journal Frontiers in Medicine

RECEIVED 21 March 2022
ACCEPTED 18 July 2022
PUBLISHED 12 September 2022

CITATION
Lehloenya RJ (2022) Disease severity and status in Stevens–Johnson syndrome and toxic epidermal necrolysis: Key knowledge gaps and research needs.
*Front. Med.* 9:901401.
doi: 10.3389/fmed.2022.901401



# Disease severity and status in Stevens–Johnson syndrome and toxic epidermal necrolysis: Key knowledge gaps and research needs

Rannakoe J. Lehloenya [1,2]*

[1]Division of Dermatology, Department of Medicine, University of Cape Town, Cape Town, South Africa, [2]Combined Drug Allergy Clinic, Groote Schuur Hospital, Cape Town, South Africa

Stevens–Johnson syndrome and toxic epidermal necrolysis (SJS/TEN) are on a spectrum of cutaneous drug reactions characterized by pan-epidermal necrosis with SJS affecting < 10% of body surface area (BSA), TEN > 30%, and SJS/TEN overlap between 10 and 30%. Severity-of-illness score for toxic epidermal necrolysis (SCORTEN) is a validated tool to predict mortality rates based on age, heart rate, BSA, malignancy and serum urea, bicarbonate, and glucose. Despite improved understanding, SJS/TEN mortality remains constant and therapeutic interventions are not universally accepted for a number of reasons, including rarity of SJS/TEN; inconsistent definition of cases, disease severity, and endpoints in studies; low efficacy of interventions; and variations in treatment protocols. Apart from mortality, none of the other endpoints used to evaluate interventions, including duration of hospitalization, is sufficiently standardized to be reproducible across cases and treatment centers. Some of the gaps in SJS/TEN research can be narrowed through international collaboration to harmonize research endpoints. A case is made for an urgent international collaborative effort to develop consensus on definitions of endpoints such as disease status, progression, cessation, and complete re-epithelialization in interventional studies. The deficiencies of using BSA as the sole determinant of SJS/TEN severity, excluding internal organ involvement and extension of skin necrosis beyond the epidermis, are discussed and the role these factors play on time to healing and mortality beyond the acute stage is highlighted. The potential role of artificial intelligence, biomarkers, and PET/CT scan with radiolabeled glucose as markers of disease status, activity, and therapeutic response is also discussed.

KEYWORDS

**Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (SJS/TEN), severity, internal organ involvement, depth, knowledge gaps**

## Background

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), collectively referred to as epidermal necrolysis (SJS/TEN), are on a spectrum of the same life-threatening drug reaction. The primary feature of SJS/TEN is pan-epidermal necrosis of the skin and mucous membranes. In SJS, there is < 10% of body surface area (BSA) with epidermal detachment while in TEN there is > 30%. SJS/TEN overlap lies between these two extremes (1). TEN is considered the more severe phenotype and is associated with significantly higher mortality of up to 40% (2). The severity-of-illness score for toxic epidermal necrolysis (SCORTEN) is currently the most widely used validated tool to predict mortality rates, although its accuracy has been questioned in certain settings and alternative scores developed (3, 4). SCORTEN predictors of higher mortality in acute settings are age > 40 years, heart rate > 120 bpm, BSA > 10%, serum urea > 10 mmol/L, serum bicarbonate < 20 mmol/L, serum glucose > 14 mmol/L, and cancer or hematological malignancies (3).

Despite improved understanding of SJS/TEN in the last 30 years, mortality has remained constant despite global efforts to find effective pharmacotherapeutic interventions (5, 6). These efforts have been hampered, among others, by rarity of SJS/TEN; inconsistent gold-standard definition of cases; inconsistent and inadequate definition of disease severity; inconsistent and inadequate definition of endpoints and clinical outcomes in studies; low clinical effectiveness of current interventions, making it difficult to conduct sufficiently powered studies; and variations in treatment protocols (5–7). A survey of North American clinicians managing SJS/TEN concluded that the length of time before cessation of disease progression and the length of time to complete re-epithelialization are some of the minimum required variables for researchers and clinicians to effectively evaluate SJS/TEN treatment efficacy in a clinically meaningful way. These, as well as mortality and duration of hospitalization, are the endpoints currently used to evaluate pharmacotherapeutic efficacy and other interventions (8). Apart from mortality, none of the others has been standardized sufficiently to be used with reproducible accuracy across individual cases and treatment centers (7).

A systematic review published in March 2022 that included only highest quality studies, namely, randomized-controlled trials and prospective observational comparative studies, found no evidence to support superiority of the following interventions when compared head to head: corticosteroids vs. no corticosteroids; intravenous immunoglobulins (IVIGs) vs. no IVIGs; and cyclosporine vs. IVIGs. However, the study reported a possible reduction in mortality with the use of the TNF-alpha inhibitor etanercept compared to corticosteroids.

The authors assessed three of the four studies included in the comparisons to have very low-certainty evidence and one to have low-certainty evidence. Time to complete re-epithelialization, length of hospital stay, and adverse effects leading to discontinuation of therapy were not reported in the majority of studies. There were no studies that compared etanercept vs. cyclosporine, etanercept vs. IVIG, IVIG vs. supportive care, IVIG vs. cyclosporine, and cyclosporine vs. corticosteroids (7). Another systematic review with a meta-analysis and meta-regression of observational studies also published in March 2022 concluded that the use of etanercept resulted in the lowest mortality rate and the highest IVIG compared to supportive care and other systemic therapies used in SJS/TEN. Corticosteroids were associated the shortest time for re-epithelialization and the shortest length of hospital stay. The authors highlight that the severity of disease seems to influence the choice of therapy by the treating physicians (9). A systematic review and meta-analysis published a few months before these two concluded that systemic glucocorticoids showed a survival benefit for patients with SJS/TEN in all analyses compared with other forms of treatment (10). A common problem highlighted in all these reviews is the heterogeneity of the studies and low confidence in their reproducibility. All conclude that better-designed prospective studies are needed. Despite these challenges, there is more emerging evidence to suggest that combination therapy of etanercept and corticosteroids or etanercept as monotherapy reduces mortality, skin healing time, and hospital stay compared to IVIG combined with corticosteroids or corticosteroid monotherapy (11–13).

The relative rarity of SJS/TEN, and to a lesser extent, the efficacy of current interventions are the two factors that are beyond the immediate control of researchers in the field. Case definition has improved over the years, allowing differentiation from other blistering disorders like erythema multiforme and bullous-fixed drug eruptions (1, 5, 14). The other variables that are inconsistently evaluated and reported in interventional studies for SJS/TEN are amenable to harmonization by a well-directed, focused, and collaborative global effort. Global collaboration, sharing of ideas, and directing research efforts on SJS/TEN are already underway. These international collaborations are an ideal platform to address these issues (15, 16). In this article, research gaps and unmet needs in SJS/TEN research that impact uniformity and consistency in studies that assess therapeutic interventions are highlighted. Also in focus are gaps relating to disease severity, disease status, disease progression or cessation of progression during the acute stage, and definition of disease resolution. Potential future research directions are suggested to address some of these gaps.

# Research gaps

## Body surface area as the sole determinant of severity

Body surface area has an important, validated, and clinically obvious association with in-hospital and early mortality (17, 18).

However, there is considerable evidence showing that BSA impacts mortality only in the first 90 days of SJS/TEN, and that increased mortality is recorded among survivors for up to a year after the acute episode (19). This suggests that factors other than the BSA influence the severity and natural history of SJS/TEN.

## Extension of skin necrosis beyond the epidermis as an additional marker of severity

The extension of tissue damage beyond the epidermis by the pathogenic factors involved in SJS/TEN, even in the absence of complications like skin infection, although largely unappreciated currently, seems to impact the time to complete re-epithelialization regardless of treatment approaches taken. Over the years, in our unit we have encountered "definite" cases of TEN based on the RegiSCAR SJS/TEN validation tool that we informally referred to as "superficial TEN." Although the BSA and mucosal involvement in these cases were extensive, the epidermal necrosis of the skin seemed to be more superficial and tended to be associated with a better prognosis than those whose necrosis was more typical with the necrosis extending comparatively deeper into the skin. The most obvious clinical difference between the two is the propensity to bleed in the latter group if denuded skin is $> 5$ cm$^2$. This suggests a differential extension of the primary pathology into the dermis. **Figure 1** illustrates two "definite" cases of SJS/TEN with comparable BSA involvement at the peak of their disease but different depths of disease extension.

To further support the hypothesis that sometimes the primary pathology in SJS/TEN extends well beyond the epidermis and affects at least progenitor and stem cell populations in affected tissues, two cases of SJS/TEN exclusively managed with supportive care in our unit are highlighted. The first, a previously published case, was a 36-year-old HIV-infected woman of African descent with a CD4+ count of 510 cells/mm$^3$ and on zidovudine, lamivudine, and efavirenz for 3 years who desired to conceive. Efavirenz was substituted with nevirapine in her antiretroviral regimen. A week later, she developed a "definite" case of TEN that peaked at 70% BSA. She also developed persistent bilateral corneal perforations despite amniotic membrane transplant. All drugs had been stopped within 48 h of the first symptoms. During her 158-day hospitalization, her skin failed to re-epithelialize despite numerous attempts to skin graft-denuded areas as well as culture and transplant her keratinocytes *in vitro* to promote healing. All the donor sites also failed to heal. Multiple skin biopsies showed lack of epithelial markers. She died of disseminated tuberculosis and septic shock (20).

The second case is a 40-year-old woman of African descent with epilepsy since the age of 12 who presented to us with a "definite" case of TEN, peaking at 40% BSA and uncharacteristically affecting the scalp. She was 24 weeks pregnant with twins. She had started lamotrigine 17 days earlier, having previously been on phenytoin and sodium valproate uneventfully. All drugs were stopped within 24 h of the first symptoms. Her course in hospital was complicated by a miscarriage of both twins 2 days post admission, keratitis, failure to re-epithelialize, and recurrent systemic bacterial infections well into the evolution of her disease. She eventually had extensive full-thickness skin grafting 122 days after the disease onset. This has been complicated by extensive keloid formation in the grafted areas, although she had no history of hypertrophic scarring or keloid formation (21).

In both cases, time to re-epithelialization and duration of hospitalization were considerably longer than averages in large studies with similar BSA (8, 22–25). A delay in the withdrawal of the offending drug, drugs with longer half-lives, preexisting comorbidities, and ethnic background have been suggested associations with prolonged progression and delayed healing in SJS/TEN, the latter a potential proxy for SJS/TEN severity (26–28). As illustrated by these two cases and others in the literature, delayed healing can be associated with different drugs, can occur in any Fitzpatrick skin type, and does not require delayed cessation of the offending drug or HIV infection (26, 29). It is not clear whether scalp involvement, hypertrophic scarring, and/or keloid formation are markers of deeper extension of the primary pathology beyond the epidermis in SJS/TEN.

## Internal organ involvement as an additional marker of Stevens–Johnson syndrome and toxic epidermal necrolysis severity

Bacterial systemic infection (BSI) and septic shock have been shown to be the major causes of intensive care unit admission and death in SJS/TEN (18, 30). In a retrospective Taiwanese study of 150 patients with SJS/TEN, 21% developed disseminated intravascular coagulation (DIC), a marker for BSI. TEN, compared with SJS and SJS/TEN overlap, was significantly associated with the development of DIC, elevated procalcitonin levels, and a 7-fold increase in mortality (31, 32). The organisms isolated from the bloodstream in BSI seem to originate from both the skin and the gut (33–35). In a study of 18 SJS/TEN cases managed in a burns center, there were 11 deaths, six of whom had a postmortem

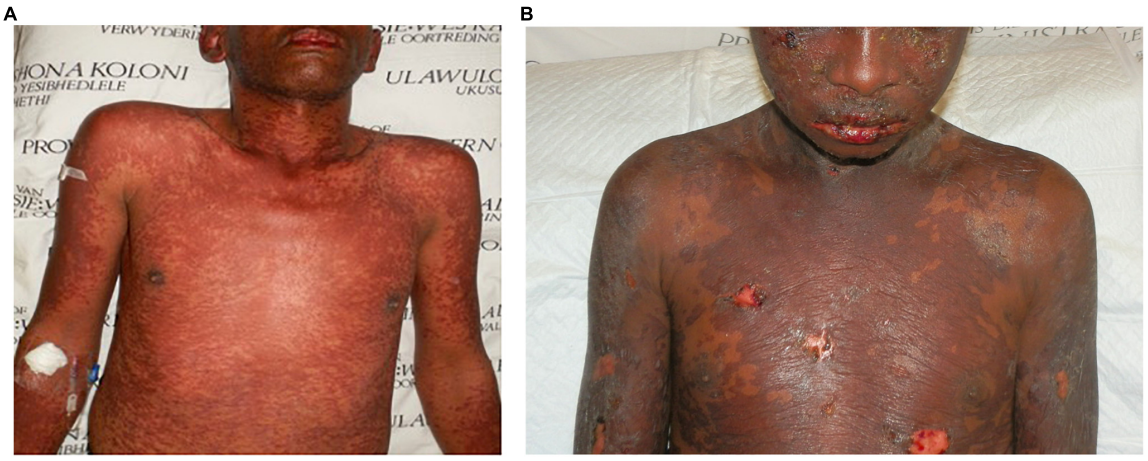


FIGURE 1
Toxic epidermal necrolysis affecting 40% body surface area in two patients: **(A)** a more superficial variant without denudation of the skin and **(B)** a variant with positive Nikolsky sign and denudation of the skin as well as frank bleeding.

examination. Four of these showed acute ulceration of the esophagus, terminal ileum, and colon ranging from complete denudation to focal ulcerations, becoming a potential source of microbial seeding into the bloodstream. The authors acknowledged that systemic corticosteroids administered to the patients could have caused the ulcers among other possible etiologies (35). These studies support the hypothesis that there may be bacterial dislocation from the gut to the bloodstream in SJS/TEN. The gastrointestinal system (GIT) involvement is further supported by reports of SJS/TEN affecting the esophagus, stomach, small intestines, colon, and the rectum. Apart from visualization on postmortem and scopes, reports of gut perforation, intussusception, bleeding, diarrhea, protein-losing enteropathy, hepatitis strictures, and stenosis following SJS/TEN further support GIT involvement in the disease (35–58).

Multitudes of other studies, case series, and case reports strongly support the involvement of other internal organs in SJS/TEN. Involvement of the respiratory system (RS) can manifest in both the acute or chronic settings. A prospective study of 41 consecutive cases of SJS/TEN found "specific" involvement of the bronchial epithelium in 27% of cases. The authors suggested that this was associated with a worse prognosis (59). Mechanical ventilation was necessary for a quarter of 221 patients with SJS/TEN seen at a French national referral center (60). A retrospective study of 32 SJS/TEN cases found 50% to have abnormal lung function tests during routine follow-up (61). In the published literature, RS involvement following SJS/TEN has been characterized by chronic lung disease, bronchiolitis obliterans, interstitial lung disease, pulmonary air leak syndrome, laryngeal obstruction, and obliterative bronchitis, among others (57, 61–76). The genitourinary system is also not spared in SJS/TEN. Approximately 30% of SJS/TEN cases have been reported to have some form of acute kidney injury, some severe enough to warrant hemodialysis (41, 64, 75, 77–79). Perforation of the uterus, vaginal and introital adenosis, cervical/vaginal adhesions and stenosis, labial synechiae, hydrocolpos, hematometra, hematometrocolpos, and endometriosis are the other reported sequelae of SJS/TEN (64, 75, 80–90). In recent years, the chronic sequelae of SJS/TEN have been recognized and described more systematically. Apart from those just described, other chronic sequelae include eye disease, depression, anxiety, post-traumatic stress disorder, nail abnormalities, pigmentary disorders, scarring, hair loss, pruritus, chronic pain, autoimmune diseases, chronic fatigue, and dental abnormalities (15, 16, 61, 63, 64, 91–93). Perhaps one of the most worrisome recent findings is the higher-than-expected mortality rate among SJS/TEN survivors up to a year after the reaction. A study of 460 patients with SJS/TEN by the RegiSCAR study group found an overall mortality of 23 and 34% 6 weeks and 1 year after the reaction, respectively. BSA was a risk factor for mortality only in the first 90 days, whereas serious comorbidities and age influenced mortality beyond 90 days and up to 1 year after onset of reaction. Even when controlling for comorbid conditions and age, SJS/TEN survivors still have excess mortality compared to the general population (19).

The existing literature suggests that SJS/TEN is a systemic disease with internal organ involvement that can influence not only outcomes but evolution of the disease. The inclusion of acute parameters like heart rate, serum urea, bicarbonate, and glucose in SCORTEN, which were normal in the premorbid state and return to normal in a proportion of survivors, further supports systemic nature and internal organ involvement in SJS/TEN. Internal organ involvement has been shown by numerous studies to impact mortality and morbidity. However,

the frequency and severity of individual organ involvement and their impact on overall morbidity and mortality are not clear. Although there have been attempts to develop severity grading systems for systemic involvement in SJS/TEN, with varying degrees of focus on cutaneous and internal organ involvement, these are yet to be validated (25, 94–96).

### Inadequate definition of disease status, progression, cessation, and complete re-epithelialization

Disease progression describes the natural history of a disease, such as pain, or levels of a biomarker such as blood pressure or enzyme levels. There are two main measures of response to a therapeutic intervention in any disease, both dependent on the time course of the disease. The most common is a symptomatic effect equivalent to a shift up or down of the natural history curve. Less common but quite clinically important is a disease-modifying effect equivalent to a change in the rate of disease progression. Both measures can be established using clinical outcomes such as symptoms, or biomarkers such as clinical signs and/or other quantifiable indicators of disease status. To adequately determine disease progression, disease status must be clearly determined at baseline (97). Survival and hospital stay are other examples of measurable outcomes.

In interventional studies designed to halt disease progress, it is necessary to have predetermined biomarkers that correlate with the different stages of the disease as it evolves through the natural history. The same biomarkers can then be used to assess disease status at initiation of therapy as well as its evolution in response to treatment or a placebo. One of the challenges confronting SJS/TEN interventional studies currently is inadequate and often inconsistent definition of disease status and consequently disease progression. A recent systematic review and meta-analysis of systemic interventions in SJS/TEN included three randomized-controlled trials and six prospective, controlled observational studies. The limitations of the included studies identified by the authors include failure to report the time to full skin healing; wide treatment variations across institutions; lack of controlling for confounders; inadequate reporting of baseline comorbidities; and the reliance by clinicians on medical history, clinical morphology, and histopathology, as there are no validated biomarkers to aid in the diagnosis or prognostication of SJS/TEN. The authors recommend all these be addressed to improve the quality of the studies (7). A closer examination of the individual studies highlights the variation in endpoints and a generally inadequate definition of these endpoints in even the most robust of interventional studies in SJS/TEN. Other than mortality, endpoints included change in prostration (level of tiredness or weakness); fever; duration of progression of skin detachment; BSA stabilization; arrest of disease progression; beginning and completion of re-epithelialization; recovery velocity index using a severity-of-illness score developed by the authors; illness auxiliary score that includes modified SCORTEN parameters; and a simplified acute physiology score. Apart from variable endpoints, most of the studies do not fully describe these endpoints in a reproducible fashion (25, 95, 96, 98–102).

## Potential future research directions

### Imaging as a global assessment of Stevens–Johnson syndrome and toxic epidermal necrolysis severity

Positron emission tomography (PET) is a non-invasive molecular imaging tool that provides tomographic images and quantitative parameters of perfusion, cell viability, proliferation, and/or metabolic activity of tissues. These images result from the use of different substances of biological interest (sugars, amino acids, metabolic precursors, hormones) labeled with positron-emitting radionuclides. A combination of important functional information provided by PET with morphological detail provided by computed tomography (CT) as PET/CT provides clinicians with a sensitive and accurate one-step whole-body diagnostic and prognostic tool. Fluorodeoxyglucose (FDG) is a radiolabeled analog of glucose and is taken up by cells *via* the first stages of the normal glucose pathway and trapped inside cells with high glycolytic activity. FDG uptake is quantifiable and correlates with metabolic activity, providing useful information on disease severity, disease progression, and therapeutic response (103). FDG-PET/CT has been used successfully to identify, localize, and quantify inflammation *in vivo* in an array of inflammatory conditions affecting the eye, RS, GIT, GUT, and the cardiovascular system. It is a useful tool to detect metabolic responses in infectious processes and other inflammatory conditions (104). The spectrum of clinical diseases on which FDG-PET/CT has shown utility includes connective tissue diseases, vasculitis, arrhythmias, arteriosclerosis, aneurysm detection and progression, sarcoidosis, amyloidosis, psoriasis and psoriatic arthropathy, malignancies, neuritis, encephalitis, eye tumors, myositis, arthritis, osteomyelitis, osteonecrosis, osteitis, transplant rejection, inflammatory bowel disease, hepatitis, glomerulonephritis, lymph node assessment, hidradenitis suppurativa, tuberculosis, and deep fungal infections (105–118). We have used FDG-PET/CT in an ongoing study to determine internal organ involvement and disease severity in patients with SJS/TEN during the acute stage and a later time point. Our preliminary data show very promising proof-of concept results that demonstrate FDG-PET/CT as relatively non-invasive

methods of identifying and quantifying tissue involvement in SJS/TEN beyond the skin.

## Artificial intelligence as an aid in the Stevens–Johnson syndrome and toxic epidermal necrolysis disease status

Artificial intelligence (AI) is a general term that implies the use of a computer to model intelligent behavior with minimal human intervention. The application of AI in medicine has two main branches, namely, virtual, and physical. The virtual component is represented by deep learning (DL), a subset of machine learning (ML) that is represented by mathematical algorithms that improve learning through experience. AI's goal is to build algorithms ("models") that perform tasks that are considered to require intelligence or training, such as recognizing objects or diseases in images. Traditionally, algorithms are built that can perform image classification tasks by first creating feature detectors (e.g., this is a round spot, this is the color of that spot), then using handcrafted prediction rules (e.g., size > 3 mm, color varying across the spot) to make classifications. However, this can be difficult and the models may be brittle (e.g., the spot detection fails, or the color quantification fails because the lighting is different, or the size detection fails because the skin is a variable distance from the camera).

There are three types of ML algorithms, namely, (1) unsupervised (ability to find patterns), (2) supervised (classification and prediction algorithms based on previous examples), and (3) reinforcement learning (use of sequences of rewards and punishments to form a strategy for operation in a specific problem space) (119). ML is a set of computational techniques to build algorithms that learn from data (i.e., "training data") instead of being engineered to detect specific features. Dermatology, as a predominantly visual specialty, is suitable for ML because there is sufficient complete training data in the form of clinical images. This is more accurate than handcrafted approaches that input data handpicked by the data scientist into the model. For example, by training an algorithm using tens or hundreds of thousands of images of SJS/TEN across a variety of lighting conditions and backgrounds, the algorithm can learn the morphologies that correspond to the disease more accurately.

Deep learning is the dominant AI technology that leverages complex data, such as images, through artificial neural networks that learn complex mappings between inputs (e.g., images) and outputs (e.g., diagnoses) without explicit human engineering. The model self-learns features from the input, such as visual patterns, that are most relevant for predicting the output. In many settings across medical specialties, DL matches healthcare professionals in detecting disease from medical imaging (120). AI is progressively being integrated into clinical care of skin diseases. An AI system has already been approved for the European market as a medical device for the management of melanoma. The device was shown to perform comparably with dermatologists who reviewed text and clinical images of melanomas in a setting simulating store-and-forward teledermatology (121). A DL system for diagnosis of early SJS/TEN images vs. non-severe cutaneous adverse drug reactions based on imaging of the individual lesions has recently been developed. This was shown to perform significantly better than all 10 board-certified dermatologists and 24 trainee dermatologists involved in the study (122). AI offers a significant opportunity to harmonize SJS/TEN disease status and endpoints across studies.

## Biomarkers as tools for measuring disease severity

Previous SJS/TEN studies have mostly focused on genetic biomarkers and others to predict mortality. There have been much fewer studies focusing on biomarkers to monitor severity, progression, and response to therapy during the acute stages of SJS/TEN and how these correlate with long-term morbidity and delayed mortality. Biomarkers that have been studied either singly or in combination in SJS/TEN include procalcitonin (32); granulysin (123); IFN-g (124); interleukin (IL)-8 and granzyme B (125); endocan, tumor necrosis factor-α, vascular endothelial growth factor, and C-reactive protein; serum IL-17 (126); complement components (127); alarmins like the heterodimeric form of S100 calcium-binding protein A8 and S100 calcium-binding protein (A9 S100A8/A9) (123); chemokines like CXCL9/MIG and CXCL10/IP-10 (124); antimicrobial peptides like LL-37 (128); exosomal nucleic acids like *miR-375-3p* (129); plasma lipid profiles (130); renal functions (78, 79); neutrophil:lymphocyte ratio; and C-reactive protein:albumin ratio (131).

Systematic pattern comparison of biochemical, inflammatory, hematological, and immune biomarkers in SJS/TEN cohorts stratified by severity and mortality may enable sufficient discrimination to warrant inclusion in risk stratification models. In these types of studies, lack of clinically or statistically significant differences does not necessarily imply a lack of association with the outcomes being measured (132). Thus, it is important to have a low threshold for biomarker inclusion in study designs and building predictive risk stratification models.

## Development of consensus on definitions of endpoints in interventional studies

Significant coherence has emerged among the leading researchers in SJS/TEN over the last decade. Numerous

meetings that brought together international experts and researchers have successfully been convened in Asia and North America. The meetings have been effective in collating together the current body of knowledge, allowing closer collaboration among researchers and mapping research agenda on SJS/TEN. Some of the highlighted gaps, including definitions of disease severity, progression, and complete re-epithelialization, can be addressed in these meetings of experts and consensus reached. Similarly, researchers at the forefront of biomarker research can collectively study the most promising biomarkers and map research direction. This would further allow sharing of progress made, including negative findings that would otherwise not make it into publication. Unless these and other similar collaborative efforts are adopted, the proposed international multicenter pharmacotherapeutic interventional studies may not provide robust evidence (133).

### Limitations

The limitations of this work include the use of individual case reports to highlight the gaps in current practice that may be outliers and not generalizable to all patients with SJS/TEN. Additionally, these are proposals that may not be successfully implemented in real-life settings.

## Conclusion

There are gaps that need to be urgently addressed in SJS/TEN research. There is an urgent need for reproducible methods of measuring disease severity that are sensitive to changes induced by therapeutic interventions and that more accurately predict outcomes beyond the acute stage by including the systemic and internal organ effects of SJS/TEN. Potential solutions include consensus on definitions, advances in diagnostic imaging and biomarker assessment, and development of AI platforms for the detection and monitoring of disease.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the author, without undue reservation.

## Ethics statement

The studies involving human participants were reviewed and approved by Human Research Ethics Committee, University of Cape Town. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## Author contributions

The author confirms being the sole contributor of this work and has approved it for publication.

## Funding

RL was supported by the South African Medical Research Council (SAMRC) IRMA 2567 and National Research Foundation (NRF) of South Africa UID 121278.

## Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

## References

1. Bastuji-Garin S, Rzany B, Stern RS, Shear NH, Naldi L, Roujeau JC. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. *Arch Dermatol.* (1993) 129:92–6. doi: 10.1001/archderm.129.1.92

2. Brown KM, Silver GM, Halerz M, Walaszek P, Sandroni A, Gamelli RL. Toxic epidermal necrolysis: does immunoglobulin make a difference? *J Burn Care Rehabil.* (2004) 25:81–8. doi: 10.1097/01.BCR.0000105096.93526.27

3. Bastuji-Garin S, Fouchard N, Bertocchi M, Roujeau JC, Revuz J, Wolkenstein P. SCORTEN: a severity-of-illness score for toxic epidermal necrolysis. *J Invest Dermatol.* (2000) 115:149–53. doi: 10.1046/j.1523-1747.2000.00061.x

4. Koh HK, Fook-Chong S, Lee HY. Assessment and comparison of performance of ABCD-10 and SCORTEN in prognostication of epidermal necrolysis. *JAMA Dermatol.* (2020) 156:1294–9. doi: 10.1001/jamadermatol.2020.3654

5. Stern RS, Divito SJ. Stevens-Johnson syndrome and toxic epidermal necrolysis: associations, outcomes, and pathobiology-thirty years of progress but still much to be done. *J Invest Dermatol.* (2017) 137:1004–8. doi: 10.1016/j.jid.2017.01.003

6. Zimmermann S, Sekula P, Venhoff M, Motschall E, Knaus J, Schumacher M, et al. Systemic immunomodulating therapies for Stevens-Johnson syndrome and toxic epidermal necrolysis: a systematic review and meta-analysis. *JAMA Dermatol.* (2017) 153:514–22. doi: 10.1001/jamadermatol.2016.5668

7. Jacobsen A, Olabi B, Langley A, Beecker J, Mutter E, Shelley A, et al. Systemic interventions for treatment of Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and SJS/TEN overlap syndrome. *Cochrane Database Syst Rev.* (2022) 3:CD013130. doi: 10.1002/14651858.CD013130.pub2

8. Kim WB, Worley B, Holmes J, Phillips EJ, Beecker J. Minimal clinically important differences for measures of treatment efficacy in Stevens-Johnson syndrome and toxic epidermal necrolysis. *J Am Acad Dermatol.* (2018) 79:1150–2. doi: 10.1016/j.jaad.2018.06.002

9. Krajewski A, Maciejewska-Markiewicz D, Jakubczyk K, Markowska M, Struzyna J, Madry R, et al. Impact of multiple medical interventions on mortality, length of hospital stay and reepithelialization time in toxic epidermal necrolysis, Steven-Johnsons syndrome, and TEN/SJS overlap – Metanalysis and metaregression of observational studies. *Burns.* (2022) 48:263–80. doi: 10.1016/j.burns.2021.11.004

10. Houschyar KS, Tapking C, Borrelli MR, Puladi B, Ooms M, Wallner C, et al. Stevens-Johnson syndrome and toxic epidermal necrolysis: a systematic review and meta-analysis. *J Wound Care.* (2021) 30:1012–9. doi: 10.12968/jowc.2021.30.12.1012

11. Ao S, Gao X, Zhan J, Ai L, Li M, Su H, et al. Inhibition of tumor necrosis factor improves conventional steroid therapy for Stevens-Johnson syndrome/toxic epidermal necrolysis in a cohort of patients. *J Am Acad Dermatol.* (2022) 86:1236–45. doi: 10.1016/j.jaad.2022.01.039

12. Zhang J, Lu CW, Chen CB, Wang CW, Chen WT, Cheng B, et al. Evaluation of combination therapy with etanercept and systemic corticosteroids for Stevens-Johnson syndrome and toxic epidermal necrolysis: a multicenter observational study. *J Allergy Clin Immunol Pract.* (2022) 10:1295–304.e6. doi: 10.1016/j.jaip.2022.01.038

13. Chen CB, Wang CW, Chung WH. Stevens-Johnson Syndrome and toxic epidermal necrolysis in the era of systems medicine. *Methods Mol Biol.* (2022) 2486:37–54. doi: 10.1007/978-1-0716-2265-0_3

14. Cho YT, Lin JW, Chen YC, Chang CY, Hsiao CH, Chung WH, et al. Generalized bullous fixed drug eruption is distinct from Stevens-Johnson syndrome/toxic epidermal necrolysis by immunohistopathological features. *J Am Acad Dermatol.* (2014) 70:539–48. doi: 10.1016/j.jaad.2013.11.015

15. Chang WC, Abe R, Anderson P, Anderson W, Ardern-Jones MR, Beachkofsky TM, et al. SJS/TEN 2019: from science to translation. *J Dermatol Sci.* (2020) 98:2–12.

16. White KD, Abe R, Ardern-Jones M, Beachkofsky T, Bouchard C, Carleton B, et al. SJS/TEN 2017: building multidisciplinary networks to drive science and translation. *J Allergy Clin Immunol Pract.* (2018) 6:38–69. doi: 10.1016/j.jaip.2017.11.028

17. Kridin K, Bruggen MC, Chua SL, Bygum A, Walsh S, Nageli MC, et al. Assessment of treatment approaches and outcomes in Stevens-Johnson syndrome and toxic epidermal necrolysis: insights from a pan-european multicenter study. *JAMA Dermatol.* (2021) 157:1182–90. doi: 10.1001/jamadermatol.2021.3154

18. George SM, Harrison DA, Welch CA, Nolan KM, Friedmann PS. Dermatological conditions in intensive care: a secondary analysis of the Intensive Care National Audit and Research Centre (ICNARC) case mix programme database. *Crit Care.* (2008) 12(Suppl. 1):S1. doi: 10.1186/cc6141

19. Sekula P, Dunant A, Mockenhaupt M, Naldi L, Bouwes Bavinck JN, Halevy S, et al. Comprehensive survival analysis of a cohort of patients with Stevens-Johnson syndrome and toxic epidermal necrolysis. *J Invest Dermatol.* (2013) 133:1197–204. doi: 10.1038/jid.2012.510

20. Lehloenya RJ, Esmail F, Christians SJ, Motsepe D, Todd G. Toxic epidermal necrolysis with failure of re-epithelialization. Could umbilical cord mesenchymal stem cell transplantation have a role? *J Eur Acad Dermatol Venereol.* (2013) 27:923–5. doi: 10.1111/j.1468-3083.2012.04667.x

21. Lehloenya RJ, Phillips EJ, Pasieka HB, Peter J. Recognizing drug hypersensitivity in pigmented skin. *Immunol Allergy Clin North Am.* (2022) 42:219–38. doi: 10.1016/j.iac.2022.01.005

22. Wang CW, Yang LY, Chen CB, Ho HC, Hung SI, Yang CH, et al. Randomized, controlled trial of TNF-alpha antagonist in CTL-mediated severe cutaneous adverse reactions. *J Clin Invest.* (2018) 128:985–96. doi: 10.1172/JCI93349

23. Valeyrie-Allanore L, Wolkenstein P, Brochard L, Ortonne N, Maitre B, Revuz J, et al. Open trial of ciclosporin treatment for Stevens-Johnson syndrome and toxic epidermal necrolysis. *Br J Dermatol.* (2010) 163:847–53. doi: 10.1111/j.1365-2133.2010.09863.x

24. Tripathi A, Ditto AM, Grammer LC, Greenberger PA, McGrath KG, Zeiss CR, et al. Corticosteroid therapy in an additional 13 cases of Stevens-Johnson syndrome: a total series of 67 cases. *Allergy Asthma Proc.* (2000) 21:101–5. doi: 10.2500/108854100778250914

25. Wolkenstein P, Latarjet J, Roujeau JC, Duguet C, Boudeau S, Vaillant L, et al. Randomised comparison of thalidomide versus placebo in toxic epidermal necrolysis. *Lancet.* (1998) 352:1586–9. doi: 10.1016/S0140-6736(98)02197-7

26. Paquet P, Jacob E, Quatresooz P, Jacquemin D, Pierard GE. Delayed reepithelialization and scarring deregulation following drug-induced toxic epidermal necrolysis. *Burns.* (2007) 33:100–4. doi: 10.1016/j.burns.2006.04.031

27. Thorel D, Delcampe A, Ingen-Housz-Oro S, Hajj C, Gabison E, Chosidow O, et al. Dark skin phototype is associated with more severe ocular complications of Stevens-Johnson syndrome and toxic epidermal necrolysis. *Br J Dermatol.* (2019) 181:212–3. doi: 10.1111/bjd.17627

28. Noe MH, Rosenbach M, Hubbard RA, Mostaghimi A, Cardones AR, Chen JK, et al. Development and validation of a risk prediction model for in-hospital mortality among patients with Stevens-Johnson syndrome/toxic epidermal necrolysis-ABCD-10. *JAMA Dermatol.* (2019) 155:448–54. doi: 10.1001/jamadermatol.2019.0998

29. Cooney R, Beck A, Gonzalez B, Gamelli RL, Mosier MJ. Not all drugs are created equal: the importance of causative agent in toxic epidermal necrolysis. *J Burn Care Res.* (2016) 37:e69–78. doi: 10.1097/BCR.0000000000000328

30. Revuz J, Penso D, Roujeau JC, Guillaume JC, Payne CR, Wechsler J, et al. Toxic epidermal necrolysis. Clinical findings and prognosis factors in 87 patients. *Arch Dermatol.* (1987) 123:1160–5. doi: 10.1001/archderm.123.9.1160

31. Chen CB, Hsu TH, Chung-Yee Hui R, Lu CW, Chen WT, Chiang PH, et al. Disseminated intravascular coagulation in Stevens-Johnson syndrome and toxic epidermal necrolysis. *J Am Acad Dermatol.* (2021) 84:1782–91. doi: 10.1016/j.jaad.2021.01.072

32. Wang Q, Tian XB, Liu W, Zhang LX. Procalcitonin as a diagnostic indicator for systemic bacterial infections in patients with Stevens-Johnson syndrome/toxic epidermal necrolysis. *J Dermatol.* (2018) 45:989–93. doi: 10.1111/1346-8138.14488

33. Lecadet A, Woerther PL, Hua C, Colin A, Gomart C, Decousser JW, et al. Incidence of bloodstream infections and predictive value of qualitative and quantitative skin cultures of patients with overlap syndrome or toxic epidermal necrolysis: a retrospective observational cohort study of 98 cases. *J Am Acad Dermatol.* (2019) 81:342–7. doi: 10.1016/j.jaad.2019.03.030

34. Knight L, Muloiwa R, Dlamini S, Lehloenya RJ. Factors associated with increased mortality in a predominantly HIV-infected population with Stevens Johnson syndrome and toxic epidermal necrolysis. *PLoS One.* (2014) 9:e93543. doi: 10.1371/journal.pone.0093543

35. Halebian PHD, Shires GT. Clinical management: a burn center experience with toxic epidermal necrolysis. *J Burn Care Rehabil.* (1983) 4:176–83. doi: 10.1097/00004630-198305000-00005

36. Zweiban B, Cohen H, Chandrasoma P. Gastrointestinal involvement complicating Stevens-Johnson syndrome. *Gastroenterology.* (1986) 91:469–74. doi: 10.1016/0016-5085(86)90585-8

37. Belafsky PC, Postma GN, Koufman JA, Bach KK. Stevens-Johnson syndrome with diffuse esophageal involvement. *Ear Nose Throat J.* (2002) 81:220. doi: 10.1177/014556130208100408

38. Michel P, Joly P, Ducrotte P, Hemet J, Leblanc I, Lauret P, et al. Ileal involvement in toxic epidermal necrolysis (Lyell syndrome). *Dig Dis Sci.* (1993) 38:1938–41. doi: 10.1007/BF01296123

39. Mahe A, Keita S, Blanc L, Bobin P. Esophageal necrosis in the Stevens-Johnson syndrome. *J Am Acad Dermatol.* (1993) 29:103–4. doi: 10.1016/S0190-9622(08)81810-5

40. Sato S, Kanbe T, Tamaki Z, Furuichi M, Uejima Y, Suganuma E, et al. Clinical features of Stevens-Johnson syndrome and toxic epidermal necrolysis. *Pediatr Int.* (2018) 60:697–702. doi: 10.1111/ped.13613

41. Yamane Y, Matsukura S, Watanabe Y, Yamaguchi Y, Nakamura K, Kambara T, et al. Retrospective analysis of Stevens-Johnson syndrome and toxic epidermal necrolysis in 87 Japanese patients–Treatment and outcome. *Allergol Int.* (2016) 65:74–81. doi: 10.1016/j.alit.2015.09.001

42. Choonhakarn C, Limpawattana P, Chaowattanapanit S. Clinical profiles and treatment outcomes of systemic corticosteroids for toxic epidermal necrolysis: a retrospective study. *J Dermatol.* (2016) 43:156–61. doi: 10.1111/1346-8138.13040

43. Slim R, Fathallah N, Aounallah A, Ksiaa M, Sriha B, Nouira R, et al. Paracetamol-induced Stevens Johnson syndrome and cholestatic hepatitis. *Curr Drug Saf.* (2015) 10:187–9. doi: 10.2174/1574886309666140827122735

44. Limpawattana P, Choonhakarn C, Kongbunkiat K. Clinical profiles of Stevens-Johnson syndrome among Thai patients. *J Dermatol.* (2014) 41:634–7. doi: 10.1111/1346-8138.12499

45. Heye P, Descloux A, Singer G, Rosenberg R, Kocher T. Perforated sigmoid diverticulitis in the presence of toxic epidermal necrolysis. *Case Rep Dermatol.* (2014) 6:49–53. doi: 10.1159/000360129

46. Pradka SP, Smith JR, Garrett MT, Fidler PE. Mesenteric ischemia secondary to toxic epidermal necrolysis: case report and review of the literature. *J Burn Care Res.* (2014) 35:e346–52. doi: 10.1097/BCR.0000000000000006

47. Jha AK, Goenka MK. Colonic involvement in Stevens-Johnson syndrome: a rare entity. *Dig Endosc.* (2012) 24:382. doi: 10.1111/j.1443-1661.2012.01248.x

48. Singalavanija S, Limpongsanurak W. Stevens-Johnson syndrome in Thai children: a 29-year study. *J Med Assoc Thai.* (2011) 9(Suppl. 3):S85–90.

49. Bouziri A, Khaldi A, Hamdi A, Borgi A, Ghorbel S, Kharfi M, et al. Toxic epidermal necrolysis complicated by small bowel intussusception: a case report. *J Pediatr Surg.* (2011) 46:e9–11. doi: 10.1016/j.jpedsurg.2010.09.011

50. Otomi M, Yano M, Aoki H, Takahashi K, Omoya T, Suzuki Y, et al. [A case of toxic epidermal necrolysis with severe intestinal manifestation]. *Nihon Shokakibyo Gakkai Zasshi.* (2008) 105:1353–61.

51. Yamane Y, Aihara M, Ikezawa Z. Analysis of Stevens-Johnson syndrome and toxic epidermal necrolysis in Japan from 2000 to 2006. *Allergol Int.* (2007) 56:419–25. doi: 10.2332/allergolint.O-07-483

52. Powell N, Munro JM, Rowbotham D. Colonic involvement in Stevens-Johnson syndrome. *Postgrad Med J.* (2006) 82:e10. doi: 10.1136/pgmj.2005.042952

53. Garza A, Waldman AJ, Mamel J. A case of toxic epidermal necrolysis with involvement of the GI tract after systemic contrast agent application at cardiac catheterization. *Gastrointest Endosc.* (2005) 62:638–42. doi: 10.1016/j.gie.2005.06.034

54. Misra SP, Dwivedi M, Misra V. Esophageal stricture as a late sequel of Stevens-Johnson syndrome in adults: incidental detection because of foreign body impaction. *Gastrointest Endosc.* (2004) 59:437–40. doi: 10.1016/S0016-5107(03)02710-X

55. Morelli MS, O'Brien FX. Stevens-Johnson Syndrome and cholestatic hepatitis. *Dig Dis Sci.* (2001) 46:2385–8.

56. Edell DS, Davidson JJ, Muelenaer AA, Majure M. Unusual manifestation of Stevens-Johnson syndrome involving the respiratory and gastrointestinal tract. *Pediatrics.* (1992) 89:429–32. doi: 10.1542/peds.89.3.429

57. Roupe G, Ahlmen M, Fagerberg B, Suurkula M. Toxic epidermal necrolysis with extensive mucosal erosions of the gastrointestinal and respiratory tracts. *Int Arch Allergy Appl Immunol.* (1986) 80:145–51. doi: 10.1159/000234043

58. Sherertz EF, Jegasothy BV, Lazarus GS. Phenytoin hypersensitivity reaction presenting with toxic epidermal necrolysis and severe hepatitis. Report of a patient treated with corticosteroid "pulse therapy". *J Am Acad Dermatol.* (1985) 12(1 Pt 2):178–81. doi: 10.1016/S0190-9622(85)80012-8

59. Lebargy F, Wolkenstein P, Gisselbrecht M, Lange F, Fleury-Feith J, Delclaux C, et al. Pulmonary complications in toxic epidermal necrolysis: a prospective clinical study. *Intensive Care Med.* (1997) 23:1237–44. doi: 10.1007/s001340050492

60. de Prost N, Mekontso-Dessap A, Valeyrie-Allanore L, Van Nhieu JT, Duong TA, Chosidow O, et al. Acute respiratory failure in patients with toxic epidermal necrolysis: clinical features and factors associated with mechanical ventilation. *Crit Care Med.* (2014) 42:118–28. doi: 10.1097/CCM.0b013e31829eb94f

61. Duong TA, de Prost N, Ingen-Housz-Oro S, Carrie AS, Zerah F, Valeyrie-Allanore L, et al. Stevens-Johnson syndrome and toxic epidermal necrolysis: follow-up of pulmonary function after remission. *Br J Dermatol.* (2015) 172:400–5. doi: 10.1111/bjd.13505

62. Seccombe EL, Ardern-Jones M, Walker W, Austin S, Taibjee S, Williams S, et al. Bronchiolitis obliterans as a long-term sequela of Stevens-Johnson syndrome and toxic epidermal necrolysis in children. *Clin Exp Dermatol.* (2019) 44:897–902. doi: 10.1111/ced.13969

63. Yang CW, Cho YT, Chen KL, Chen YC, Song HL, Chu CY. Long-term sequelae of Stevens-Johnson syndrome/toxic epidermal necrolysis. *Acta Derm Venereol.* (2016) 96:525–9. doi: 10.2340/00015555-2295

64. Saeed H, Mantagos IS, Chodosh J. Complications of Stevens-Johnson syndrome beyond the eye and skin. *Burns.* (2016) 42:20–7. doi: 10.1016/j.burns.2015.03.012

65. Wang WP, Ni YF, Wei YN, Li XF, Cheng QS, Lu Q. Bronchiolitis obliterans complicating a pneumothorax after Stevens-Johnson syndrome induced by lamotrigine. *J Formos Med Assoc.* (2015) 114:285–9. doi: 10.1016/j.jfma.2012.02.026

66. Park H, Ko YB, Kwon HS, Lim CM. Bronchiolitis obliterans associated with Stevens-Johnson syndrome: a case report. *Yonsei Med J.* (2015) 56:578–81. doi: 10.3349/ymj.2015.56.2.578

67. Thimmesch M, Gilbert A, Tuerlinckx D, Bodart E. Chronic respiratory failure due to toxic epidermal necrosis in a 10 year old girl. *Acta Clin Belg.* (2015) 70:69–71. doi: 10.1179/2295333714Y.0000000086

68. Ellenburg JT, Josey D Jr. An atypical presentation of pulmonary air-leak syndrome and multisystem toxic epidermal necrolysis. *Pediatr Pulmonol.* (2014) 49:E130–4. doi: 10.1002/ppul.22908

69. Sugino K, Hebisawa A, Uekusa T, Hatanaka K, Abe H, Homma S. Bronchiolitis obliterans associated with Stevens-Johnson syndrome: histopathological bronchial reconstruction of the whole lung and immunohistochemical study. *Diagn Pathol.* (2013) 8:134. doi: 10.1186/1746-1596-8-134

70. Tanaka A, Nakano M, Tani M, Kira M, Katayama I, Nakagawa J, et al. Adult case of Stevens-Johnson syndrome possibly induced by *Chlamydophila pneumoniae* infection with severe involvement of bronchial epithelium resulting in constructive respiratory disorder. *J Dermatol.* (2013) 40:492–4. doi: 10.1111/1346-8138.12136

71. Woo T, Saito H, Yamakawa Y, Komatsu S, Onuma S, Okudela K, et al. Severe obliterative bronchitis associated with Stevens-Johnson syndrome. *Intern Med.* (2011) 50:2823–7. doi: 10.2169/internalmedicine.50.5582

72. Shah AP, Xu H, Sime PJ, Trawick DR. Severe airflow obstruction and eosinophilic lung disease after Stevens-Johnson syndrome. *Eur Respir J.* (2006) 28:1276–9. doi: 10.1183/09031936.00036006

73. Kamada N, Kinoshita K, Togawa Y, Kobayashi T, Matsubara H, Kohno M, et al. Chronic pulmonary complications associated with toxic epidermal necrolysis: report of a severe case with anti-Ro/SS-A and a review of the published work. *J Dermatol.* (2006) 33:616–22. doi: 10.1111/j.1346-8138.2006.00142.x

74. Liu XY, Jiang ZF, Shen KL, Zeng JJ, Xu SY. [Clinical feature of four cases with bronchiolitis obliterans]. *Zhonghua Er Ke Za Zhi.* (2003) 41:839–41.

75. Garcia Suarez A, Gonzalez Hervas C, Moreno Garcia MI, Moreno Garcia MJ, Azcon Gonzalez De Aguilar P. [Fatal respiratory and renal manifestation of Stevens-Johnson syndrome. Pathological anatomical study]. *An Esp Pediatr.* (2002) 57:71–3. doi: 10.1016/S1695-4033(02)77897-1

76. Koch WM, McDonald GA. Stevens-Johnson syndrome with supraglottic laryngeal obstruction. *Arch Otolaryngol Head Neck Surg.* (1989) 115:1381–3. doi: 10.1001/archotol.1989.01860350115026

77. Wang L, Mei XL. Retrospective analysis of Stevens-Johnson syndrome and toxic epidermal necrolysis in 88 Chinese patients. *Chin Med J (Engl).* (2017) 130:1062–8. doi: 10.4103/0366-6999.204929

78. Park HJ, Yun J, Kang DY, Park JW, Koh YI, Kim S, et al. Unique clinical characteristics and prognosis of allopurinol-induced severe cutaneous adverse reactions. *J Allergy Clin Immunol Pract.* (2019) 7:2739–49.e3. doi: 10.1016/j.jaip.2019.05.047

79. Lee TH, Lee CC, Ng CY, Chang MY, Chang SW, Fan PC, et al. The influence of acute kidney injury on the outcome of Stevens-Johnson syndrome and toxic epidermal necrolysis: the prognostic value of KDIGO staging. *PLoS One.* (2018) 13:e0203642. doi: 10.1371/journal.pone.0203642

80. Baccaro LM, Sakharpe A, Miller A, Amani H. The first reported case of ureteral perforation in a patient with severe toxic epidermal necrolysis syndrome. *J Burn Care Res.* (2014) 35:e265–8. doi: 10.1097/BCR.0b013e31829a4374

81. Pliskow S. Severe gynecologic sequelae of Stevens-Johnson syndrome and toxic epidermal necrolysis caused by ibuprofen: a case report. *J Reprod Med.* (2013) 58:354–6.

82. de Jesus LE, Dekermacher S, Manhaes CR, Faria LM, Barros ML. Acquired labial sinechiae and hydrocolpos secondary to Stevens-Johnson syndrome. *Urology.* (2012) 80:919–21. doi: 10.1016/j.urology.2012.06.051

83. Emberger M, Lanschuetzer CM, Laimer M, Hawranek T, Staudach A, Hintner H. Vaginal adenosis induced by Stevens-Johnson syndrome. *J Eur Acad Dermatol Venereol.* (2006) 20:896–8. doi: 10.1111/j.1468-3083.2006.01586.x

84. Hart R, Minto C, Creighton S. Vaginal adhesions caused by Stevens-Johnson syndrome. *J Pediatr Adolesc Gynecol.* (2002) 15:151–2. doi: 10.1016/S1083-3188(02)00146-8

85. Blum L, Chosidow O, Rostoker G, Philippon C, Revuz J, Roujeau JC. Renal involvement in toxic epidermal necrolysis. *J Am Acad Dermatol.* (1996) 34:1088–90. doi: 10.1016/S0190-9622(96)90297-2

86. Bonafe JL, Thibaut I, Hoff J. Introital adenosis associated with the Stevens-Johnson syndrome. *Clin Exp Dermatol.* (1990) 15:356–7. doi: 10.1111/j.1365-2230.1990.tb02112.x

87. Wilson EE, Malinak LR. Vulvovaginal sequelae of Stevens-Johnson syndrome and their management. *Obstet Gynecol.* (1988) 71(3 Pt 2):478–80.

88. Marquette GP, Su B, Woodruff JD. Introital adenosis associated with Stevens-Johnson syndrome. *Obstet Gynecol.* (1985) 66:143–5.

89. Graham-Brown RA, Cochrane GW, Swinhoe JR, Sarkany I, Epsztejn LJ. Vaginal stenosis due to bullous erythema multiforme (Stevens-Johnson syndrome). Case report. *Br J Obstet Gynaecol.* (1981) 88:1156–7. doi: 10.1111/j.1471-0528.1981.tb01772.x

90. Lerat MF, Magre J. [Endometriosis of obstetrical vulvo-vaginal cicatrices]. *Bull Fed Soc Gynecol Obstet Lang Fr.* (1971) 23:688–9.

91. Lefaucheur JP, Valeyrie-Allanore L, Wing Ng, Tin S, Abgrall G, Colin A, et al. Chronic pain: a long-term sequela of epidermal necrolysis (Stevens-Johnson syndrome/toxic epidermal necrolysis) – Prevalence, clinical characteristics and risk factors. *J Eur Acad Dermatol Venereol.* (2021) 35:188–94. doi: 10.1111/jdv.16891

92. Olteanu C, Shear NH, Chew HF, Hashimoto R, Alhusayen R, Whyte-Croasdaile S, et al. Severe physical complications among survivors of Stevens-Johnson syndrome and toxic epidermal necrolysis. *Drug Saf.* (2018) 41:277–84. doi: 10.1007/s40264-017-0608-0

93. Lee HY, Walsh SA, Creamer D. Long-term complications of Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN): the spectrum of chronic problems in patients who survive an episode of SJS/TEN necessitates multidisciplinary follow-up. *Br J Dermatol.* (2017) 177:924–35. doi: 10.1111/bjd.15360

94. Kinoshita F, Yokota I, Mieno H, Ueta M, Bush J, Kinoshita S, et al. Multi-state model for predicting ocular progression in acute Stevens-Johnson syndrome/toxic epidermal necrolysis. *PLoS One.* (2021) 16:e0260730. doi: 10.1371/journal.pone.0260730

95. Han F, Zhang J, Guo Q, Feng Y, Gao Y, Guo L, et al. Successful treatment of toxic epidermal necrolysis using plasmapheresis: a prospective observational study. *J Crit Care.* (2017) 42:65–8. doi: 10.1016/j.jcrc.2017.07.002

96. Paquet P, Jennes S, Rousseau AF, Libon F, Delvenne P, Pierard GE. Effect of N-acetylcysteine combined with infliximab on toxic epidermal necrolysis. A proof-of-concept study. *Burns.* (2014) 40:1707–12. doi: 10.1016/j.burns.2014.01.027

97. Holford N. Treatment response and disease progression. *Transl Clin Pharmacol.* (2019) 27:123–6. doi: 10.12793/tcp.2019.27.4.123

98. Azfar NA, Zia MA, Malik LM, Khan AR, Jahangir M. Role of systemic steroids in the outcome of Stevens-Johnson syndrome and toxic epidermal necrolysis. *J Pak Assoc Dermatol.* (2010) 20:158–62.

99. Jagadeesan S, Sobhanakumari K, Sadanandan SM, Ravindran S, Divakaran MV, Skaria L, et al. Low dose intravenous immunoglobulins and steroids in toxic epidermal necrolysis: a prospective comparative open-labelled study of 36 cases. *Indian J Dermatol Venereol Leprol.* (2013) 79:506–11. doi: 10.4103/0378-6323.113080

100. Kakourou T, Klontza D, Soteropoulou F, Kattamis C. Corticosteroid treatment of erythema multiforme major (Stevens-Johnson syndrome) in children. *Eur J Pediatr.* (1997) 156:90–3. doi: 10.1007/s004310050561

101. Gonzalez-Herrada C, Rodriguez-Martin S, Cachafeiro L, Lerma V, Gonzalez O, Lorente JA, et al. Cyclosporine use in epidermal necrolysis is associated with an important mortality reduction: evidence from three different approaches. *J Invest Dermatol.* (2017) 137:2092–100. doi: 10.1016/j.jid.2017.05.022

102. Agrawal P, Mahajan S, Khopkar U. Stevens-Johnson syndrome and toxic epidermal necrolysis: a prospective study of epidemiology and clinical course. *Allergy.* (2013) 68(Suppl. 97):140.

103. Sathekge M, Warwick JM, Doruyter A, Vorster M. Appropriate indications for positron emission tomography/computed tomography: College of Nuclear Physicians of the Colleges of Medicine of South Africa. *S Afr Med J.* (2015) 105:894–6. doi: 10.7196/SAMJ.2015.v105i11.10180

104. Lawal I, Zeevaart J, Ebenhan T, Ankrah A, Vorster M, Kruger HG, et al. Metabolic imaging of infection. *J Nucl Med.* (2017) 58:1727–32. doi: 10.2967/jnumed.117.191635

105. Dahl A, Hernandez-Meneses M, Perissinotti A, Vidal B, Quintana E, Miro JM, et al. Echocardiography and FDG-PET/CT scan in gram-negative bacteremia and cardiovascular infections. *Curr Opin Infect Dis.* (2021) 34:728–36. doi: 10.1097/QCO.0000000000000781

106. Eibschutz LS, Rabiee B, Asadollahi S, Gupta A, Assadi M, Alavi A, et al. FDG-PET/CT of COVID-19 and other lung infections. *Semin Nucl Med.* (2022) 52:61–70. doi: 10.1053/j.semnuclmed.2021.06.017

107. Pijl JP, Nienhuis PH, Kwee TC, Glaudemans A, Slart R, Gormsen LC. Limitations and pitfalls of FDG-PET/CT in infection and inflammation. *Semin Nucl Med.* (2021) 51:633–45. doi: 10.1053/j.semnuclmed.2021.06.008

108. Wareham NE, Nielsen SD, Sorensen SS, Fischer BM. FDG PET/CT for detection of infectious complications following solid organ transplantation. *Semin Nucl Med.* (2021) 51:321–34. doi: 10.1053/j.semnuclmed.2020.12.007

109. van der Geest KSM, Treglia G, Glaudemans A, Brouwer E, Jamar F, Slart R, et al. Diagnostic value of [18F]FDG-PET/CT in polymyalgia rheumatica: a systematic review and meta-analysis. *Eur J Nucl Med Mol Imaging.* (2021) 48:1876–89. doi: 10.1007/s00259-020-05162-6

110. Fassio A, Matzneller P, Idolazzi L. Recent advances in imaging for diagnosis, monitoring, and prognosis of psoriatic arthritis. *Front Med (Lausanne).* (2020) 7:551684. doi: 10.3389/fmed.2020.551684

111. Li Y, Behr S. Acute findings on FDG PET/CT: key imaging features and how to differentiate them from malignancy. *Curr Radiol Rep.* (2020) 8:22. doi: 10.1007/s40134-020-00367-x

112. Keijsers RGM, Grutters JC. In which patients with sarcoidosis is FDG PET/CT indicated? *J Clin Med.* (2020) 9:890. doi: 10.3390/jcm9030890

113. El-Galaly TC, Villa D, Gormsen LC, Baech J, Lo A, Cheah CY. FDG-PET/CT in the management of lymphomas: current status and future directions. *J Intern Med.* (2018) 284:358–76. doi: 10.1111/joim.12813

114. Slart R, Writing Group, Reviewer Group, Members of EANM Cardiovascular, Members of EANM Infection & Inflammation, Members of Committees, SNMMI Cardiovascular, et al. FDG-PET/CT(A) imaging in large vessel vasculitis and polymyalgia rheumatica: joint procedural recommendation of the EANM, SNMMI, and the PET Interest Group (PIG), and endorsed by the ASNC. *Eur J Nucl Med Mol Imaging.* (2018) 45:1250–69. doi: 10.1007/s00259-018-3973-8

115. Kouijzer IJE, Mulders-Manders CM, Bleeker-Rovers CP, Oyen WJG. Fever of unknown origin: the value of FDG-PET/CT. *Semin Nucl Med.* (2018) 48:100–7. doi: 10.1053/j.semnuclmed.2017.11.004

116. Hess S, Hansson SH, Pedersen KT, Basu S, Hoilund-Carlsen PF. FDG-PET/CT in infectious and inflammatory diseases. *PET Clin.* (2014) 9:497–519, vi–vii. doi: 10.1016/j.cpet.2014.07.002

117. Murofushi Y, Kimura M, Iijima Y, Yamazaki M, Kaneko M. Studies on griseolic acid derivatives. IV. Synthesis and phosphodiesterase inhibitory activity of acylated derivatives of griseolic acid. *Chem Pharm Bull (Tokyo).* (1987) 35:1036–43. doi: 10.1248/cpb.35.1036

118. Ferrans CE, Powers MJ. The employment potential of hemodialysis patients. *Nurs Res.* (1985) 34:273–7. doi: 10.1097/00006199-198509000-00004

119. Hamet P, Tremblay J. Artificial intelligence in medicine. *Metabolism.* (2017) 69S:S36–40. doi: 10.1016/j.metabol.2017.01.011

120. Chartrand G, Cheng PM, Vorontsov E, Drozdzal M, Turcotte S, Pal CJ, et al. Deep learning: a primer for radiologists. *Radiographics.* (2017) 37:2113–31. doi: 10.1148/rg.2017170077

121. Young AT, Xiong M, Pfau J, Keiser MJ, Wei ML. Artificial intelligence in dermatology: a primer. *J Invest Dermatol.* (2020) 140:1504–12. doi: 10.1016/j.jid.2020.02.026

122. Fujimoto A, Iwai Y, Ishikawa T, Shinkuma S, Shido K, Yamasaki K, et al. Deep neural network for early image diagnosis of Stevens-Johnson syndrome/toxic epidermal necrolysis. *J Allergy Clin Immunol Pract.* (2022) 10:277–83. doi: 10.1016/j.jaip.2021.09.014

123. Panpruk R, Puangsricharern V, Klaewsongkram J, Rerknimitr P, Kittipibul T, Chongpison Y, et al. Clinical parameters and biological markers associated with acute severe ocular complications in Stevens-Johnson syndrome and toxic epidermal necrolysis. *Sci Rep.* (2021) 11:20275. doi: 10.1038/s41598-021-99370-1

124. Miyagawa F, Asada H. Chemokines in severe cutaneous adverse reactions (SCARs). *Biomolecules.* (2021) 11:847. doi: 10.3390/biom11060847

125. Yoshikawa Y, Ueta M, Nishigaki H, Kinoshita S, Ikeda T, Sotozono C. Predictive biomarkers for the progression of ocular complications in chronic Stevens-Johnson syndrome and toxic eeidermal necrolysis. *Sci Rep.* (2020) 10:18922. doi: 10.1038/s41598-020-76064-8

126. Morsy H, Taha EA, Nigm DA, Shahin R, Youssef EMK. Serum IL-17 in patients with erythema multiforme or Stevens-Johnson syndrome/toxic epidermal necrolysis drug reaction, and correlation with disease severity. *Clin Exp Dermatol.* (2017) 42:868–73. doi: 10.1111/ced.13213

127. Wang F, Huang L, Yu J, Zang D, Ye L, Zhu Q. Altered levels of complement components associated with non-immediate drug hypersensitivity reactions. *J Immunotoxicol.* (2020) 17:1–9. doi: 10.1080/1547691X.2019.1695985

128. Kinoshita M, Ogawa Y, Hama N, Ujiie I, Hasegawa A, Nakajima S, et al. Neutrophils initiate and exacerbate Stevens-Johnson syndrome and toxic epidermal necrolysis. *Sci Transl Med.* (2021) 13:eaax2398. doi: 10.1126/scitranslmed.aax2398

129. Zhang C, Zhu Z, Gao J, Yang L, Dang E, Fang H, et al. Plasma exosomal miR-375-3p regulates mitochondria-dependent keratinocyte apoptosis by targeting XIAP in severe drug-induced skin reactions. *Sci Transl Med.* (2020) 12:eaaw6142. doi: 10.1126/scitranslmed.aaw6142

130. Saito K, Ueta M, Maekawa K, Sotozono C, Kinoshita S, Saito Y. Plasma Lipid profiling of patients with chronic ocular complications caused by Stevens-Johnson syndrome/toxic epidermal necrolysis. *PLoS One.* (2016) 11:e0167402. doi: 10.1371/journal.pone.0167402

131. Wang Q, Lan YP, Qi B, Yin L, Zhang LX, Liu W. Neutrophil : lymphocyte ratio is associated with disease severity and mortality in patients with Stevens-Johnson syndrome/toxic epidermal necrolysis. *J Dermatol.* (2021) 48:1394–400. doi: 10.1111/1346-8138.15968

132. Altman DG, Bland JM. Statistics notes: absence of evidence is not evidence of absence. *BMJ.* (1995) 311:485. doi: 10.1136/bmj.311.7003.485

133. Roujeau JC, Mockenhaupt M, Guillaume JC, Revuz J. New evidence supporting cyclosporine efficacy in epidermal necrolysis. *J Invest Dermatol.* (2017) 137:2047–9. doi: 10.1016/j.jid.2017.07.828

frontiers | Frontiers in Oncology

TYPE Case Report
PUBLISHED 28 September 2022
DOI 10.3389/fonc.2022.954027



OPEN ACCESS

EDITED BY
Mohamed Alsharedi,
University of Kentucky, United States

REVIEWED BY
Catherine Grace Chung,
Wexner Medical Center, The Ohio State University, United States
Pooja Advani,
Mayo Clinic Florida, United States

*CORRESPONDENCE
Christine Jane Kurian
kurian-christine@cooperhealth.edu

SPECIALTY SECTION
This article was submitted to Breast Cancer, a section of the journal Frontiers in Oncology

RECEIVED 26 May 2022
ACCEPTED 05 September 2022
PUBLISHED 28 September 2022

CITATION
Kurian CJ, Desai A, Rafferty W and Abou Hussein AK (2022) Case Report: Case report: Alpelisib-induced Stevens–Johnson syndrome. *Front. Oncol.* 12:954027. doi: 10.3389/fonc.2022.954027



# Case report: Alpelisib-induced Stevens–Johnson syndrome

Christine Jane Kurian[1]*, Akshay Desai[2], William Rafferty[3] and Ahmed Kamel Abou Hussein[1]

[1]Department of Hematology and Medical Oncology, MD Anderson Cancer Center at Cooper University Healthcare, Camden, NJ, United States, [2]Department of Internal Medicine, Cooper University Healthcare, Camden, NJ, United States, [3]Department of Pathology, Cooper University Healthcare, Camden, NJ, United States

**Background:** Alpelisib is a recently approved treatment for hormone receptor-positive, HER2-negative, PIK3CA-mutated advanced breast cancer. It has been associated with alopecia and rash, but there are no documented cases of Stevens–Johnson Syndrome (SJS) associated with this drug. Here, we detail the first case of SJS associated with alpelisib.

**Case description:** Our patient is a 60-year-old woman with a past medical history of metastatic hormone receptor-positive (ER+ 80% and PR+ 1%), HER2-negative metastatic breast cancer who presented with acute odynophagia, fevers, and diffuse body rash after receiving her first doses of alpelisib and fulvestrant in the preceding days. She presented to the emergency department after developing a whole-body rash and severe ulceration of her buccal mucosa. She was started on methylprednisolone with remarkable improvement in symptoms.

**Conclusion:** This case report details the only report of SJS following alpelisib treatment. Immediate cessation of drugs and initiation of steroids are the cornerstone of treatment. Patients who experience such side effects will have to be monitored closely for long-term sequelae associated with SJS, including cutaneous, ocular, and oral sequelae, all of which can profoundly affect the quality of life for cancer patients.

KEYWORDS

**breast cancer, metastatic breast cancer, alpelisib, Stevens Johnson syndrome (SJS), Stevens Johnson Syndrome**

## Introduction

As therapies continue to evolve for the treatment of metastatic breast cancer, clinicians must be aware of new possible adverse effects that they may encounter. Alpelisib is a novel oral treatment for advanced hormone receptor-positive, HER2-negative, PIK3CA-mutated breast cancer. All-grade rash related to alpelisib was reported in 53.9% of patients and grade 3 rash in 20.1% in the landmark SOLAR1 trial, which resulted since the approval of this medication (1). This is an on-target side effect. Here, we discuss the first reported case of Stevens–Johnson syndrome likely precipitated by alpelisib.

## Case description

A 60-year-old woman with a past medical history of metastatic hormone receptor-positive (ER+ 80% and PR+ 1%), HER2-negative breast cancer with pulmonary, hepatic, and osseous metastases presented to the emergency department with acute odynophagia, fevers, and diffuse body rash. She had started fulvestrant (500 mg intramuscular (IM) injection) 15 days prior and alpelisib (300 mg daily) 19 days prior to presentation. The patient was not previously taking any antibiotics or CYP3A4 inhibitors prior to presentation. Her symptoms started 4 days prior to presentation when she noticed oral lesions initially with mild erythema and a small ulcer on the inner lower lip mucosa. The ulcers increased in size and number, and she was febrile to 100.7°F, which prompted a call to her primary care physician. She was prescribed magic mouthwash, which worsened her symptoms. She then noticed an erythematous, non-pruritic rash starting on her chest and spreading to her back and presented to the ED. She was noted to have worsening oral pain, sloughing, severe odynophagia, and dysphagia.

## Diagnostic assessment

On admission, she was febrile to 100.7°F and tachycardic with a heart rate of 108. She was normotensive. She noted no nausea, vomiting, chest pain, shortness of breath, and abdominal pain. Complete blood count showed leukocytosis at 13,100. Physical exam was notable for exudative and hemorrhagic sloughing of the lips and buccal mucosa and morbilliform and blanching erythema on the trunk with a superficial erosion on the chest (Figures 1–3). She was also noted to have tearing in both eyes. She was evaluated by ophthalmology, and the evaluation showed no change in vision with the anterior segment unremarkable and conjunctiva with trace hyperemia and injection without significant discharge or conjunctivitis. No symblepharon formation, episcleritis, or iritis was observed upon examination. On genital exam, she was noted to have erythema localized to the vagina.

Differential diagnoses included Stevens–Johnson Syndrome (SJS)/toxic epidermal necrolysis (TEN), paraneoplastic pemphigus, and reactive infectious mucocutaneous eruption (RIME). However, given the extensive skin sloughing of her lips and oral mucosa, the leading diagnosis was SJS/TEN.

A punch biopsy of the back showed features consistent with mild interface dermatitis with basal layer vacuolization and scattered necrotic keratinocytes consistent with the erythema

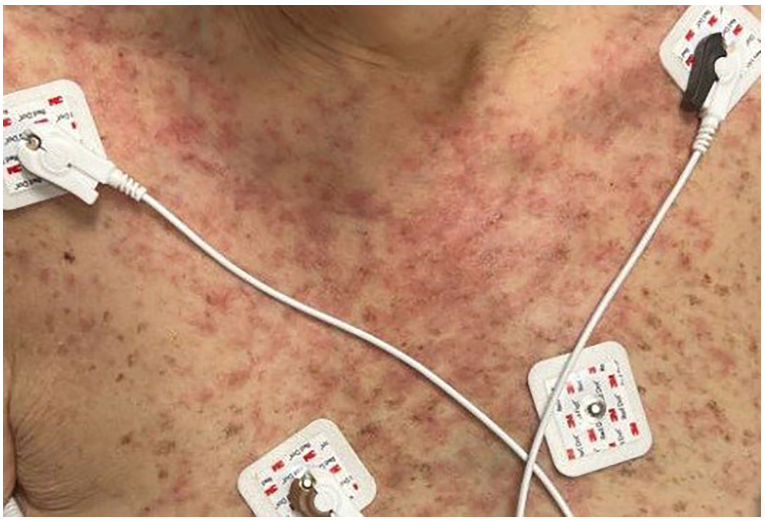

FIGURE 1
Morbiliform rash and blanching erythema on the back.

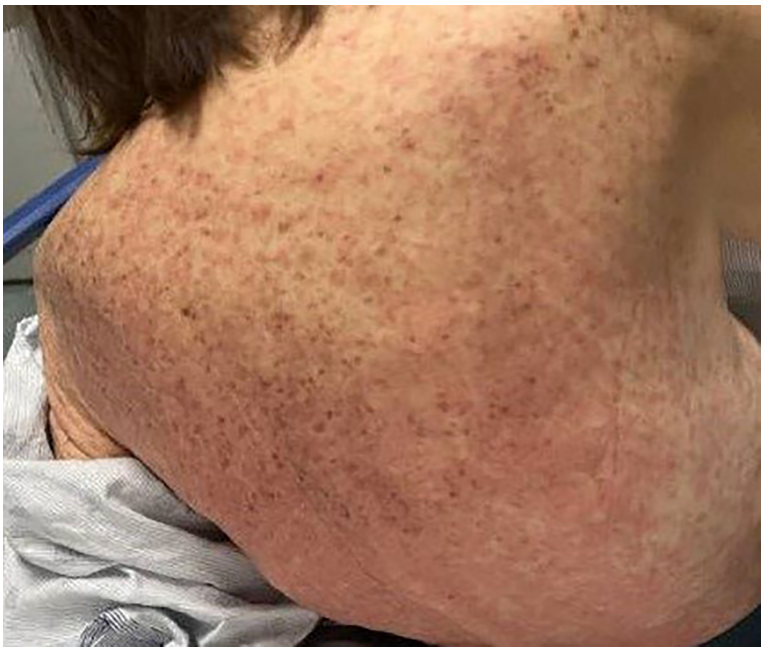

FIGURE 2
Morbilliform rash and blanching erythema on the trunk.

multiforme spectrum of disorders (Figure 4). Both alpelisib and fulvestrant were stopped. She was started on 1 mg/kg of methylprednisolone daily, and her symptoms improved markedly (Figures 5, 6). She was then transitioned to oral steroids with a regimen of 60 mg of prednisone daily for 7 days, then 40 mg of prednisone daily for 7 days, and then 20 mg of prednisone daily for 7 days. She had no long-term sequelae of SJS. Systemic treatment was held until her steroid taper was completed. Of note, she later tolerated subsequent fulvestrant therapy without any side effects.

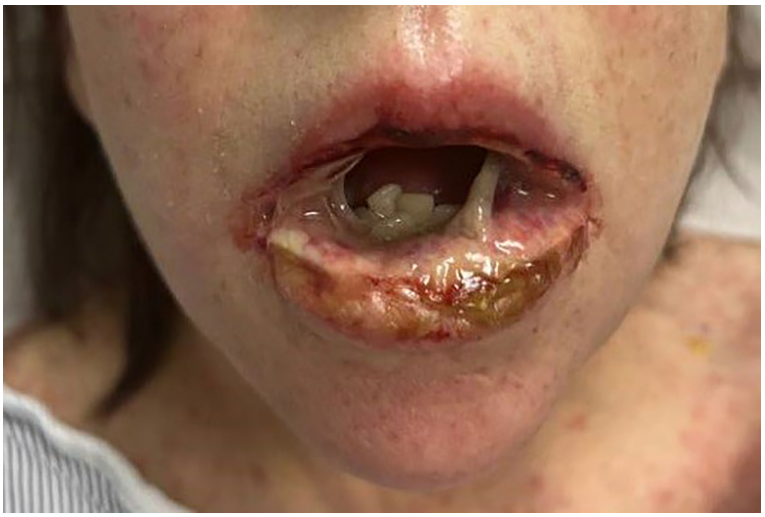

FIGURE 3
morbiliform rash Exudative and hemorrhagic sloughing of the lips and buccal mucosa.

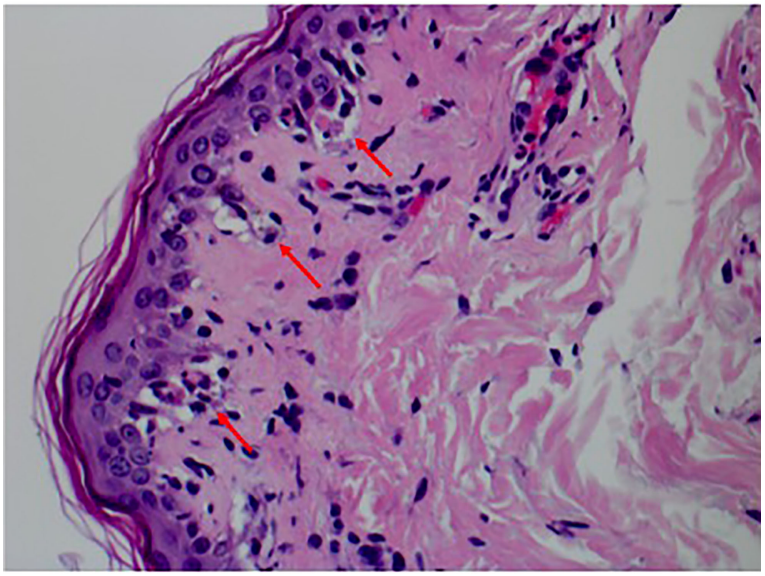

FIGURE 4
Punch biopsy pathology showing interface dermatitis with basal layer vacuolization, several apoptotic keratinocytes, and a sparse lymphocytic infiltrate.

## Discussion

SJS and TEN represent a spectrum of febrile, mucocutaneous drug-induced reactions. Annually, the incidence of SJS in adults in the United States is estimated to be approximately nine cases per million per year (2). Cases of SJS/TEN have often been associated with various types of antibiotics. These include sulfonamides, tetracyclines, and cephalosporins (3–5). Cases involving other medications including allopurinol, lamotrigine, and imidazole antifungals have also been seen (6–8). The distinction between

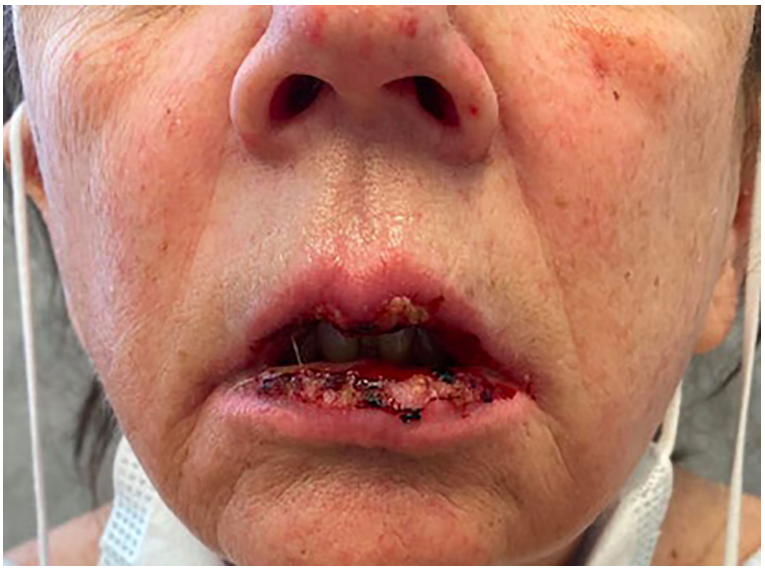

FIGURE 5
Patient's mouth 11 days after initial presentation.

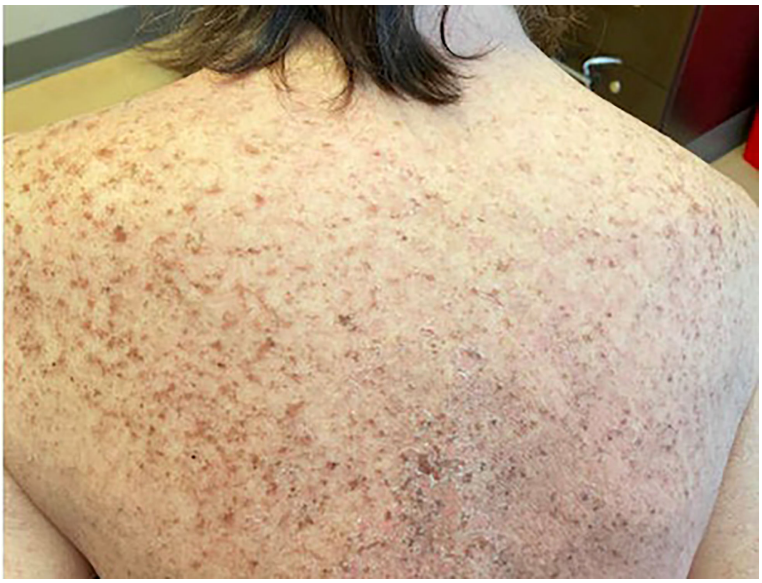

FIGURE 6
Patient's back 11 days after initial presentation.

SJS and TEN is based on the surface area, with SJS being diffuse and involving less than 10% of the total body surface area. It often manifests with widespread erythematous or purpuric macules or flat atypical target-shaped lesions. Conversely, TEN involves greater than 30% of body surface area and may present without any discrete lesions. Skin findings between 10% and 30% are classified as SJS/TEN overlap syndrome.

Alpelisib is indicated for the treatment of advanced or metastatic hormone receptor-positive (HR+), HER2-negative, and PIK3CA-mutated breast cancer, given in combination with fulvestrant (1). It functions *via* the inhibition of phosphatidylinositol-3-kinase (PI3K), primarily acting through the inhibition of PI3K-alpha (9). This facilitates an increase in estrogen receptor transcription, providing new receptor targets for fulvestrant. Although common dermatologic manifestations including alopecia and rash have been associated with alpelisib, serious dermatologic adverse effects such as SJS have been rare (10, 11). While there are additional risk factors that can predispose a patient to SJS/TEN, such as certain human leukocyte antigens (HLAs) or documented cross-reactivity to other medications, our patient did not have such a history that could explain her symptoms. SJS has been seen previously with older chemotherapeutic agents including bleomycin and thalidomide, EGFR inhibitors such as afatinib and cetuximab, and immunotherapeutic agents including nivolumab and pembrolizumab (12). There are no other reported cases of SJS following alpelisib. In addition, this patient's timeline of symptoms would align with the expected onset of SJS following a new medication, as symptoms often develop within 1–2 weeks of a new treatment.

## Conclusion

This case report details the only report of SJS following alpelisib treatment. The patient tolerated fulvestrant treatment after this incident without reaction. Immediate cessation of the drug is required. Further therapy may involve steroids, cyclosporine, etanercept, or intravenous immunoglobulin (IVIG). Patients who experience such side effects will have to be monitored closely for long-term sequelae associated with SJS, including cutaneous, ocular, and oral sequelae, all of which can profoundly affect the quality of life of cancer patients.

## Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

## Author contributions

CK and AD wrote the manuscript. AH reviewed and edited the manuscript. WR helped with the pathology slide and explanation. All authors contributed to the article and approved the submitted version.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.954027/full#supplementary-material

## References


1. André F, Ceruelos E, Rubovszky G, Capone M, Loibl S, Rugo HS, et al. Alpelisib for PIK3CA -mutated, hormone receptor–positive advanced breast cancer. *N Engl J Med* (2019) 380(20):1929–40. doi: 10.1056/NEJMOA1813904/SUPPL_FILE/NEJMOA1813904_DATA-SHARING.PDF

2. Hsu DY, Brieva J, Silverberg NB, Silverberg JI. Morbidity and mortality of stevens-Johnson syndrome and toxic epidermal necrolysis in United States adults. *J Invest Dermatol* (2016) 136(7):1387–97. doi: 10.1016/J.JID.2016.03.023

3. Khan DA, Knowles SR, Shear NH. Clinical commentary review sulfonamide hypersensitivity: Fact and fiction *Drug Healthc Patient Saf* (2022) 14:113–24. doi: 10.2147/DHPS.S347522

4. Lerch M, Mainetti C, Terziroli Beretta-Piccoli B, Harr T. Current perspectives on stevens-Johnson syndrome and toxic epidermal necrolysis. *Clin Rev Allergy Immunol* (2017) 54(1):147–76. doi: 10.1007/S12016-017-8654-Z

5. Murray KM, Camp MS. Cephalexin-induced stevens-johnson syndrome. *Ann Pharmacother* (1992) 26(10):1230–3. doi: 10.1177/106002809202601006

6. Gupta SS, Sabharwal N, Patti R, Kupfer Y. Allopurinol-induced stevens-Johnson syndrome CASE PRESENTATION. *Am J Med Sci* (2019) 357(4):348–51. doi: 10.1016/j.amjms.2018.11.018

7. Edinoff AN, Nguyen LH, Fitz-Gerald MJ, Crane E, Lewis K, St Pierre S, et al. Lamotrigine and stevens-Johnson syndrome prevention. *Psychopharmacol Bull* (2021) 51(2):96.

8. Curigliano G, Formica V, De Pas T, Spitaleri G, Pietri E, Fazio N, et al. Life-threatening toxic epidermal necrolysis during voriconazole therapy for invasive aspergillosis after chemotherapy. *Ann Oncol* (2006) 17(7):1174–5. doi: 10.1093/ANNONC/MDJ126

9. Markham A. Alpelisib: First global approval. *Drugs* (2019) 79(11):1249–53. doi: 10.1007/S40265-019-01161-6

10. *Dosing | PIQRAY® (alpelisib) tablets*. Available at: https://www.hcp.novartis.com/products/piqray/metastatic-breast-cancer/dosing/ (Accessed 28-Apr-2022). HCP.

11. Narayan P, Prowell TM, Gao JF, Fernandez LL, Li E, Jiang X, et al. FDA Approval summary: Alpelisib plus fulvestrant for patients with HR-positive, HER2-negative, PIK3CA-mutated, advanced or metastatic breast cancer. *Clin Cancer Res* (2021) 27(7):1842. doi: 10.1158/1078-0432.CCR-20-3652

12. Ng CY, Chen C-B, Wu M-Y, Wu J, Yang C-H, Chung-Yee Hui R, et al. Anticancer drugs induced severe adverse cutaneous drug reactions: An updated review on the risks associated with anticancer targeted therapy or immunotherapies. *J Immunol Res* (2018) 9 doi: 10.1155/2018/5376476

frontiers | Frontiers in Medicine

TYPE Review
PUBLISHED 13 October 2022
DOI 10.3389/fmed.2022.923991



OPEN ACCESS

EDITED BY
Elizabeth Phillips,
Vanderbilt University, United States

REVIEWED BY
Claudia Zeidler,
University Hospital Münster, Germany
Chun-Bing Chen,
Linkou Chang Gung Memorial Hospital, Taiwan

*CORRESPONDENCE
Ana Maria Copaescu
ana.copaescu@gmail.com

SPECIALTY SECTION
This article was submitted to Dermatology, a section of the journal Frontiers in Medicine

RECEIVED 20 April 2022
ACCEPTED 26 August 2022
PUBLISHED 13 October 2022

CITATION
Copaescu AM, Ben-Shoshan M and Trubiano JA (2022) Tools to improve the diagnosis and management of T-cell mediated adverse drug reactions.
*Front. Med.* 9:923991.
doi: 10.3389/fmed.2022.923991



# Tools to improve the diagnosis and management of T-cell mediated adverse drug reactions

Ana Maria Copaescu[1,2,3]*, Moshe Ben-Shoshan[3,4] and Jason A. Trubiano[1,5,6,7]

[1]Department of Infectious Diseases, Centre for Antibiotic Allergy and Research, Austin Health, Heidelberg, VIC, Australia, [2]Division of Allergy and Clinical Immunology, Department of Medicine, McGill University Health Centre (MUHC), Montreal, QC, Canada, [3]The Research Institute of the McGill University Health Centre, McGill University Health Centre (MUHC), Montreal, QC, Canada, [4]Division of Allergy, Immunology and Dermatology, Montreal Children's Hospital, McGill University Health Centre (MUHC), Montreal, QC, Canada, [5]Department of Oncology, Sir Peter MacCallum Cancer Centre, The University of Melbourne, Parkville, VIC, Australia, [6]Department of Medicine, Austin Health, The University of Melbourne, Heidelberg, VIC, Australia, [7]The National Centre for Infections in Cancer, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia

Delayed drug T-cell immune-mediated hypersensitivity reactions have a large clinical heterogeneity varying from mild maculopapular exanthema (MPE) to severe cutaneous adverse reactions (SCARs) such as acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS) and severe skin necrosis and blistering as seen in Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Given the knowledge gaps related to the immunopathogenesis of these conditions, the absence of validated diagnostic tools and the significant associated morbidity and mortality, patients with SCARs often have limited drug choices. We performed a comprehensive review aiming to evaluate *in vivo* diagnostic tools such as delayed intradermal skin and patch testing and *ex vivo/in vitro* research assays such as the lymphocyte transformation test (LTT) and the enzyme-linked ImmunoSpot (ELISpot) assay. We searched through *PubMed* using the terms "drug allergy," "*in vivo*" and "*ex vivo*" for original papers in the last 10 years. A detailed meticulous approach adapted to the various clinical phenotypes is recommended for the diagnostic and management of delayed drug hypersensitivity reactions. This review highlights the current diagnostic tools for the delayed drug hypersensitivity phenotypes.

KEYWORDS

**drug allergy, *in vivo*, *ex vivo*, diagnostic tools, delayed hypersensitivity reaction, drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), severe cutaneous adverse reactions (SCARs)**

## Introduction

Delayed immune-mediated drug hypersensitivity reactions (DHR) are inflammatory reactions with a predominant manifestation in the skin that can be associated with systemic manifestations, and are hypothesized to be T-cell mediated. These reactions are not anticipated and not dependent on the dose administered (1).

Severe cutaneous adverse reactions (SCARs) are DHR that cause severe damage to the skin and/or internal organs and are associated with significant acute and long-term morbidity and increased mortality risk (2). Risk factors include cystic fibrosis, severe asthma, chronic lymphatic leukemia, human immunodeficiency virus or genetic susceptibility (3). For the purpose of this review, we will focus on mild maculopapular exanthema (MPE) as well as SCAR syndromes: acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS) and Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Our main goal is to portray the diagnostic methods, including a description of the currently used clinical skin testing and novel investigational *ex vivo* methods for the delayed DHR.

## Methods

We formulated a research question focusing on the available diagnostic tools aimed to improve the diagnosis and management of delayed T-cell mediated drug reactions. The objective of the comprehensive review was established using the PICO method, including population, interventions, comparators and outcomes. We searched *PubMed* for peer-reviewed original articles with the terms drug, antibiotic, antimicrobial, sulfonamide, non-steroidal anti-inflammatory, anti-epileptic or anti-convulsant; allergy, hypersensitivity or T-cell mediated; and *in vivo* as well as *ex vivo* diagnostic methods.

We used the key words: {[drug*(Title/Abstract)] OR [antibiotic*(Title/Abstract)] OR [antimicrobial*(Title/Abstract)] OR [sulfonamide*(Title/Abstract)] OR [non-steroidal anti-inflammator*(Title/Abstract)] OR [amoxicillin*(Title/Abstract)] OR [anti-epileptic*(Title/Abstract)] OR [anti-convulsant*(Title/Abstract)]} AND {[*ex vivo* (Title/Abstract)] OR [*in vitro* (Title/Abstract)] OR [skin testing*(Title/Abstract)] OR [patch testing*(Title/Abstract)] OR [enzyme-linked immunoSpot assay*(Title/Abstract)] OR [ELISpot(Title/Abstract)] OR [lymphocyte transformation test*(Title/Abstract)] OR [lymphocyte proliferation*(Title/Abstract)] OR [stimulation test*(Title/Abstract)] OR [IFN*(Title/Abstract)] OR [flow cytometry*(Title/Abstract)]} AND {[allergy*[Title/Abstract)] OR [hypersensitivity*(Title/Abstract)] OR [T-cell mediated*(Title/Abstract)]}.

Articles relevant to the topic of interest were examined following the inclusion criteria: (1) original human studies (pediatric and adult population), (2) academic articles published in peer-reviewed journals, (3) available in English or French language, and (4) published between January 1st 2012 and June 2nd 2022. The search provided 1,440 results (**Figure 1**). The first screening was based on the titles and abstracts followed by a second round of screening performed by reviewing the full-text articles for selected studies. For the purpose of this study, meta-analysis-based research articles were not considered in the original studies subcategory. Articles on immediate and vaccine hypersensitivity were excluded as these were considered beyond the scope of this review. To better illustrate the existing literature, original articles were further sub-categorized in studies containing information on *in vivo* tools, *ex vivo* tools and HLA-related research. The descriptive/epidemiological reports published that did not address any diagnostic tools were added to another subgroup (**Figure 1**).

## Delayed hypersensitivity reactions

Delayed hypersensitivity reactions can occur hours to days following exposure to a drug or drug metabolite. It is hypothesized that uncontrolled T-cell production triggers the different immune manifestations (**Figure 2**). Matured antigen-presenting cells such as dendritic cells and macrophages interact with antigen-specific T CD4+ helper cells as well as CD8+ cytotoxic T-cells leading to drug-specific cell-mediated immunity (4). While adaptive immunity plays an essential role, an implication of the innate immune response has been demonstrated *in vitro* for agents such as allopurinol (5).

There is a limited number of cohort studies that focus on providing a better understanding of the incidence, clinical description and mortality of DHR. The majority of the data is extrapolated from small older studies. Some reports suggest that drug-induced SCARs are less prevalent in the pediatric population compared to an adult population (6–9). A description of the main delayed drug related T-cell mediated hypersensitivity reactions is portrayed in **Table 1** with an illustration of the immunopathogenesis and treatment options in **Figure 2**.

### Maculopapular exanthema

#### Clinical description

The MPE, morbilliform drug eruption or benign exanthem is the most common benign skin reaction associated with

Abbreviations: AGEP, acute generalized exanthematous pustulosis; DRESS, drug reaction with eosinophilia and systemic symptoms; ELISpot, enzyme-linked ImmunoSpot; MPE, maculopapular exanthema; SCAR, severe cutaneous adverse reaction; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

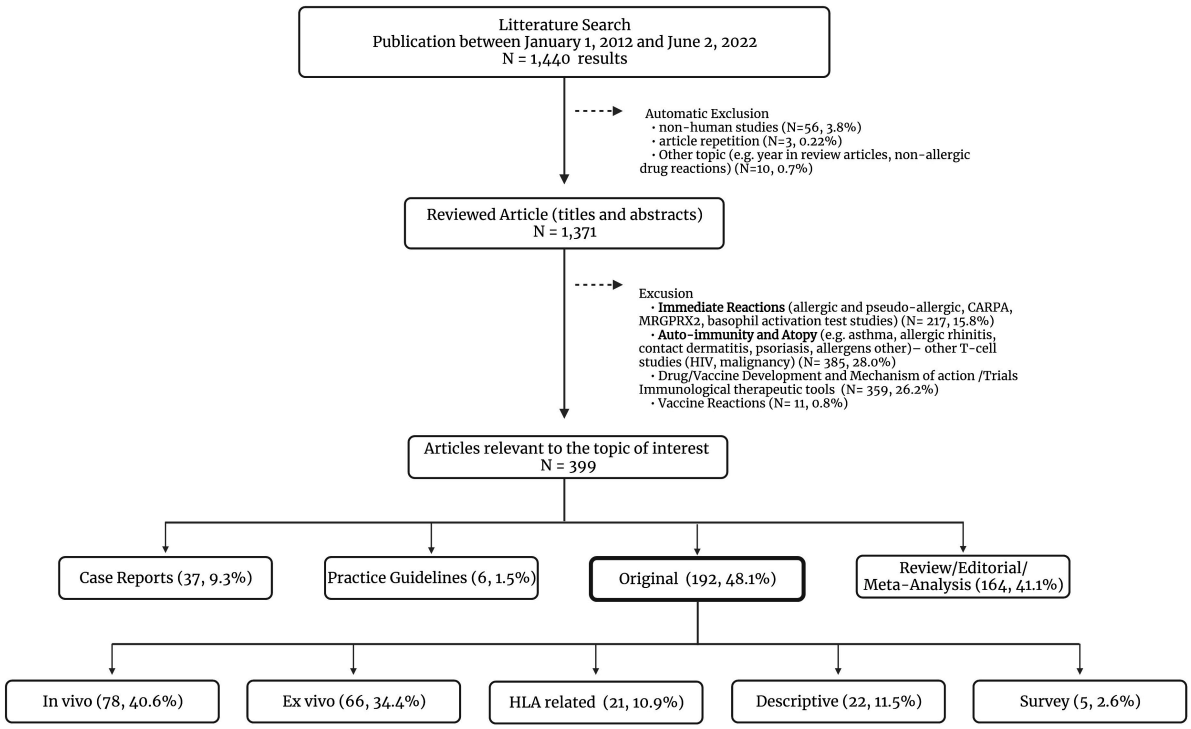


FIGURE 1
Comprehensive literature review–article selection. CARPA, complement activation-related pseudoallergy; HIV, human immunodeficiency virus; HLA, human leukocyte antigen; MRGPRX2, Mas-related G-protein coupled receptor member X2. The *ex vivo* original studies can also describe the use of *in vivo* diagnostic tools in the methods or study design.

drugs. This condition is characterized by a maculopapular erythematous eruption that can become widespread and confluent and can be associated with pruritus and/or mild eosinophilia (10). The onset of the reaction typically occurs in the first 7–10 days of treatment for patients not previously exposed to the medication. However, in previously sensitized individual, re-exposure can lead to a skin eruption as rapid as 6–72 h after treatment initiation. In the pediatric population, viral exanthemas are an important differential diagnosis (11).

### Epidemiology

Early studies suggest a prevalence of 2% for cutaneous drug eruptions in general (12), with up to 90% representing a mild phenotype. However, there is limited recent reliable data describing this non-severe type phenotypes. Another aspect is the non-immune mediated nature of some MPE that may result in overestimating the prevalence of this condition (13).

### Drugs

All drug categories could, in theory, induce a skin eruption and there is a fine line between a recognized side effect and a mild skin hypersensitivity reaction. However, few studies that focus on a limited number of drugs have demonstrated how drugs induce T-cell mediated reaction mainly looking at antibiotics (penicillins, cephalosporins, sulfonamides) and anticonvulsants.

### Management

Treating through in MPE is part of the accepted management options especially when the treatment alternatives could jeopardize the quality of the treatment or the treatment outcome (14, 15). The skin manifestation can be controlled with oral second-generation antihistamines as well as topical corticosteroids (15). A multidisciplinary approach is suggested for all delayed hypersensitivity conditions from MPE to TEN. Specialists implicated in the management vary depending on the organ involvement with allergy immunology, dermatology and infectious disease usually at the center of the management team (16).

## Acute generalized exanthematous pustulosis

### Clinical description

The AGEP is a non-follicular, sterile, pustular rash over widespread erythema, with a preference for the flexural folds. This condition can be accompanied by systemic symptoms such

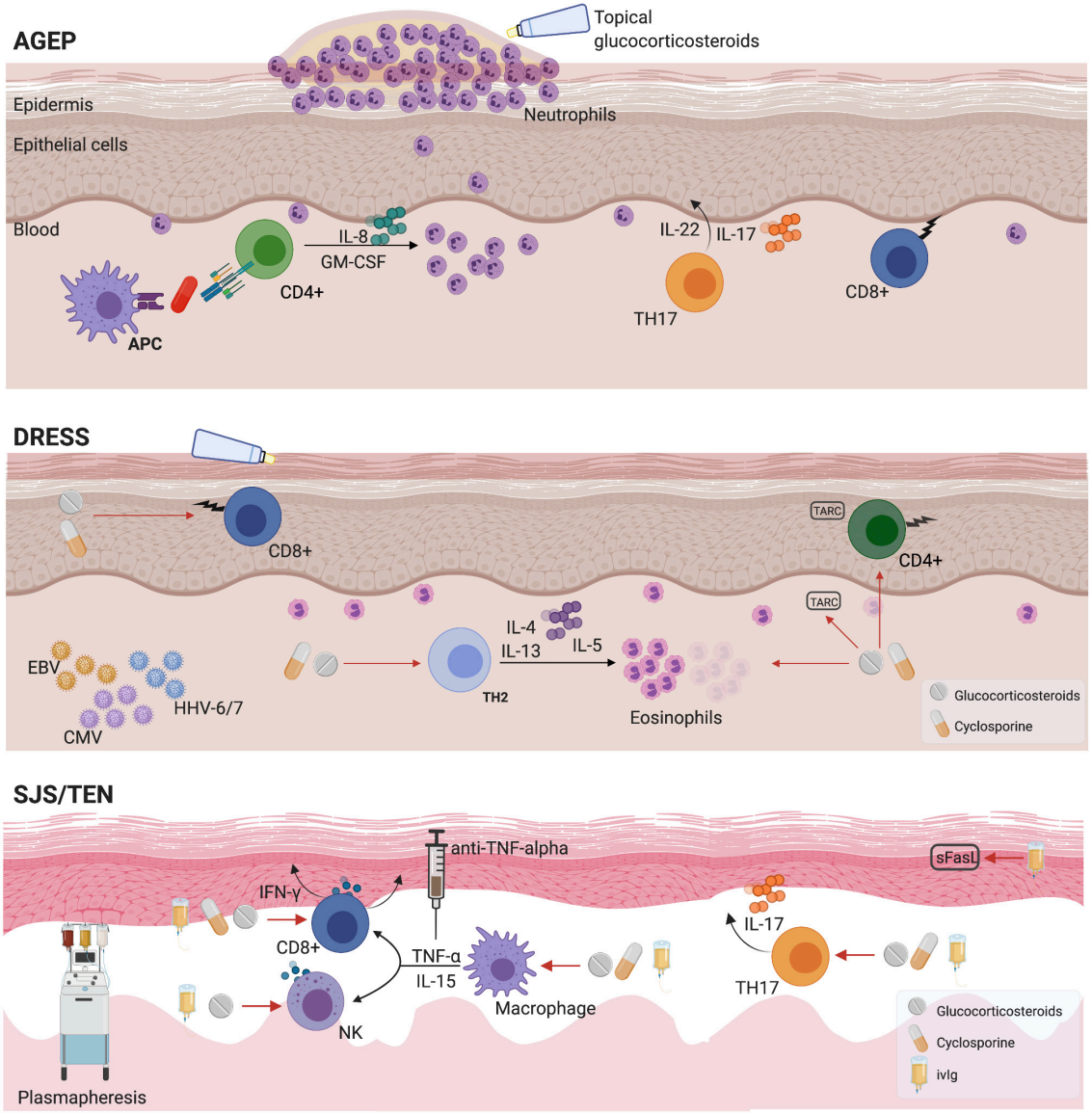


FIGURE 2
Mechanisms and pharmacological management for T-cell mediated reactions. AGEP, acute generalized exanthematous pustulosis; APC, antigen presenting cell; CMV, cytomegalovirus; DRESS, drug reaction with eosinophilia and systemic symptoms; EBV, Epstein-Barr virus; HHV, Human Herpesvirus; GM-CSF, granulocyte macrophage-colony stimulating factor; IFN-γ, Interferon gamma; IL, interleukin; sFasL, soluble Fas ligand; SJS, Stevens-Johnson syndrome; TARC, thymus and activation-regulated chemokine; TEN, toxic epidermal necrolysis; TNF, tumor necrosis factor.

as fever and/or biological abnormalities (10). A validation score from the EuroSCAR group criteria can be used to confirm the clinical diagnostic for AGEP cases (17). Part of the differential diagnosis of pustules localized on an erythematous skin is generalized pustular psoriasis (GPP), a rare subtype of psoriasis (18). During the initial clinical presentation, AGEP and GPP can be difficult to distinguish. The clinical evolution, with a shorter disease course for AGEP, as well as the biopsy with psoriasiform changes of the epidermis seen with GPP and absent in AGEP, allows the clinician to clarify the diagnosis (19, 20).

## Epidemiology

A landmark study for AGEP comes from the 2001 EuroSCAR group that reports an incidence of 1–5 cases per million persons per year (17). The mortality rate was reported to be 2–4% (21, 22) while understanding that this condition has a favorable prognosis following culprit drug withdrawal (23).

## Drugs

Multiple agents have been associated with AGEP (17) with antibiotics and antimycotics commonly described (21, 22). The

TABLE 1 Delayed drug related T-cell mediated hypersensitivity reactions.

| Phenotype | Incidence | Clinical description | Average latency | Mortality | Skin biopsy | Common drugs (10) | Clinical score | Laboratory Investigations | *In vivo* Tools | *Ex vivo* tools | HLA association | Management options |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| MPE | 2% (12) | Maculopapular erythematous eruption that can be associated with pruritus and/or mild eosinophilia | 4–12 days | n/a | Vacuolar interface dermatitis and tissue eosinophilia | Antibiotics (penicillins, cephalosporins, sulfonamides); anticonvulsants | Naranjo score | CBC + Diff (Eosinophils) | IDT–Delayed reading<br>PT<br>Drug Challenge | n/a | n/a | Drug withdrawal<br>Symptomatic treatment♦<br>Treating through |
| AGEP | 1–5/million/ year (17) | Non-follicular sterile pustular rash over widespread erythema, fever and/or biological abnormalities | Hours–2 days (aminopenicillins) +2 weeks | 2–4% (21, 22) | Spongiform subcorneal and/or intraepidermal pustules; perivascular and interstitial infiltrate | Antibiotics (penicillins, cephalosporins); antimycotics; other (diltiazem, oxicam, analgesics) | Naranjo score<br>AGEP validation score | CBC + Diff (Neutrophils) | IDT–Delayed reading<br>PT<br>Drug Challenge♣ | ELISpot<br>LTT | n/a | Drug withdrawal<br>Symptomatic treatment♦ |
| DRESS | 09-2/100,000 (32, 188) | Erythematous urticaria-like or violaceous skin eruption, facial and extremity edema, lymphadenopathy, fever, biological abnormalities and internal organ involvement. | 2–8 weeks (<2 weeks antibiotics and contrast product) | 3–10% (9, 189) | Interface dermatitis with basal vacuolization | Anticonvulsants; antibiotics (sulfonamides, vancomycin, minocycline); allopurinol | Naranjo score<br>RegiSCAR score | CBC + Diff (Eosinophils)<br>Liver panel<br>Renal panel | IDT–Delayed reading<br>PT<br>Drug Challenge♣ | ELISpot<br>LTT | A*32:01 (84) (Vancomycin)<br>B*58:01 (190) (Allopurinol)<br>B*13:01 (191) (Dapsone)<br>A*31:01 (Carbamazepine) | Drug withdrawal<br>Symptomatic treatment♦<br>Systemic glucocorticoids (36)<br>Cyclosporine (40) |
| SJS/TEN | 2–7/million/ year (15) | Skin necrosis, skin detachment (Nikolsky sign) and blistering of the mucous membranes accompanied by serious systemic manifestations | 4–28 days | 30% (47) | Keratinocyte necrosis (partial to full-thickness necrosis of all epidermis layers) | Allopurinol; anticonvulsants; antibacterial sulfonamides; nevirapine; NSAIDs; antituberculosis agents | Naranjo score<br>SCORTEN | CBC + Diff<br>Liver panel<br>Renal panel | PT | ELISpot<br>LTT | B*15:02 (191) (Carbamazepine)<br>B*58:01 (190) (Allopurinol) | Drug withdrawal<br>Supportive wound care (51, 52)<br>IVIG (54)<br>Systemic glucocorticoids and IVIG (55)<br>Cyclosporine (56, 57)<br>TNF inhibitor (58) |

AGEP, acute generalized exanthematous pustulosis; ALDEN, algorithm of drug causality for epidermal necrolysis; CBC, complete blood count; Diff, differential; DRESS, drug reaction with eosinophilia and systemic symptoms; ELISpot, enzyme-linked ImmunoSpot; IDT, intradermal testing, IVIG, intravenous immunoglobulin; LTT, lymphocyte transformation test; MPE, maculopapular exanthema; Naranjo score, the Adverse Drug Reaction (ADR) Probability Scale; PT, patch testing; RegiSCAR, European Registry of Severe Cutaneous Adverse Reactions; SCORTEN, Score of toxic epidermal necrosis; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; TNF, tumor necrosis factor.

♣ In specific cases were investigations provide conclusive results, drug challenge can be considered with less likely or alternative drugs.

♦Symptomatic treatment consists of emollients, moderate to high-potency topical corticosteroid and second generation non-sedating oral antihistamines.

[1]Peter et al. (10); [2]Bigby et al. (12); [3]Sidoroff et al. (17); [4]Saissi et al. (21); [5]Sidoroff et al. (22); [6]Wolfson et al. (32); [7]Muller et al. (188); [8]Kim et al. (9); [9]Chiou et al. (189); [10]Konvinse et al. (84); [11]Hung et al. (204); [12]Zhang et al. (205); [13]Shiohara and Kano (36); [14]Kuschel and Reedy (40); [15]Rzany et al. (48); [16]Sekula et al. (47); [17]Schwartz et al. (51); [18]Seminario-Vidal et al. (52); [19]Huang et al. (54); [20]Micheletti et al. (55); [21]Gonzalez-Herrada et al. (56); [22]Ng et al. (57); [23]Wang et al. (58).





10.3389/fmed.2022.923991

short latency period for AGEP and certain specific clinical characteristics are considered agent specific (24). Case reports have described an association with infections (viral, bacterial or parasitic), spider insect bites and contrast agents (24).

### Management

The main goal is to offer supportive care and to control the skin inflammation and pruritus. Similar to MPE, topical medium potency corticosteroids and second-generation antihistamines are commonly prescribed (25). In a retrospective review of electronic medical records from Singapore of 43 AGEP cases, where 9 (21%) patients were treated with systemic corticosteroids, the use of systemic corticosteroids compared with topical corticosteroids was associated with a reduction in the hospital stay (26). During the acute reaction, a skin biopsy can aid with the identification of the underlying phenotype. While this is not routinely performed for the mild drug eruption or for some of the classic manifestations, the histopathologic findings can support the diagnostic of a drug related reaction particularly in atypical cases or when GPP is suspected (**Table 1**).

## Drug reaction with eosinophilia and systemic symptoms

### Clinical description

Drug reaction with eosinophilia and systemic symptoms or drug-induced hypersensitivity syndrome (DIHS) is a polymorphic erythematous urticaria-like or violaceous skin eruption that can progress to exfoliative dermatitis, facial and extremity edema. Patients can present with lymphadenopathy as well as fever, biological abnormalities and internal organ involvement. It is suggested that reactivation of viruses from the *Herpesviridae* family such as human herpesvirus (HHV)-6, HHV-7, Epstein-Barr virus (EBV), cytomegalovirus (CMV) play a major role in the pathogenesis (27, 28). This condition is characterized by a delayed onset, the time from the drug exposure varying from 2 to 6 weeks (29). Recent reports have described a shorter latency period (less than 15 days) for antibiotics and contrast agents (30). The RegiSCAR is calculated using clinical and laboratory data to estimate the probability of this condition (definite, probable, possible, or no case) (31).

### Epidemiology

There are no large cohort studies or registries for DRESS. Using electronic health records, a recent report calculated the incidence at 2/100,000 (32) and a Spanish pharmacovigilance program described an incidence of 4/10,000 patients (33). The incidence of DRESS is drug and population dependent.

### Drugs

The primary culprit drugs are antibiotics and anticonvulsants (32) as well as allopurinol (34). Recently, other agents such as contrast product have been described (35).

### Management

Drug withdrawal is an essential part of acute management with patients often being restricted in terms of future drug options. The culprit agents and all possible cross-reactive drugs are avoided. As multiple organ involvement is frequent, systemic corticosteroids are usually initiated besides the usual supportive care (36–38). For refractory cases of DRESS with persistent elevated liver function, viral infections should be rule out as possible mimickers include infectious mononucleosis (EBV), CMV, and HIV (39). Case reports and small cases series demonstrate a role for cyclosporine as a second line agent (40, 41). There might be a role for other immunosuppressive agents but no randomized trials have showed a benefit and they are not part of routine management.

## Stevens-Johnson syndrome and toxic epidermal necrolysis

### Clinical description

Stevens-Johnson syndrome and toxic epidermal necrolysis are characterized by skin necrosis, skin detachment (positive Nikolsky sign) and blistering of the mucous membranes accompanied by serious systemic manifestations. The mortality for this condition can reach 30–50% (42). The distinction between SJS and TEN is determined by affected body surface area (BSA): 1–10% for SJS, 10–30% for SJS/TEN overlap and >30% for TEN (10). The time interval from drug exposure to the development of symptoms can vary from 4 to 28 days and in a third of cases no causal agent is identified (29). In the pediatric population, *Mycoplasma pneumoniae* infection has been associated with SJS (43). A clinical score (SCORTEN) can be calculated to indicate prognostic value (44). The ALDEN score is an algorithm that helps identify the most likely culprit drug based on criteria such as type of drug, timing and possible alternative causes (45, 46). An ALDEN score of 4 or more is usually required for the SJS/TEN phenotype.

### Epidemiology

The incidence of SJS/TEN is estimated at 2–7 cases per million people per year using a German population based-registry with an increase prevalence of SJS cases compared to TEN (47, 48). Recently, data from the FDA adverse event reporting system (FAERS) indicated a rate of 0.15% with 30,202 reactions among the 20,406,852 adverse drug events reported in the database (49). In lower- and middle-income countries where

TB and HIV are more prevalent, the rates of SJS/TEN are up to 10-fold higher (10).

### Drugs

The agents most commonly implicated are allopurinol, anticonvulsants and antibiotics (50). However, in about one third of cases, a drug cannot clearly be associated with the development of the SJS/TEN (46).

### Management

Following drug withdrawal and avoidance of cross-reactive medications, for SJS/TEN, given the multiorgan involvement, various specialties must be involved in the acute setting such as ophthalmology, head and neck, gastroenterology, gynecology, etc. Patients are usually transferred to burn units in order to be able to receive the adequate wound care, nutritional and fluid support (51, 52). The role of adjunctive therapies is unclear at this time with the use of systemic corticosteroids being controversial (47). While reports on mortality show contradictory results, a meta-analysis regrouping 1,209 patients indicated a benefit with corticosteroid treatment (decreased mortality) compared to supportive treatment alone (53). Intravenous immunoglobulins (IVIG), while part of the management in various centers, have an unclear clinical benefit (54). The combination of systemic corticosteroids and IVIG seems to be associated with the lowest mortality rates compared to each treatment alone (55). Cyclosporine has also been used with promising results in terms on mortality reduction (56, 57). Considering the high mortality rate for this condition, novel therapies are required. Recent studies have shown a possible benefit in the acute phase of the disease following the use of TNF-alpha inhibitors such as etanercept. These agents improved skin healing and decreased mortality as estimated by predictive scores (58).

## Generalized bullous fixed drug eruption

### Clinical description

The generalized bullous fixed drug eruption (GBFDE) is considered a rare type of fixed drug eruption that is multifocal and widespread, characterized by sharply defined bullae at the same site following recurrent administration of offending drug (59). The skin surface under the large flaccid bullae is often widespread red or brown (59). Systemic symptoms such as fever and arthralgias have also been described. The main differential diagnosis for this condition is SJS/TEN but GBFDE has a milder course with rapid skin healing in absence of scarring following drug discontinuation (60, 61).

### Epidemiology

While fixed drug eruption (FDE) has been commonly described with an incidence of 14–22% (61), the incidence of GBFDE is unknown at this time.

### Drugs

Fixed drug eruption has been associated with numerous drugs from antibiotics to analgesics and NSAIDS as well as sedatives (61). In a cohort of 48 GBFDE cases, the mean time to disease after drug administration was 2.9 days and the suspected drugs varied from antibiotics to analgesics and NSAIDS (59).

### Management

As for all the previously described conditions, the main treatment is culprit drug removal followed by symptomatic management to decrease pain or related pruritus (61). A biopsy excluding alternative cause (e.g., SJS/TEN, TEN-like lupus and immunobullous disease such as bullous pemphigoid, linear IgA disease) is required. The biological marker granulysin has been shown to help differentiate SJS/TEN from other conditions (62). While the aim of this review is to present diagnostic tools, the GBFDE has been presented as part of the differential diagnostic for SJS/TEN and will not discussed in detail in the subsequent sections.

# Diagnostic tools

## History and drug timeline

A detailed clinical history is crucial to diagnose drug-related reactions. For beta-lactam allergy, it has been demonstrated that beta-lactam allergy interviews, in absence of skin testing, can assist in ruling out an allergy and reduce the use of non-beta-lactam antibiotics such as fluoroquinolones, considered high-*Clostridioides difficile* infection-risk antibiotics (63, 64). However, this has been infrequently deployed in moderate to severe presumed T-cell mediated reactions.

Following a detailed history, assessing the temporal association between symptoms and drug exposure with the help of a drug timeline is crucial. Any drug started more than 6–8 weeks before the reaction is less likely to be causal (65). The drug half-life must also be considered. SJS/TEN reactions associated with drugs that have a long half-life (more than 20 h) have been associated with an increase in mortality (26%) compared to drugs with shorter half-life (5% mortality) (66). This suggests that the time of drug discontinuation is also important. Using validated causality scores such as the Naranjo score can help guide clinicians in identifying the culprit agents. All agents administered must be considered causal with recent reports showing that T-cell mediated reactions can rarely occur after the administration of agents such as proton pump

inhibitors (67) or anti-histamine receptors such as ranitidine (68). Among the agents commonly used in the hospital setting, contrast agents are often reported to be culprit (69, 70). The nursing and the pharmacy team can provide valuable assistance with identifying the agents for the drug timeline. Further, the pharmacy team can assist with pharmacovigilance researches by exploring existing databases (71).

## *In vivo* allergy assessment tools

### Intradermal testing

Previous prospective studies and both international and local allergy society guidelines support the use of skin prick and intradermal testing (IDT) for drug allergy assessment (72–80). The concentration administered is designed to cause the least amount of irritation as per published guidelines (72, 74, 81–83), although validated concentrations for T-cell mediated reactions are less well described. Further, the true concentrations required to induce a positive T-cell response are unknown with recent studies showing that the use drugs such as vancomycin at the highest non-irritating concentrations are not enough to evoke a T-cell mediated reaction at the injection site (84). All the agents used are usually approved by local health regulations and have been safely administered via the intradermal route (77, 85–89). However, the sensitivity and specificity of skin tests are not validated for non-immediate reactions and, apart from penicillin, there are no current standardized extracts for skin tests.

Intradermal testing implies that a small quantity (0.02–0.05 mL) of a drug at a non-irritant concentration is gently injected under the skin. The testing is usually performed on the volar surface of the forearm and it is recommended to keep sufficient space (approximately 2–2.5 cm) between each injected agent. The preferred area is 5 cm from the wrist and 3 cm from the antecubital fossa. An immediate reading is performed after 15–20 min and a delayed reading after 24–48 h. A positive reaction translates as erythema and a local reaction when compared with the injection of a negative control, usually saline. A histamine prick test is used as a positive control for immediate reactions and several medications such as antihistamines have been identified as being able to suppress this local reaction. In this context, all drug known to affect the skin testing should be stopped depending on the described duration of suppression. There is no positive control for delayed reactions.

For penicillin non-severe allergic reactions, performing testing with the major allergenic determinant (penicilloyl polylysine), a minor determinant mixture (penicillin G, penicilloate, penilloate), and amoxicillin translated to a negative predictive value of 97.9% (90) for immediate reactions. There is currently a clear recommendation for skin testing followed by challenge for pregnant women with a history of penicillin allergy considering the importance of a beta-lactam treatment for *Group B Streptococcus* (91–93). In a cohort of children with low risk beta-lactam delayed-type reactions, delayed IDT was considered a useful tool (94).

There is a clear role for delayed IDT reading in delayed reactions to penicillin with evidence showing that delayed reading would have identified an additional 25% of patients in a prospective cohort of 37 patients (95). Furthermore, there is increasing evidence that IDT is safe even for the severe delayed phenotypes (96, 97). Cases of disease reactivation with mild isolated skin symptoms following skin testing have been described, especially when the testing was performed in the first 4–6 weeks following the acute reaction (98). The sensitivity of delayed IDT for antimicrobials ranges from 40% (96, 99) to 56% (98) for the severe phenotypes, excluding SJS/TEN (**Table 2**). However, the specificity and the false positive rate are not known.

### Patch testing

In patients considered sensitized or allergic, antigen specific T-cells can be found on the surface of the skin. By applying non-irritant drug allergen concentrations under occlusion on the intact skin, patch testing (PT) aims to reproduce in the small limited area of the test the original delayed reaction. The PT is usually applied on the back or lateral upper arm area. There is no positive control that has been used with PT but the testing uses a negative control such as petroleum gel. Patch testing is usually left in place for a duration of 48 h with some studies showing benefit of performing a 7-day reading especially for certain preservatives (100). This is a time-consuming process as patients are asked to avoid showers and an increase in heat/humidity.

Non-irritant concentrations of various drugs for use in patch testing have been established (101, 102). However, there are currently no international guidelines for PT preparation as to ensure the quality of the products with large differences in active ingredient concentrations when using commercially available pure drugs compared with commercialized forms (103). Some alternatives for the classic PT method have been provided such as the scratch-patch involving the scarification or stripping of the epidermis with specialized tapes prior applying the PT (104). While this method proved to be non-irritant compared to the PT, carefully consideration is required especially for the severe phenotypes such as SJS/TEN. Indeed, cases of disease reactivation following PT have been reported in the literature, particularly in the immunosuppressed population (105).

The current published clinical studies underline a low sensitivity of this tool while the specificity is elevated, favoring a role of this tool for the more severe immune-mediated hypersensitivity reactions (102, 106, 107) (**Table 3**). Another advantage of this tool, compared to the IDT, is the possibility to use non-sterile and oral drug formulations. It is also interesting to note that the positivity of this tool seems to depend on the assessed drug as well as the reported reaction (108). In the clinical setting, considering this low reported sensitivity, lack of a validated positive control and less than 100% negative predictive value, removal of the allergy label should not be

TABLE 2 Recent reported sensitivity and specificity for delayed intradermal testing in drug allergy.

| Reference | Study | Patients | Conditions | Drug Category | Sensitivity | Specificity |
|---|---|---|---|---|---|---|
| Fransson et al. (95) | Prospective | 57 | MPE | Antibiotics | 25% | n/a |
| Copaescu et al. (98) | Prospective | 69 | MPE<br>AGEP<br>DRESS<br>GBFDE<br>SJS | Antibiotics | 46% | n/a |
| Trubiano et al. (157) | Prospective | 32 | MPE<br>AGEP<br>DRESS | Antibiotics | 56% | n/a |
| Nakkam et al. (192) | Prospective | 15 | DRESS | Vancomycin | n/a | n/a |
| Konvinse et al. (84) | Retrospective | 23 | DRESS | Vancomycin | 33% | n/a |
| Trubiano et al. (96) | Prospective | 31 | FDE<br>AGEP<br>DRESS<br>SJS/TEN | Antibiotics | 42% | n/a |
| Romano et al. (193) | Prospective | 214 | MPE<br>AGEP<br>Bullous exanthema<br>TEN | Antibiotics | 97% | n/a |
| Buonomo et al. (194) | Retrospective | 97 | MPE | Antibiotics | 95% | n/a |
| Cabanas et al. (99) | Retrospective | 3 | DRESS | Antibiotics | 100% (3/3) | n/a |
| Barbaud et al. (102) | Prospective | 4 | DRESS | Antibiotics | 3/4 | n/a |

AGEP, acute generalized exanthematous pustulosis; DRESS, drug reaction with eosinophilia and systemic symptoms; GBFDE, generalized bullous fixed drug eruption; MPE, maculopapular exanthema; n/a, non-applicable; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

performed following a negative PT. In the pediatric population, while the literature is very limited, the sensitivity seems to be lower compared to the adult population (94). A positive PT should help confirm an immunologic mechanism with studies showing an increased reproducibility with positive PT not been affected by the time interval between testing, sex or age (111, 112). However, this is still dependent on the drug and the use of patch testing, IDT and *ex vivo/in vitro* testing and genetic testing are likely to be complementary (109, 110).

## Drug ingestion challenge test

Several protocols have been suggested for challenge testing in non-severe delayed reactions: (1) single step direct challenge (113–115), (2) 2-step graded challenge (116), (3) single or multiple step challenge following negative delayed intradermal skin testing/patch testing (117–120), (4) direct multiple days challenge or (5) multiple days challenge following negative skin testing (117, 121). In absence of an immediate objective reaction, the "immediate" protocols have often led to the removal of the allergy label even in the context on a reported delayed reaction.

The benefits of penicillin allergy assessment based on clinical history (in person or telemedicine visit) (122, 123), skin testing (124) and challenge have been demonstrated in various studies in recent years (122, 125). Furthermore, for the non-severe delayed reactions such as MPE, algorithms based on direct challenge (with no prior skin tests) are considered a safe and cost-effective option (64, 126–129). However, currently, there are no clear guidelines on the optimal assessment tools for these low risk penicillin allergies with a need to compare skin testing followed by oral challenge, if negative, to direct oral challenge. Pharmacist led protocols have been instrumental in providing safe and rapid in hospital delabeling (130–132). This literature has evolved from pediatric penicillin and aminopenicillin allergic cohorts, where direct challenge without skin testing is considered part of standard of care (133–135). In these non-severe cases, the presence of an underlying immune mechanism is unclear and the majority of the skin isolated drug eruptions could be related to a non-allergic condition such as a viral illness or a drug-viral interaction (13). For the pediatric population, there is a need to develop clinical decision scores that can be used outside the allergy clinic assessment as to allow improvement of antibiotic stewardship.

While the literature provides interesting evidence for the non-severe reactions, strict drug avoidance is still part of the recommendations for the severe phenotypes associated with an increased mortality (16, 65). In these cases, the use of structurally non-related drugs in recommended. In particular

TABLE 3 Recent reported sensitivity and specificity for patch testing in drug allergy.

| Reference | Study | Patients | Conditions | Drug category | Sensitivity | Specificity |
|---|---|---|---|---|---|---|
| Gilisen et al. (107) | Retrospective | *N* = 9 | MPE (6)<br>AGEP (2)<br>DRESS (1)<br>*Healthy (78) | Clindamycin | 100% | 100% |
| Prasertvit et al. (195) | Retrospective | *N* = 20 | HIV NVP hypersensitivity (20)<br>*Healthy (15) | Nevirapine (NVP) | 10% | 100% |
| Ben Mahmoud et al. (192) | Retrospective | *N* = 20 | MPE (11)<br>DRESS (6)<br>SJS (2)<br>FDE (2)<br>Erythroderma (2) | Antiepileptics | 95% | n/a |
| Atanaskovic-Markovic et al. (94) | Prospective | *N* = 57 (pediatric) | MPE (57) | Antibiotics | 32% | n/a |
| Hassoun-Kheir et al. (106) | Prospective | *N* = 25 | MPE (13)<br>SJS (4)<br>DRESS (3)<br>AGEP 1<br>FDE (2)<br>Vasculitis (1)<br>SDRIFE (1)<br>*Healthy (25) | Antibiotics<br>Antiepileptics | 32% | 92% |
| Buonome et al. (194) | Retrospective | *N* = 97 | Delayed Reactions | Antibiotics | 100% | n/a |
| Cabanas et al. (99) | Retrospective | *N* = 8 | DRESS (8) | Piperacillin-Tazobactam | 1/4 (25%) | n/a |
| Barbaud et al. (102) | Prospective | *N* = 134 | DRESS (72)<br>AGEP (45)<br>SJS/TEN (17) | Antibiotics<br>Corticosteroids<br>Antiepileptics<br>Other agents | 57% | n/a |

AGEP, acute generalized exanthematous pustulosis; DRESS, drug reaction with eosinophilia and systemic symptoms; FDE, fixed drug eruption; HIV, Human immunodeficiency virus; MPE, maculopapular exanthema; n/a, non-applicable; SDRIFE, Symmetrical drug-related intertriginous and flexural exanthema; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis. *Indicated the total number of patients.

scenarios such as reported in a South African study with anti-tuberculosis drugs, drug re-challenge with empirically initiated intravenous corticosteroids following the first clinical signs has been associated with a majority of mild to moderate reactions (136, 137). There is also evidence that *ex vivo* assays such as the enzyme-linked immunoSpot (ELISpot) could help risk stratify patients providing diagnostic accuracy compared to the current gold standard, the drug ingestion challenge (138). Large, multi-center international studies are required to further characterize drug re-challenge as a tool to provide optimal drug treatment following *in vivo* and *ex vivo* testing.

## *Ex vivo* tools

### Lymphocyte transformation test

The lymphocyte transformation test (LTT) has been widely used for past 30 years and is considered the forefather of *ex vivo* testing in drug allergy (139). It is reported that patient isolated memory T-cells can be stimulated with causal agents leading to a drug-specific T-cell proliferation. Because of this mechanism, the LTT is also addressed as a lymphocyte proliferation test of a lymphocyte stimulation or activation test (140). This cell proliferation is defined according to a stimulation index (SI) or the proportion between the drug stimulated lymphocytes and the background lymphocyte proliferation. This ratio aims to take into consideration the biological variation. For the classic LTT, it is calculated based on a radioactive uptake marker directly proportional to the degree of T-cell proliferation in response to a drug antigen (140). In recent years, variations of the LTT platform have been proposed in the literature.

The reported sensitivity of LTT in delayed hypersensitivity reactions ranges from 27% (141) to 74% (142) and specificity was quoted as 85–100% (141–144) (**Table 4**). When this tool was studied for a specific phenotype, its accuracy greatly improved. For example, in a cohort of 41 DRESS patients, the reported sensitivity was 73% and the specificity was 82%, using samples from a recovery phase and not an acute phase (145). Further, the sensitivity can vary depending on the drug studied and expression of either granulysin, granzyme B or IFN-γ. In a cohort of 63 patients with SCAR associated to the use of anti-epileptics, the sensitivity increased when using granulysin-based lymphocyte activation tests stimulated with carbamazepine (73.9%). Other experimental techniques to increase the sensitivity of this tool have been described such CTLA-4 blocking of lymphocytes, demonstrating the importance of T-cell regulatory pathways (146, 147).

TABLE 4 Reported cases and cohorts showing clinical advantage with the use of the LTT.

| Author | *N* | Country | Phenotypes | Drug(s) | Controls | Sensitivity | Specificity |
|---|---|---|---|---|---|---|---|
| Cabanas et al. (145) | 41 | Spain | DRESS | Antibiotics<br>Anticonvulsants<br>Antifungals | n/a | 73% | 82% |
| Suthumchai et al. (155) | 23 | Thailand | DRESS (9)<br>AGEP (4)<br>SJS/TEN (10) | Allopurinol<br>Anticonvulsants<br>Antibiotics<br>Other* | Non-allergic individuals (20) | 52% | n/a |
| Ye et al. (196) | 8 | South Korea | MPE<br>DRESS | Isoniazid or rifampicin | n/a | 100% | n/a |
| Haw et al. (159) | 16 | UK | MPE (7)<br>DRESS (5)<br>SJS (3)<br>SJS/TEN (1) | Antibiotics<br>Anticonvulsants<br>Antifungals | n/a | 78% | n/a |
| Sun et al. (150) | 57 | China | MPE | Antituberculosis drugs | Control group (96) | 23–58% | 93–98% |
| Meller et al. (197) | 22 | Germany | MPE | Pegylated interferon | Control group (7) | 23% | 100% |
| Porebski et al. (144) | 23 | Poland | MPE | Anticonvulsants | Control group (24) | 30% | 100% |
| Cabanas et al. (99) | 8 | Spain | DRESS | Piperacillin-Tazobactam | n/a | 100% | n/a |
| Porebski et al. (141) | 15 | Poland | SJS | Antibiotics<br>Anticonvulsants | Control group (18) | 27% | 95% |

Case reports were excluded from this table. AGEP, acute generalized exanthematous pustulosis; DRESS, drug reaction with eosinophilia and systemic symptoms; FDE, fixed drug eruption; MPE, maculopapular exanthema; n/a, non-applicable; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis. *Other drugs included tramadol, ibuprofen, and mefenamic acid.

The value of this test was exemplified in various cohort studies and case reports where this tool provided clinical assistance in determining the optimal drug options in both a pediatric (148, 149) and an adult population (141, 150). However, some of these cases can be subject to misclassification bias as the initial reported phenotype was not always consistent with a hypersensitivity reaction (148).

## Enzyme-linked immunoSpot assay

The T-cell ELISpot assays measuring IFN-γ cytokine response to different agents has been used to assist drug hypersensitivity causality investigations in patients with drug allergy (143, 151–154). Compared to LTT, in an adult cohort of 23 SCAR patients, the ELISpot IFN-γ helped identify more drug-specific IFN-γ releasing cells (155). Similar to LTT, this laboratory technique requires viable well-preserved patient T lymphocytes and involves the use of complex manipulations for which an operator-dependent variability could influence the assay results.

In general, standardized concentrations for *ex vivo* diagnostics can be based on confirmatory data from performed cytotoxicity assays (97, 156). However, various studies using non-studied concentrations have been published. Given that antibiotics are a major culprit for SCAR, these agents have been commonly used for the ELISpot assays (98, 157, 158). Other commonly reviewed agents are anticonvulsants, antituberculosis drugs and allopurinol (141, 155, 158, 159).

Depending on the used definition and the studied drugs, the sensitivity of this assay varied from 35% (158) to 86% (84, 160) with a reported specificity of 100% (**Table 5**). As very few cohort studies from specialized centers are available, there is a need to further explore this promising *ex vivo* method. In the pediatric population, an interesting study regrouping a cohort of 9 SCAR and 7 MPE compared LTT with ELISpot in both an acute and post-recovery phase. The authors showed the ELISpot assay using IFN-γ and IL-4 as cytokine outputs, produced a higher drug-specific response contributing to the diagnosis of the culprit drugs (159). However, the sample size is relatively small and hence results are non-conclusive at this point.

The increase in serum level of the IFN-γ cytokine in conditions such as MPE and SJS/TEN has been previously documented (161). But other cytokines have been identified such as IL-8, IL-17, and IL-22 in AGEP (162–164), IL-4, IL-5, IL-13, and TARC In DRESS (165, 166) and IL-15 in SJS/TEN (167, 168). This provides relevance for possible outputs to explore in functional assays as to increase the sensitivity of these tools.

## Genetic testing

There have been an increasing number of HLA associations described with many drugs and SCAR (**Table 6**). Some examples include HLA-B*57:01 screening prior prescription of the anti-retroviral drug abacavir (169–171) and HLA-B*15:02 screening before carbamazepine prescription in many South-East Asian countries where this allele is prevalent (172, 173). A study from Thailand reported that 21.2% of SCAR could have been prevented by screening for HLA-B alleles prior to drug exposure (158). Recently, studies have reported that DNA methylation, identified using genome-scale methylation

TABLE 5 Reported cases and cohorts showing clinical advantage with the use of the ELISpot.

| Author | *N* | Country | Phenotypes | Drug(s) | Controls | Sensitivity | Specificity | Conclusions |
|---|---|---|---|---|---|---|---|---|
| Copaescu et al. (98) | 63 | Australia | MPE (17)<br>AGEP (5)<br>DRESS (34)<br>SJS (5)<br>TEN (1)<br>GBFDE (1) | Antibiotics | Tolerant controls (5) | 54% | 100% | IFN-γ positive in 34/63 (≥50 SFU/$10^6$) |
| Trubiano et al. (157) | 12 | Australia | DRESS (3)<br>AGEP (3)<br>MPE (6)<br>B-lactams | Antibiotics | n/a | 42% | n/a | IFN-γ positive in 5/12 (≥50 SFU/$10^6$) |
| Klaewsongkram et al. (158) | 116 | Thailand | DRESS (50)<br>AGEP (16)<br>SJS/TEN (50) | Antibiotics<br>Allopurinol<br>Antituberculosis drugs<br>Anticonvulsants | Non-allergic control drugs from 62 SCAR patients | 35% | n/a | IFN-γ positive in 19/50 DRESS, 4/16 AGEP and 18/50 SJS/TEN (>95% CI controls SFCs) |
| Konvinse et al. (84) | 23 | United States | DRESS (14) | Vancomycin | n/a | 86% | n/a | IFN-γ positive in 12/14 (≥50 SFU/$10^6$) |
| Suthumchai et al. (155) | 23 | Thailand | AGEP (4)<br>DRESS (9)<br>SJS/TEN (10) | Allopurinol<br>Anticonvulsants<br>Antibiotics<br>Other* | Non-allergic control (20) | 70% | n/a | IFN-γ positive in 17/23 (>18 SFU/$10^6$) |
| Trubiano et al. (97) | 19 | Australia | AGEP (2)<br>DRESS (14)<br>SJS (2)<br>TEN (1) | Antibiotics | Tolerant controls (16) | 52% | 100% | IFN-γ positive in 10/19 patients and 0/16 controls (>50 SFU/$10^6$) |
| Xiong et al. (198) | 1 | China | SJS (1) | Sulphapyridine | n/a | n/a | n/a | IFN-γ positive (300 spots/$10^6$) |
| Trubiano et al. (199) | 1 | Australia | TEN (1) | Teicoplanin | n/a | n/a | n/a | IFN-γ positive (≥50 SFU/$10^6$) |
| Ye et al. (196) | 8 | South Korea | MPE (4)<br>DRESS (4) | Antituberculosis drugs | n/a | 63% | n/a | IFN-γ and GrbB positive (>0 Spots/$10^4$ cells) for T-cell clones with reactivity for INH/RFP (5/8) |
| Kato et al. (200) | 16 | Japan | MPE (1)<br>DRESS (5)<br>EM-like (7)<br>SJS/TEN (3) | Allopurinol<br>Antibiotics<br>Anticonvulsants<br>Celecoxib | n/a | 19% | 100% | IFN-γ positive in 3/16 patients |
| Haw et al. (159) | 16 | UK | MPE (7)<br>DRESS (5)<br>SJS/TEN (4) | Antibiotics<br>Antifungals<br>Anticonvulsants | n/a | IFN-γ: 77%<br>IL-4: 85% | n/a | IFN-γ positive in 14/18 patients<br>IL-4 positive in 11/13 patients |
| Klaewsongkram et al. (201) | 24 | Thailand | DRESS (13)<br>SJS/TEN (11) | Allopurinol | Controls (21) | 71% | 95% | IFN-γ positive in 15/24 (>16 SFU/$10^6$) and 1/21 controls |
| Porebski et al. (144) | 23 | Poland | MPE (23) | Anticonvulsants | Tolerant controls (24) | GrB: 55%<br>Grl: 39.1% | 100% | GrB positive in 12/22 (SFU > 50)<br>Grl positive in 9/22 |
| Lucas et al. (202) | 12 | Australia | Abacavir HSR<br>HLA-B*57:01 Positive | Abacavir | HLA-B*57:01 + Abacavir naive (3), HLA B*57:01 tolerant (15) or Abacavir naïve (9) | 100% | 97–100% | IFN-γ positive in 12/12 (>10 SFU$10^6$) and 0/3, 1/15 and 0/9 controls |
| Ben-Said et al. (13) | 21 | France | DRESS (9)<br>MPE (12) | Antibiotics | n/a | 71% | n/a | IFN-γ positive in 9/9 DRESS and 6/12 MPE |
| Keane et al. (203) | 19 | Australia | Nevirapine HSR | Nevirapine | n/a | 40% | n/a | Nevirapine-specific responses were detected in 4/12 (>100 SFU/$10^6$) |
| Tanvarasethee et al. (204) | 25 | Thailand | MPE (15) | Cephalosporins | Non-allergic controls (20) | 24% (IFN-γ or IL-5)<br>40% (IFN-γ and IL-5) | 100% | IFN-γ and IL-5 positive in 10/25 (mean > 20 SFU/$10^6$) |
| Porebski et al. (141) | 15 | Switzerland | SJS/TEN (15) | Allopurinol (1)<br>Anticonvulsants (9)<br>Sulfonamide (4)<br>Mefenamic acid (1) | Drug-exposed controls (18) | GrB: 33%<br>Grl:40% (NKp46+)<br>Grl: 53% (CD3+CD4+) | 95–100% | GrB positive in 5/15 patients<br>Grl positive in 6/15 (NKp46+) patients and 8/15 (CD3+CD4+) |

*(Continued)*

TABLE 5 (Continued)

| Author | *N* | Country | Phenotypes | Drug(s) | Controls | Sensitivity | Specificity | Conclusions |
|---|---|---|---|---|---|---|---|---|
| Phatharacharukul et al (205) | 1 | Thailand | DRESS (1) | Sulfasalazine | n/a | n/a | n/a | IFN-γ positive (1 048 SFU/$10^6$) |
| El-Ghaiesh et al. (160) | 8 | UK | Piperacillin HRS (8) | Piperacillin | Tolerant controls (5) | 87–100% | 100% | IFN-γ positive in 8/8 (>10 SFU/$10^6$); 7/8 (>30 SFU/$10^6$) |
| Bensaid et al. (152) | 1 | France | DRESS (1) | Amikacin | n/a | n/a | n/a | IFN-γ positive (213 SFU/$10^6$) |

AGEP, acute generalized exanthematous pustulosis; DRESS, drug reaction with eosinophilia and systemic symptoms; ELISpot, enzyme linked ImmunoSpot; EM, erythema multiforme; GBFDE, generalized bullous fixed drug eruption; GrB: Granzyme B; Grl, granulysin; HSR, hypersensitivity; MPE, maculopapular exanthema; n/a, non-applicable; SFU, spot forming unit; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis. *Other drugs are tramadol, ibuprofen (2) and mefenamic acid.

TABLE 6 Human leukocyte antigen (HLA) associations in delayed drug hypersensitivity.

| Author (year) | Drug | HLA | Phenotype | Ethnicity | Screening | NPV (%) | PPV (%) | NNT |
|---|---|---|---|---|---|---|---|---|
| Mallal et al. (206) | Abacavir | B*57:01 | AB HS | Caucasian (5–8%)<br>African/Asia (<1%)<br>African American (2.5%) | **Routine screening** HIV Positive patients | 100 | 55 | 13 |
| Chung et al. (62) | Carbamazepine | B*15:02[c] | SJS/TEN | Han Chinese (10–15%)<br>Koreans, Japanese (<1%)<br>European Ancestry (<0.1%) | **Routine screening** in Southeast Asian countries | 100 | 3 | 1000 |
| Hung et al. (190) | Allopurinol | B*58:01 | SJS/TEN<br>DRESS | Han Chinese (9–11%)<br>European ancestry (1–6%) | Selective screening[b] | 100 | 3 | 250 |
| Zhang (191) | Dapsone | B*13:01 | DRESS | Papuans/Australian aborigines (28%)<br>Chinese (2–20%)<br>Japanese (1.5%)<br>Indian (1–12%)<br>African and African American (<2%) | **Routine screening** for leprosy patients in countries with increased prevalence | 99.8 | 7.8 | 84 |
| Konvinse et al. (84) | Vancomycin | A*32:01 | DRESS | European ancestry (6.8%)<br>African American (4%)<br>Southeast Asian (<1.5%) | Pre-emptive[a] | 99.99 | 0.51 | 75 |

AB HS, abacavir hypersensitivity syndrome; HIV, human immunodeficiency virus; NNT, numbers needed to test (to prevent one case); NPV, negative predictive value; PPV, positive predictive value. [a]HLA-A*32:01 testing could have a role in determining the culprit drug (vancomycin) when multiple drugs are implicated in a delayed hypersensitivity reaction. [b]The American College of Rheumatology has recommended preventive screening for patients of Korean ethnicity with chronic kidney disease stage 3 or worse and patients of Han Chinese or Thai ethnicity irrespective of renal function before starting allopurinol (207). [c]Other described alleles: HLA-B*15:21, HLA-B*15:11, and HLA-B*15:18.

analysis, might play a role in allopurinol SJS/TEN (174). The presence of HLA-B*58:01 is considered a predisposing factor for developing allopurinol/oxypurinol induced SCAR in Southeast Asian populations but not in European and African ancestry populations (175).

Vancomycin induced DRESS was associated with the expression of HLA-A*32:01 (84) and evidence shows that vancomycin directly interacts with naïve T-cells expressing HLA-A*32:01 (176). In the Thai population, HLA-B*15:02, HLA-C*06:02, HLA-C*08:01, and HLA-B*13:01 were associated with co-trimoxazole hypersensitivity reactions and mostly SJS/TEN (177, 178). Dapsone and its reactive metabolite, nitroso dapsone, induced hypersensitivities such as DRESS in individuals with HLA-B*13:01 (179, 180). Carbamazepine triggered SCAR, was linked to HLA-A*31:01 in Caucasian and Japanese populations (181). Following genome-wide association studies, HLA-B*57:01 and HLA-B*57:03 were reported in patients with drug-induced liver injury caused by flucloxacillin (182, 183) and (HLA)-DRB1*01:01 has been associated with nevirapine-induced hepatic hypersensitivity reactions (184). Anti-osteoporotic agents induced SJS were suggested to be associated with HLA-A*33:03 (185).

However, genetic screening is not currently integrated in routine practice and a comprehensive description of the current identified genetic markers is beyond the scope of this review. The biggest concern with HLA screening for many drugs is the fact that HLA risk is necessary but not sufficient for the development of the hypersensitivity in question. In many cases this means that an extremely high number of patients would need to be tested in order to prevent one case of hypersensitivity and hence this is not a cost-effective confirmatory test. However, there could be scenarios where HLA testing could be used beyond screening and could have a diagnosis role such as the

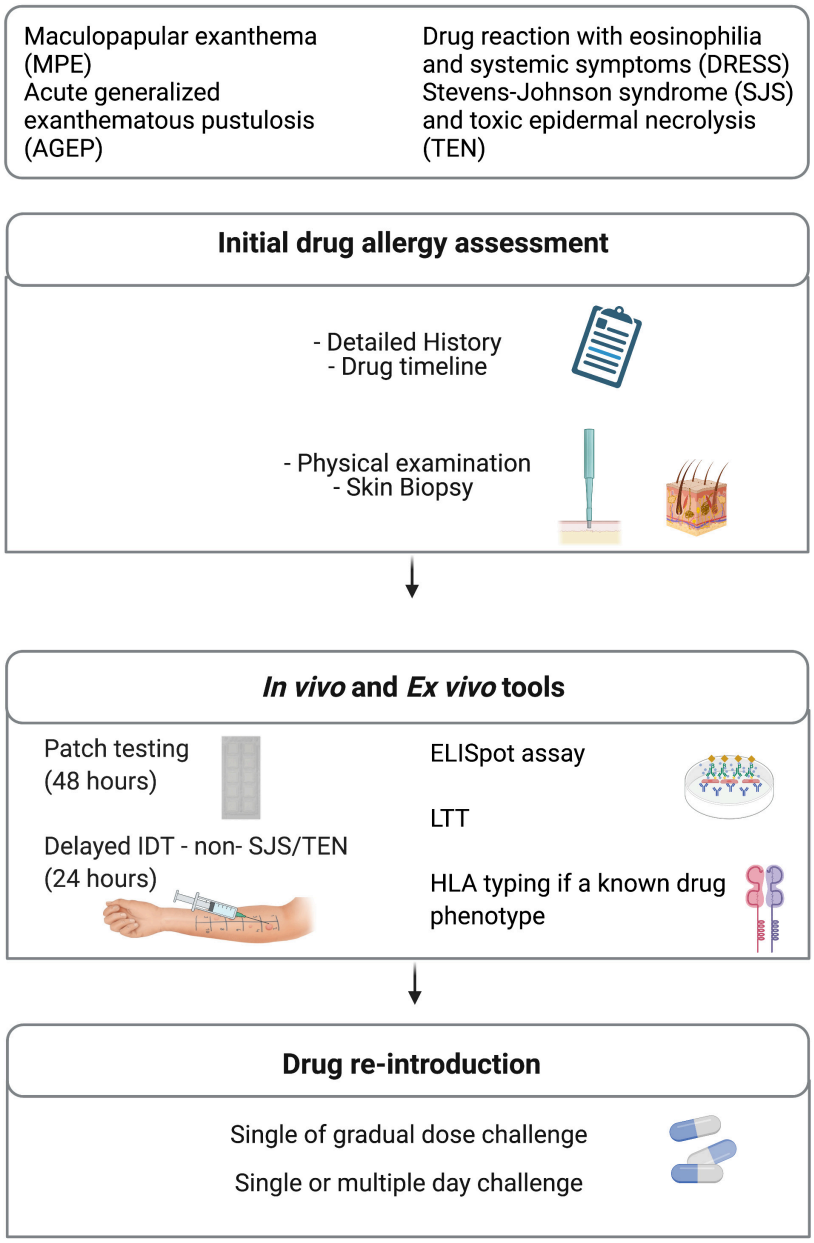


FIGURE 3
Diagnostic management. ELISpot, enzyme-linked immunoSpot; HLA, human leukocyte antigen; IDT, intradermal testing; LTT, Lymphocyte transformation test.

HLA-A*32:01 testing for vancomycin DRESS in the setting of multiple implicated drugs.

## Lessons learned from *in vivo* and *ex vivo* drug diagnostic tools

Drug allergy labels have important impact on patient care by limiting not only the use of appropriate medications but also by increasing costs and quality of patient care (10, 124, 186). A multidisciplinary patient-centered risk/benefit-based assessment must be part of the management plan (Figure 3). What is the optimal management for the patient's acute condition? What is the reported reaction or described phenotype and what was the most likely causal drug? If the culprit drug is stopped, are there any other drug alternatives available for the patient? Another important inquiry often unexplored is regarding the patient's willingness to take the medication or alternative drugs again. Unfortunately, the clinical investigations can sometimes be limited by the patient's

refusal of *in vivo* investigations. In this scenario, *ex vivo* tools are appealing as the safety of the procedure can be guaranteed (**Figure 3**). However, as discussed, these tools are not available in the majority of health facilities. Another limit of these tools is their lack of validity. It is possible that the low sensitivity of these diagnostic tools is due to the fact that current assays rely on drug or drug metabolites that are not effectively recognized by the immune system (187). Also, considering that none of these diagnostic tools have a 100% negative predictive value, their use should aim to complement each other as to improve the sensitivity and the specificity of the diagnosis.

There is a current need to provide internationally accepted management algorithms for *in vivo* and *ex vivo* diagnostic tools and/or challenge while understanding the possibility that these algorithms might not apply to all phenotypes. The currently available tools must be prospectively used as to allow safe drug re-introduction.

## Conclusion

Despite the increased mortality associated with SCAR, diagnostic tools remain limited and unstandardized. Ongoing research is required to better understand the epidemiology, the diagnostic approach and management strategies for these delayed drug reactions. Furthermore, large scale studies validating clinical diagnostic tools used for DHR are required.

## Author contributions

AC performed the literature review and wrote the manuscript text with supervision from MB-S and JT. All authors reviewed the manuscript, made a substantial, direct, and intellectual contribution to the work, and approved the manuscript for publication.

## Funding

AC receives support from The Montreal General Hospital Foundation and The Research Institute of the McGill University Health Centre (RI-MUHC) and was awarded University of Melbourne Research Scholarship, The Anna Maria Solinas Laroche Career Award in Immunology, and the Anita Garbarino Girard, Anna Maria Solinas, Dr. Phil Gold Award of Distinction. JT was supported by the Austin Medical Research Foundation and by a National Health and Medical Research Council postgraduate scholarship (GNT 1139902).

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

## References

1. Pichler WJ. Immune pathomechanism and classification of drug hypersensitivity. *Allergy.* (2019) 74:1457–71. doi: 10.1111/all.13765

2. Trubiano JA, Aung AK, Nguyen M, Fehily SR, Graudins L, Cleland H, et al. A comparative analysis between antibiotic– and nonantibiotic-associated delayed cutaneous adverse drug reactions. *J Allergy Clin Immunol Pract.* (2016) 4:1187–93. doi: 10.1016/j.jaip.2016.04.026

3. Greenberger PA. Drug allergy. *Allergy Asthma Proc.* (2019) 40:474–9. doi: 10.2500/aap.2019.40.4275

4. Iulini M, Maddalon A, Galbiati V, Marinovich M, Corsini E. In vitro identification of drugs inducing systemic hypersensitivity reactions known in vivo to be associated with specific HLA genotypes. *Toxicol In Vitro.* (2020) 68:104953. doi: 10.1016/j.tiv.2020.104953

5. Nakajima A, Oda S, Yokoi T. Allopurinol induces innate immune responses through mitogen-activated protein kinase signaling pathways in HL-60 cells. *J Appl Toxicol.* (2016) 36:1120–8. doi: 10.1002/jat.3272

6. Jares EJ, Sanchez-Borges M, Cardona-Villa R, Ensina LF, Arias-Cruz A, Gomez M, et al. Multinational experience with hypersensitivity drug reactions in Latin America. *Ann Allergy Asthma Immunol.* (2014) 113:282–9. doi: 10.1016/j.anai.2014.06.019

7. Dibek Misirlioglu E, Guvenir H, Bahceci S, Haktanir Abul M, Can D, Usta Guc BE, et al. Severe cutaneous adverse drug reactions in pediatric patients: a multicenter study. *J Allergy Clin Immunol Pract.* (2017) 5:757–63. doi: 10.1016/j.jaip.2017.02.013

8. Cekic S, Canitez Y, Sapan N. Evaluation of the patients diagnosed with Stevens Johnson syndrome and toxic epidermal necrolysis: a single center experience. *Turk Pediatri Ars.* (2016) 51:152–8. doi: 10.5152/TurkPediatriArs.2016.3836

9. Kim GY, Anderson KR, Davis DMR, Hand JL, Tollefson MM. Drug reaction with eosinophilia and systemic symptoms (DRESS) in the pediatric population: a systematic review of the literature. *J Am Acad Dermatol.* (2020) 83:1323–30. doi: 10.1016/j.jaad.2020.03.081

10. Peter JG, Lehloenya R, Dlamini S, Risma K, White KD, Konvinse KC, et al. Severe delayed cutaneous and systemic reactions to drugs: a global perspective on the science and art of current practice. *J Allergy Clin Immunol Pract.* (2017) 5:547–63. doi: 10.1016/j.jaip.2017.01.025

11. Tsabouri S, Atanaskovic-Markovic M. Skin eruptions in children: drug hypersensitivity vs viral exanthema. *Pediatr Allergy Immunol.* (2021) 32:824–34. doi: 10.1111/pai.13485

12. Bigby M, Jick S, Jick H, Arndt K. Drug-induced cutaneous reactions. A report from the Boston collaborative drug surveillance program on 15,438 consecutive inpatients, 1975 to 1982. *JAMA*. (1986) 256:3358–63. doi: 10.1001/jama.256.24.3358

13. Ben-Said B, Arnaud-Butel S, Rozieres A, Rodet K, Berard F, Nicolas JF, et al. Allergic delayed drug hypersensitivity is more frequently diagnosed in drug reaction, eosinophilia and systemic symptoms (DRESS) syndrome than in exanthema induced by beta-lactam antibiotics. *J Dermatol Sci.* (2015) 80:71–4. doi: 10.1016/j.jdermsci.2015.07.014

14. Trubiano JA, Soria A, Torres MJ, Trautmann A. Treating through drug-associated exanthems in drug allergy management: current evidence and clinical aspects. *J Allergy Clin Immunol Pract.* (2021) 9:2984–93. doi: 10.1016/j.jaip.2021.04.008

15. Trautmann A, Benoit S, Goebeler M, Stoevesandt J. "Treating through" decision and follow-up in antibiotic therapy-associated exanthemas. *J Allergy Clin Immunol Pract.* (2017) 5:1650–6. doi: 10.1016/j.jaip.2017.03.032

16. Phillips EJ, Bigliardi P, Bircher AJ, Broyles A, Chang YS, Chung WH, et al. Controversies in drug allergy: testing for delayed reactions. *J Allergy Clin Immunol.* (2019) 143:66–73. doi: 10.1016/j.jaci.2018.10.030

17. Sidoroff A, Halevy S, Bavinck JN, Vaillant L, Roujeau JC. Acute generalized exanthematous pustulosis (AGEP)–a clinical reaction pattern. *J Cutan Pathol.* (2001) 28:113–9. doi: 10.1034/j.1600-0560.2001.028003113.x

18. Lofvendahl S, Norlin JM, Schmitt-Egenolf M. Prevalence and incidence of generalized pustular psoriasis in Sweden: a population-based register study. *Br J Dermatol.* (2022) 186:970–6. doi: 10.1111/bjd.20966

19. Isom J, Braswell DS, Siroy A, Auerbach J, Motaparthi K. Clinical and histopathologic features differentiating acute generalized exanthematous pustulosis and pustular psoriasis: a retrospective series. *J Am Acad Dermatol.* (2020) 83:265–7. doi: 10.1016/j.jaad.2020.03.015

20. Kardaun SH, Kuiper H, Fidler V, Jonkman MF. The histopathological spectrum of acute generalized exanthematous pustulosis (AGEP) and its differentiation from generalized pustular psoriasis. *J Cutan Pathol.* (2010) 37:1220–9. doi: 10.1111/j.1600-0560.2010.01612.x

21. Saissi EH, Beau-Salinas F, Jonville-Bera AP, Lorette G, Autret-Leca E. Centres Régionaux de Pharmacovigilance. [Drugs associated with acute generalized exanthematic pustulosis]. *Ann Dermatol Venereol.* (2003) 130:612–8.

22. Sidoroff A, Dunant A, Viboud C, Halevy S, Bavinck JN, Naldi L, et al. Risk factors for acute generalized exanthematous pustulosis (AGEP)-results of a multinational case-control study (EuroSCAR). *Br J Dermatol.* (2007) 157:989–96. doi: 10.1111/j.1365-2133.2007.08156.x

23. Mebazaa A, Kort R, Zaiem A, Elleuch D, Moula H, Cheikhrouhou R, et al. [Acute generalized exanthematous pustulosis. Study of 22 cases]. *Tunis Med.* (2010) 88:910–5.

24. Creadore A, Desai S, Alloo A, Dewan AK, Bakhtiar M, Cruz-Diaz C, et al. Clinical characteristics, disease course, and outcomes of patients with acute generalized exanthematous pustulosis in the US. *JAMA Dermatol.* (2022) 158:176–83. doi: 10.1001/jamadermatol.2021.5390

25. Ingen-Housz-Oro S, Hotz C, Valeyrie-Allanore L, Sbidian E, Hemery F, Chosidow O, et al. Acute generalized exanthematous pustulosis: a retrospective audit of practice between 1994 and 2011 at a single centre. *Br J Dermatol.* (2015) 172:1455–7. doi: 10.1111/bjd.13540

26. Oh DAQ, Yeo YW, Choo KJL, Pang SM, Oh CC, Lee HY. Acute generalized exanthematous pustulosis: epidemiology, clinical course, and treatment outcomes of patients treated in an Asian academic medical center. *JAAD Int.* (2021) 3:1–6. doi: 10.1016/j.jdin.2020.12.004

27. Hashizume H, Fujiyama T, Kanebayashi J, Kito Y, Hata M, Yagi H. Skin recruitment of monomyeloid precursors involves human herpesvirus-6 reactivation in drug allergy. *Allergy.* (2013) 68:681–9. doi: 10.1111/all.12138

28. Neuman MG, McKinney KK, Nanau RM, Kong V, Malkiewicz I, Mazulli T, et al. Drug-induced severe adverse reaction enhanced by human herpes virus-6 reactivation. *Transl Res.* (2013) 161:430–40. doi: 10.1016/j.trsl.2012.12.012

29. Duong TA, Valeyrie-Allanore L, Wolkenstein P, Chosidow O. Severe cutaneous adverse reactions to drugs. *Lancet.* (2017) 390:1996–2011. doi: 10.1016/S0140-6736(16)30378-6

30. Soria A, Bernier C, Veyrac G, Barbaud A, Puymirat E, Milpied B. Drug reaction with eosinophilia and systemic symptoms may occur within 2 weeks of drug exposure: a retrospective study. *J Am Acad Dermatol.* (2020) 82:606–11. doi: 10.1016/j.jaad.2019.09.036

31. Kardaun SH, Sidoroff A, Valeyrie-Allanore L, Halevy S, Davidovici BB, Mockenhaupt M, et al. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? *Br J Dermatol.* (2007) 156:609–11. doi: 10.1111/j.1365-2133.2006.07704.x

32. Wolfson AR, Zhou L, Li Y, Phadke NA, Chow OA, Blumenthal KG. Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome identified in the electronic health record allergy module. *J Allergy Clin Immunol Pract.* (2019) 7:633–40. doi: 10.1016/j.jaip.2018.08.013

33. Ramirez E, Medrano-Casique N, Tong HY, Bellon T, Cabanas R, Fiandor A, et al. Eosinophilic drug reactions detected by a prospective pharmacovigilance programme in a tertiary hospital. *Br J Clin Pharmacol.* (2017) 83:400–15. doi: 10.1111/bcp.13096

34. Bluestein S, Yu R, Stone CA, Phillips E. A review of drug reaction with eosinophilia and systemic symptoms in the FDA adverse event reporting system (FAERS). *J Allergy Clin Immunol.* (2021) 147:AB12. doi: 10.1016/j.jaci.2020.12.085

35. Soria A, Amsler E, Bernier C, Milpied B, Tetart F, Morice C, et al. DRESS and AGEP reactions to iodinated contrast media: a french case series. *J Allergy Clin Immunol Pract.* (2021) 9:3041–50. doi: 10.1016/j.jaip.2021.02.060

36. Shiohara T, Kano Y. Drug reaction with eosinophilia and systemic symptoms (DRESS): incidence, pathogenesis and management. *Expert Opin Drug Saf.* (2017) 16:139–47. doi: 10.1080/14740338.2017.1270940

37. Roujeau JC, Haddad C, Paulmann M, Mockenhaupt M. Management of nonimmediate hypersensitivity reactions to drugs. *Immunol Allergy Clin North Am.* (2014) 34:473–87; vii. doi: 10.1016/j.iac.2014.04.012

38. Sandhu S, Neema S, Vashisht D, Venugopal R, Sengupta P, Radhakrishnan S. Drug reaction with eosinophilia and systemic symptoms: a single center descriptive observational study. *Dermatol Ther.* (2021) 34:e14670. doi: 10.1111/dth.14670

39. Anci E, Braun C, Marinosci A, Rodieux F, Midun E, Torres MJ, et al. Viral infections and cutaneous drug-related eruptions. *Front Pharmacol.* (2020) 11:586407. doi: 10.3389/fphar.2020.586407

40. Kuschel SL, Reedy MS. Cyclosporine treatment of drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome: a case report and brief review of the literature. *Pract Dermatol.* (2018) 2018:41–3.

41. Su HJ, Chen CB, Yeh TY, Chung WH. Successful treatment of corticosteroid-dependent drug reaction with eosinophilia and systemic symptoms with cyclosporine. *Ann Allergy Asthma Immunol.* (2021) 127:674–81. doi: 10.1016/j.anai.2021.08.012

42. Rive CM, Bourke J, Phillips EJ. Testing for drug hypersensitivity syndromes. *Clin Biochem Rev.* (2013) 34:15–38.

43. Olson D, Watkins LK, Demirjian A, Lin X, Robinson CC, Pretty K, et al. Outbreak of mycoplasma pneumoniae-associated stevens-johnson syndrome. *Pediatrics.* (2015) 136:e386–94. doi: 10.1542/peds.2015-0278

44. Bastuji-Garin S, Fouchard N, Bertocchi M, Roujeau JC, Revuz J, Wolkenstein P. SCORTEN: a severity-of-illness score for toxic epidermal necrolysis. *J Invest Dermatol.* (2000) 115:149–53. doi: 10.1046/j.1523-1747.2000.00061.x

45. Shear NH, Dodiuk-Gad RP. *Advances in Diagnosis and Management of Cutaneous Adverse Drug Reactions*. Singapore: ADIS (2019). p. 307 doi: 10.1007/978-981-13-1489-6

46. Sassolas B, Haddad C, Mockenhaupt M, Dunant A, Liss Y, Bork K, et al. ALDEN, an algorithm for assessment of drug causality in Stevens-Johnson syndrome and toxic epidermal necrolysis: comparison with case-control analysis. *Clin Pharmacol Ther.* (2010) 88:60–8. doi: 10.1038/clpt.2009.252

47. Sekula P, Dunant A, Mockenhaupt M, Naldi L, Bouwes Bavinck JN, Halevy S, et al. Comprehensive survival analysis of a cohort of patients with Stevens-Johnson syndrome and toxic epidermal necrolysis. *J Invest Dermatol.* (2013) 133:1197–204. doi: 10.1038/jid.2012.510

48. Rzany B, Mockenhaupt M, Baur S, Schroder W, Stocker U, Mueller J, et al. Epidemiology of erythema exsudativum multiforme majus, Stevens-Johnson syndrome, and toxic epidermal necrolysis in Germany (1990-1992): structure and results of a population-based registry. *J Clin Epidemiol.* (1996) 49:769–73. doi: 10.1016/0895-4356(96)00035-2

49. Krantz MS, Yoon B, Stone CA, Yu R, Phillips E. Stevens-Johnson syndrome and toxic epidermal necrolysis in the FDA adverse event reporting system (FAERS) from 1995-2020. In: *Proceeding of the 2022 AAAAI Annual Meeting*. Phoenix (2022). doi: 10.1016/j.jaci.2021.12.233

50. Mockenhaupt M, Viboud C, Dunant A, Naldi L, Halevy S, Bouwes Bavinck JN, et al. Stevens-Johnson syndrome and toxic epidermal necrolysis: assessment of medication risks with emphasis on recently marketed drugs. The EuroSCAR-study. *J Invest Dermatol.* (2008) 128:35–44. doi: 10.1038/sj.jid.5701033

51. Schwartz RA, McDonough PH, Lee BW. Toxic epidermal necrolysis: part II. Prognosis, sequelae, diagnosis, differential diagnosis, prevention, and treatment. *J Am Acad Dermatol.* (2013) 69:e1–16. doi: 10.1016/j.jaad.2013.05.003

52. Seminario-Vidal L, Kroshinsky D, Malachowski SJ, Sun J, Markova A, Beachkofsky TM, et al. Society of dermatology hospitalists supportive care

guidelines for the management of Stevens-Johnson syndrome/toxic epidermal necrolysis in adults. *J Am Acad Dermatol.* (2020) 82:1553–67. doi: 10.1016/j.jaad.2020.02.066

53. Zimmermann S, Sekula P, Venhoff M, Motschall E, Knaus J, Schumacher M, et al. Systemic immunomodulating therapies for Stevens-Johnson syndrome and toxic epidermal necrolysis: a systematic review and meta-analysis. *JAMA Dermatol.* (2017) 153:514–22. doi: 10.1001/jamadermatol.2016.5668

54. Huang YC, Li YC, Chen TJ. The efficacy of intravenous immunoglobulin for the treatment of toxic epidermal necrolysis: a systematic review and meta-analysis. *Br J Dermatol.* (2012) 167:424–32. doi: 10.1111/j.1365-2133.2012.10965.x

55. Micheletti RG, Chiesa-Fuxench Z, Noe MH, Stephen S, Aleshin M, Agarwal A, et al. Stevens-Johnson syndrome/toxic epidermal necrolysis: a multicenter retrospective Study of 377 adult patients from the united States. *J Invest Dermatol.* (2018) 138:2315–21. doi: 10.1016/j.jid.2018.04.027

56. Gonzalez-Herrada C, Rodriguez-Martin S, Cachafeiro L, Lerma V, Gonzalez O, Lorente JA, et al. Cyclosporine use in epidermal necrolysis is associated with an important mortality reduction: evidence from three different approaches. *J Invest Dermatol.* (2017) 137:2092–100. doi: 10.1016/j.jid.2017.05.022

57. Ng QX, De Deyn M, Venkatanarayanan N, Ho CYX, Yeo WS. A meta-analysis of cyclosporine treatment for Stevens-Johnson syndrome/toxic epidermal necrolysis. *J Inflamm Res.* (2018) 11:135–42. doi: 10.2147/JIR.S160964

58. Wang CW, Yang LY, Chen CB, Ho HC, Hung SI, Yang CH, et al. Randomized, controlled trial of TNF-alpha antagonist in CTL-mediated severe cutaneous adverse reactions. *J Clin Invest.* (2018) 128:985–96. doi: 10.1172/JCI93349

59. Perron E, Viarnaud A, Marciano L, Karkouche R, Wechsler J, De Prost N, et al. Clinical and histological features of fixed drug eruption: a single-centre series of 73 cases with comparison between bullous and non-bullous forms. *Eur J Dermatol.* (2021) 31:372–80. doi: 10.1684/ejd.2021.4051

60. Lipowicz S, Sekula P, Ingen-Housz-Oro S, Liss Y, Sassolas B, Dunant A, et al. Prognosis of generalized bullous fixed drug eruption: comparison with Stevens-Johnson syndrome and toxic epidermal necrolysis. *Br J Dermatol.* (2013) 168:726–32. doi: 10.1111/bjd.12133

61. Patel S, John AM, Handler MZ, Schwartz RA. Fixed drug eruptions: an update, emphasizing the potentially lethal generalized bullous fixed drug eruption. *Am J Clin Dermatol.* (2020) 21:393–9. doi: 10.1007/s40257-020-00505-3

62. Chung WH, Pan RY, Chu MT, Chin SW, Huang YL, Wang WC, et al. Oxypurinol-specific T cells possess preferential TCR clonotypes and express granulysin in allopurinol-induced severe cutaneous adverse reactions. *J Invest Dermatol.* (2015) 135:2237–48. doi: 10.1038/jid.2015.165

63. Covington EW, Baldwin BJ, Warren E. Pharmacy-led beta-lactam allergy interview (BLAI) reduces duration of fluoroquinolones within a community hospital. *Ann Pharmacother.* (2019) 53:588–95. doi: 10.1177/1060028019826223

64. Turner NA, Wrenn R, Sarubbi C, Kleris R, Lugar PL, Radojicic C, et al. Evaluation of a pharmacist-led penicillin allergy assessment program and allergy delabeling in a tertiary care hospital. *JAMA Netw Open.* (2021) 4:e219820. doi: 10.1001/jamanetworkopen.2021.9820

65. Lehloenya RJ, Peter JG, Copaescu A, Trubiano JA, Phillips EJ. Delabeling delayed drug hypersensitivity: how far can you safely go? *J Allergy Clin Immunol Pract.* (2020) 8:2878–95.e6. doi: 10.1016/j.jaip.2020.07.005

66. Garcia-Doval I, LeCleach L, Bocquet H, Otero XL, Roujeau JC. Toxic epidermal necrolysis and Stevens-Johnson syndrome: does early withdrawal of causative drugs decrease the risk of death? *Arch Dermatol.* (2000) 136:323–7. doi: 10.1001/archderm.136.3.323

67. Lin CY, Wang CW, Hui CR, Chang YC, Yang CH, Cheng CY, et al. Delayed-type hypersensitivity reactions induced by proton pump inhibitors: a clinical and in vitro T-cell reactivity study. *Allergy.* (2018) 73:221–9. doi: 10.1111/all.13235

68. Bouvette, G, Copaescu A, Masse MS. A case of ranitidine induced exanthema. *Allergy Asthma Clin Immunol.* (2019) 15:1–31.

69. Berti A, Della-Torre E, Yacoub M, Tombetti E, Canti V, Sabbadini MG, et al. Patients with breakthrough reactions to iodinated contrast media have low incidence of positive skin tests. *Eur Ann Allergy Clin Immunol.* (2016) 48:137–44.

70. Trautmann A, Brockow K, Behle V, Stoevesandt J. Radiocontrast media hypersensitivity: skin testing differentiates allergy from nonallergic reactions and identifies a safe alternative as proven by intravenous provocation. *J Allergy Clin Immunol Pract.* (2019) 7:2218–24. doi: 10.1016/j.jaip.2019.04.005

71. Shrestha S, Danekhu K, Kc B, Palaian S, Ibrahim MIM. Bibliometric analysis of adverse drug reactions and pharmacovigilance research activities in Nepal. *Ther Adv Drug Saf.* (2020) 11:2042098620922480. doi: 10.1177/2042098620922480

72. Demoly P, Adkinson NF, Brockow K, Castells M, Chiriac AM, Greenberger PA, et al. International consensus on drug allergy. *Allergy.* (2014) 69:420–37. doi: 10.1111/all.12350

73. Bergmann KC, Demoly P, Worm M, Fokkens WJ, Carrillo T, Tabar AI, et al. Efficacy and safety of sublingual tablets of house dust mite allergen extracts in adults with allergic rhinitis. *J Allergy Clin Immunol.* (2014) 133:1608–14e6. doi: 10.1016/j.jaci.2013.11.012

74. Joint Task Force on Practice Parameters, American Academy of Allergy Asthma Immunology, American College of Allergy Asthma Immunology, Joint Council of Allergy Asthma Immunology. Drug allergy: an updated practice parameter. *Ann Allergy Asthma Immunol.* (2010) 105:259–73. doi: 10.1016/j.anai.2010.08.002

75. Blanca M, Romano A, Torres MJ, Fernandez J, Mayorga C, Rodriguez J, et al. Update on the evaluation of hypersensitivity reactions to betalactams. *Allergy.* (2009) 64:183–93. doi: 10.1111/j.1398-9995.2008.01924.x

76. Australasian Society of Clinical Immunology and Allergy. *Skin Prick Testing for the Diagnosis of Allergic Disease [Manual]*. Brookvale, NSW: ASCIA (2013).

77. Fernandez J, Torres MJ, Campos J, Arribas-Poves F, Blanca M, Group DA-D. Prospective, multicenter clinical trial to validate new products for skin tests in the diagnosis of allergy to penicillin. *J Investig Allergol Clin Immunol.* (2013) 23:398–408.

78. Romano A, Viola M, Bousquet PJ, Gaeta F, Valluzzi R, Caruso C, et al. A comparison of the performance of two penicillin reagent kits in the diagnosis of beta-lactam hypersensitivity. *Allergy.* (2007) 62:53–8. doi: 10.1111/j.1398-9995.2006.01272.x

79. Mirakian R, Leech SC, Krishna MT, Richter AG, Huber PA, Farooque S, et al. Management of allergy to penicillins and other beta-lactams. *Clin Exp Allergy.* (2015) 45:300–27. doi: 10.1111/cea.12468

80. Broyles AD, Banerji A, Barmettler S, Biggs CM, Blumenthal K, Brennan PJ, et al. Practical guidance for the evaluation and management of drug hypersensitivity: specific drugs. *J Allergy Clin Immunol Pract.* (2020) 8:S16–116. doi: 10.1016/j.jaip.2020.08.002

81. Brockow K, Garvey LH, Aberer W, Atanaskovic-Markovic M, Barbaud A, Bilo MB, et al. Skin test concentrations for systemically administered drugs – an ENDA/EAACI drug allergy interest group position paper. *Allergy.* (2013) 68:702–12. doi: 10.1111/all.12142

82. Empedrad R, Darter AL, Earl HS, Gruchalla RS. Nonirritating intradermal skin test concentrations for commonly prescribed antibiotics. *J Allergy Clin Immunol.* (2003) 112:629–30. doi: 10.1016/S0091-6749(03)01783-4

83. Testi S, Severino M, Iorno ML, Capretti S, Ermini G, Macchia D, et al. Nonirritating concentration for skin testing with cephalosporins. *J Investig Allergol Clin Immunol.* (2010) 20:171–2.

84. Konvinse KC, Trubiano JA, Pavlos R, James I, Shaffer CM, Bejan CA, et al. HLA-A∗32:01 is strongly associated with vancomycin-induced drug reaction with eosinophilia and systemic symptoms. *J Allergy Clin Immunol.* (2019) 144:183–92. doi: 10.1016/j.jaci.2019.01.045

85. Yoon SY, Park SY, Kim S, Lee T, Lee YS, Kwon HS, et al. Validation of the cephalosporin intradermal skin test for predicting immediate hypersensitivity: a prospective study with drug challenge. *Allergy.* (2013) 68:938–44. doi: 10.1111/all.12182

86. Romano A, Torres MJ, Namour F, Mayorga C, Artesani MC, Venuti A, et al. Immediate hypersensitivity to cephalosporins. *Allergy.* (2002) 57:52–7. doi: 10.1034/j.1398-9995.57.s72.18.x

87. Seitz CS, Brocker EB, Trautmann A. Diagnostic testing in suspected fluoroquinolone hypersensitivity. *Clin Exp Allergy.* (2009) 39:1738–45. doi: 10.1111/j.1365-2222.2009.03338.x

88. Romano A, Gaeta F, Valluzzi RL, Alonzi C, Maggioletti M, Zaffiro A, et al. Absence of cross-reactivity to carbapenems in patients with delayed hypersensitivity to penicillins. *Allergy.* (2013) 68:1618–21. doi: 10.1111/all.12299

89. Broz P, Harr T, Hecking C, Grize L, Scherer K, Jaeger KA, et al. Nonirritant intradermal skin test concentrations of ciprofloxacin, clarithromycin, and rifampicin. *Allergy.* (2012) 67:647–52. doi: 10.1111/j.1398-9995.2012.02807.x

90. Solensky R, Jacobs J, Lester M, Lieberman P, McCafferty F, Nilsson T, et al. Penicillin allergy evaluation: a prospective, multicenter, open-label evaluation of a comprehensive penicillin skin test kit. *J Allergy Clin Immunol Pract.* (2019) 7:1876–85.e3. doi: 10.1016/j.jaip.2019.02.040

91. Dhudasia MB, Flannery DD, Pfeifer MR, Puopolo KM. Updated guidance: prevention and management of perinatal group B streptococcus infection. *Neoreviews.* (2021) 22:e177–88. doi: 10.1542/neo.22-3-e177

92. Kuder MM, Lennox MG, Li M, Lang DM, Pien L. Skin testing and oral amoxicillin challenge in the outpatient allergy and clinical immunology clinic in pregnant women with penicillin allergy. *Ann Allergy Asthma Immunol.* (2020) 125:646–51. doi: 10.1016/j.anai.2020.08.012

93. Patel V, Gleeson PK, Delaney K, Ralston SJ, Feldman S, Fadugba O. Safety and outcomes of penicillin allergy evaluation in pregnant women. *Ann Allergy Asthma Immunol.* (2022) 128:568–74. doi: 10.1016/j.anai.2022.01.032

94. Atanaskovic-Markovic M, Gaeta F, Medjo B, Gavrovic-Jankulovic M, Cirkovic Velickovic T, Tmusic V, et al. Non-immediate hypersensitivity reactions to beta-lactam antibiotics in children – our 10-year experience in allergy work-up. *Pediatr Allergy Immunol.* (2016) 27:533–8. doi: 10.1111/pai.12565

95. Fransson S, Mosbech HF, Elberling J, Kappel M, Garvey LH. Intradermal Testing Identifies 1 in 4 Patients with Nonimmediate Penicillin Allergy. *Int Arch Allergy Immunol.* (2021) 182:827–34. doi: 10.1159/000515080

96. Trubiano JA, Douglas AP, Goh M, Slavin MA, Phillips EJ. The safety of antibiotic skin testing in severe T-cell-mediated hypersensitivity of immunocompetent and immunocompromised hosts. *J Allergy Clin Immunol Pract.* (2019) 7:1341–43.e1. doi: 10.1016/j.jaip.2018.09.014

97. Trubiano JA, Strautins K, Redwood AJ, Pavlos R, Konvinse KC, Aung AK, et al. The combined utility of ex vivo IFN-gamma release enzyme-linked immunospot assay and in vivo skin testing in patients with antibiotic-Associated severe cutaneous adverse reactions. *J Allergy Clin Immunol Pract.* (2018) 6:1287–96.e1. doi: 10.1016/j.jaip.2017.09.004

98. Copaescu A, Mouhtouris E, Vogrin S, James F, Chua KYL, Holmes NE, et al. The role of in vivo and Ex vivo diagnostic tools in severe delayed immune-mediated adverse antibiotic drug reactions. *J Allergy Clin Immunol Pract.* (2021) 9:2010-15.e4. doi: 10.1016/j.jaip.2020.12.052

99. Cabanas R, Calderon O, Ramirez E, Fiandor A, Prior N, Caballero T, et al. Piperacillin-induced DRESS: distinguishing features observed in a clinical and allergy study of 8 patients. *J Investig Allergol Clin Immunol.* (2014) 24:425–30.

100. Chaudhry HM, Drage LA, El-Azhary RA, Hall MR, Killian JM, Prakash AV, et al. Delayed patch-test reading after 5 days: an update from the mayo clinic contact dermatitis group. *Dermatitis.* (2017) 28:253–60. doi: 10.1097/DER.0000000000000297

101. Brockow K, Romano A, Blanca M, Ring J, Pichler W, Demoly P. General considerations for skin test procedures in the diagnosis of drug hypersensitivity. *Allergy.* (2002) 57:45–51. doi: 10.1046/j.0105-4538.2001.00001.x-i8

102. Barbaud A, Collet E, Milpied B, Assier H, Staumont D, Avenel-Audran M, et al. A multicentre study to determine the value and safety of drug patch tests for the three main classes of severe cutaneous adverse drug reactions. *Br J Dermatol.* (2013) 168:555–62. doi: 10.1111/bjd.12125

103. Agui Callejas A, Cuervas-Mons Vendrell M, Bernaola Abraira M, González Andrés D, Arrieta Loitegui M, Ranz Ortega P, et al. 3PC-013 Pharmaceutical compounding in paediatric patch testing: are we sure about the actual active ingredient concentration? *Eur J Hosp Pharm.* (2022) 29:A1–187. doi: 10.1136/ejhpharm-2022-eahp.38

104. Hug K, Yawalkar N, Helbling A, Pichler WJ. Scratch-patch and patch testing in drug allergy–an assessment of specificity. *J Investig Allergol Clin Immunol.* (2003) 13:12–9.

105. Shebe K, Ngwanya MR, Gantsho N, Lehloenya RJ. Severe recurrence of drug rash with eosinophilia and systemic symptoms syndrome secondary to rifampicin patch testing in a human immunodeficiency virus-infected man. *Contact Dermatitis.* (2014) 70:125–7. doi: 10.1111/cod.12155

106. Hassoun-Kheir N, Bergman R, Weltfriend S. The use of patch tests in the diagnosis of delayed hypersensitivity drug eruptions. *Int J Dermatol.* (2016) 55:1219–24. doi: 10.1111/ijd.13306

107. Gilissen L, Huygens S, Goossens A, Breynaert C, Schrijvers R. Utility of patch testing for the diagnosis of delayed-type drug hypersensitivity reactions to clindamycin. *Contact Dermatitis.* (2020) 83:237–9. doi: 10.1111/cod.13575

108. Woodruff CM, Botto N. The Role of patch testing in evaluating delayed hypersensitivity reactions to medications. *Clin Rev Allergy Immunol.* (2022) 62:548–61. doi: 10.1007/s12016-022-08924-2

109. Kaplan Y, Goldberg I, Sprecher E, Slodownik D. Patch testing versus interferon-gamma release assay in evaluation of drug eruptions. *Fundam Clin Pharmacol.* (2022) 36:414–20. doi: 10.1111/fcp.12733

110. de Groot AC. Patch testing in drug reaction with eosinophilia and systemic symptoms (DRESS): a literature review. *Contact Dermatitis.* (2022) 86:443–79. doi: 10.1111/cod.14090

111. Pinho A, Marta A, Coutinho I, Goncalo M. Long-term reproducibility of positive patch test reactions in patients with non-immediate cutaneous adverse drug reactions to antibiotics. *Contact Dermatitis.* (2017) 76:204–9. doi: 10.1111/cod.12720

112. Horita K, Tanoue C, Yasoshima M, Ohtani T, Matsunaga K. Study of the usefulness of patch testing and use test to predict the safety of commercial topical drugs. *J Dermatol.* (2014) 41:505–13. doi: 10.1111/1346-8138.12505

113. Vezir E, Dibek Misirlioglu E, Civelek E, Capanoglu M, Guvenir H, Ginis T, et al. Direct oral provocation tests in non-immediate mild cutaneous reactions related to beta-lactam antibiotics. *Pediatr Allergy Immunol.* (2016) 27:50–4. doi: 10.1111/pai.12493

114. Kuruvilla M, Shih J, Patel K, Scanlon N. Direct oral amoxicillin challenge without preliminary skin testing in adult patients with allergy and at low risk with reported penicillin allergy. *Allergy Asthma Proc.* (2019) 40:57–61. doi: 10.2500/aap.2019.40.4184

115. Li J, Cvetanovski V, Fernando S. Single-step direct drug provocation testing is safe for delabelling selected non-low-risk penicillin allergy labels. *Ann Allergy Asthma Immunol.* (2021) 127:232–5. doi: 10.1016/j.anai.2021.04.008

116. Iammatteo M, Alvarez Arango S, Ferastraoaru D, Akbar N, Lee AY, Cohen HW, et al. Safety and outcomes of oral graded challenges to amoxicillin without prior skin testing. *J Allergy Clin Immunol Pract.* (2019) 7:236–43. doi: 10.1016/j.jaip.2018.05.008

117. Hjortlund J, Mortz CG, Skov PS, Bindslev-Jensen C. Diagnosis of penicillin allergy revisited: the value of case history, skin testing, specific IgE and prolonged challenge. *Allergy.* (2013) 68:1057–64. doi: 10.1111/all.12195

118. Rimawi RH, Cook PP, Gooch M, Kabchi B, Ashraf MS, Rimawi BH, et al. The impact of penicillin skin testing on clinical practice and antimicrobial stewardship. *J Hosp Med.* (2013) 8:341–5. doi: 10.1002/jhm.2036

119. Marwood J, Aguirrebarrena G, Kerr S, Welch SA, Rimmer J. De-labelling self-reported penicillin allergy within the emergency department through the use of skin tests and oral drug provocation testing. *Emerg Med Australas.* (2017) 29:509–15. doi: 10.1111/1742-6723.12774

120. Cook DJ, Barbara DW, Singh KE, Dearani JA. Penicillin skin testing in cardiac surgery. *J Thorac Cardiovasc Surg.* (2014) 147:1931–5. doi: 10.1016/j.jtcvs.2014.01.019

121. Confino-Cohen R, Rosman Y, Meir-Shafrir K, Stauber T, Lachover-Roth I, Hershko A, et al. Oral challenge without skin testing safely excludes clinically significant delayed-onset penicillin hypersensitivity. *J Allergy Clin Immunol Pract.* (2017) 5:669–75. doi: 10.1016/j.jaip.2017.02.023

122. Staicu ML, Holly AM, Conn KM, Ramsey A. The use of telemedicine for penicillin allergy skin testing. *J Allergy Clin Immunol Pract.* (2018) 6:2033–40. doi: 10.1016/j.jaip.2018.04.038

123. Livirya S, Pithie A, Chua I, Hamilton N, Doogue M, Isenman H. Oral amoxicillin challenge for low-risk penicillin allergic patients. *Intern Med J.* (2022) 52:295–300. doi: 10.1111/imj.14978

124. King EA, Challa S, Curtin P, Bielory L. Penicillin skin testing in hospitalized patients with beta-lactam allergies: effect on antibiotic selection and cost. *Ann Allergy Asthma Immunol.* (2016) 117:67–71. doi: 10.1016/j.anai.2016.04.021

125. Ramsey A, Staicu ML. Use of a penicillin allergy screening algorithm and penicillin skin testing for transitioning hospitalized patients to first-line antibiotic therapy. *J Allergy Clin Immunol Pract.* (2018) 6:1349–55. doi: 10.1016/j.jaip.2017.11.012

126. Banks TA, Tucker M, Macy E. Evaluating penicillin allergies without skin testing. *Curr Allergy Asthma Rep.* (2019) 19:27. doi: 10.1007/s11882-019-0854-6

127. Chua KYL, Vogrin S, Bury S, Douglas A, Holmes NE, Tan N, et al. The penicillin allergy delabeling program: a multicenter whole-of-hospital health services intervention and comparative effectiveness study. *Clin Infect Dis.* (2021) 73:487–96. doi: 10.1093/cid/ciaa653

128. Trubiano JA, Vogrin S, Chua KYL, Bourke J, Yun J, Douglas A, et al. Development and validation of a penicillin allergy clinical decision rule. *JAMA Intern Med.* (2020) 180:745–52. doi: 10.1001/jamainternmed.2020.0403

129. Iammatteo M, Lezmi G, Confino-Cohen R, Tucker M, Ben-Shoshan M, Caubet JC. Direct challenges for the evaluation of beta-lactam allergy: evidence and conditions for not performing skin testing. *J Allergy Clin Immunol Pract.* (2021) 9:2947–56. doi: 10.1016/j.jaip.2021.04.073

130. Gugkaeva Z, Crago JS, Yasnogorodsky M. Next step in antibiotic stewardship: pharmacist-provided penicillin allergy testing. *J Clin Pharm Ther.* (2017) 42:509–12. doi: 10.1111/jcpt.12530

131. Jones BM, Bland CM. Penicillin skin testing as an antimicrobial stewardship initiative. *Am J Health Syst Pharm.* (2017) 74:232–7. doi: 10.2146/ajhp160233

132. Torney NP, Tiberg MD. Description of a pharmacist-managed/administered penicillin allergy skin testing service at a community hospital. *Am J Health Syst Pharm.* (2021) 78:1066–73. doi: 10.1093/ajhp/zxab068

133. Prieto A, Munoz C, Bogas G, Fernandez-Santamaria R, Palomares F, Mayorga C, et al. Single-dose prolonged drug provocation test, without previous skin testing, is safe for diagnosing children with mild non-immediate reactions to beta-lactams. *Allergy.* (2021) 76:2544–54. doi: 10.1111/all.14800

134. Mustafa SS, Conn K, Ramsey A. Comparing direct challenge to penicillin skin testing for the outpatient evaluation of penicillin allergy: a randomized

controlled trial. *J Allergy Clin Immunol Pract.* (2019) 7:2163–70. doi: 10.1016/j.jaip.2019.05.037

135. Arikoglu T, Kuyucu S, Caubet JC. New diagnostic perspectives in the management of pediatric beta-lactam allergy. *Pediatr Allergy Immunol.* (2022) 33:e13745. doi: 10.1111/pai.13745

136. Lehloenya RJ, Isaacs T, Nyika T, Dhana A, Knight L, Veenstra S, et al. Early high-dose intravenous corticosteroids rapidly arrest Stevens Johnson syndrome and drug reaction with eosinophilia and systemic symptoms recurrence on drug re-exposure. *J Allergy Clin Immunol Pract.* (2021) 9:582–4.e1. doi: 10.1016/j.jaip.2020.08.012

137. Lehloenya RJ, Todd G, Badri M, Dheda K. Outcomes of reintroducing antituberculosis drugs following cutaneous adverse drug reactions. *Int J Tuberc Lung Dis.* (2011) 15:1649–57. doi: 10.5588/ijtld.10.0698

138. Porter M, Choshi P, Pedretti S, Chimbetete T, Smith R, Meintjes G, et al. IFN-gamma ELISpot in severe cutaneous adverse reactions to first-line antituberculosis drugs in an HIV endemic setting. *J Invest Dermatol.* (2022). [Epub ahead of print]. doi: 10.1016/j.jid.2022.05.1059

139. Srinoulprasert Y. Lymphocyte transformation test and cytokine detection assays: determination of read out parameters for delayed-type drug hypersensitivity reactions. *J Immunol Methods.* (2021) 496:113098. doi: 10.1016/j.jim.2021.113098

140. Sachs B, Fatangare A, Sickmann A, Glassner A. Lymphocyte transformation test: history and current approaches. *J Immunol Methods.* (2021) 493:113036. doi: 10.1016/j.jim.2021.113036

141. Porebski G, Pecaric-Petkovic T, Groux-Keller M, Bosak M, Kawabata TT, Pichler WJ. In vitro drug causality assessment in Stevens-Johnson syndrome – alternatives for lymphocyte transformation test. *Clin Exp Allergy.* (2013) 43:1027–37. doi: 10.1111/cea.12145

142. Nyfeler B, Pichler WJ. The lymphocyte transformation test for the diagnosis of drug allergy: sensitivity and specificity. *Clin Exp Allergy.* (1997) 27:175–81. doi: 10.1046/j.1365-2222.1997.d01-495.x

143. Rozieres A, Hennino A, Rodet K, Gutowski MC, Gunera-Saad N, Berard F, et al. Detection and quantification of drug-specific T cells in penicillin allergy. *Allergy.* (2009) 64:534–42. doi: 10.1111/j.1398-9995.2008.01674.x

144. Porebski G, Czarnobilska E, Bosak M. Cytotoxicbased assays in delayed drug hypersensitivity reactions induced by antiepileptic drugs. *Pol Arch Med Wewn.* (2015) 125:823–34. doi: 10.20452/pamw.3160

145. Cabanas R, Calderon O, Ramirez E, Fiandor A, Caballero T, Heredia R, et al. Sensitivity and specificity of the lymphocyte transformation test in drug reaction with eosinophilia and systemic symptoms causality assessment. *Clin Exp Allergy.* (2018) 48:325–33. doi: 10.1111/cea.13076

146. Sugita K, Kabashima K, Sawada Y, Haruyama S, Yoshioka M, Mori T, et al. Blocking of CTLA-4 on lymphocytes improves the sensitivity of lymphocyte transformation tests in a patient with nickel allergy. *Eur J Dermatol.* (2012) 22:268–9. doi: 10.1684/ejd.2012.1641

147. Hammond S, Thomson P, Meng X, Naisbitt D. In-vitro approaches to predict and study T-cell mediated hypersensitivity to drugs. *Front Immunol.* (2021) 12:630530. doi: 10.3389/fimmu.2021.630530

148. Wada S, Kumagai H, Yokoyama K, Ito T, Miyauchi A, Sakamoto S, et al. Mesalazine allergy in a boy with ulcerative colitis: clinical usefulness of mucosal biopsy criteria. *Clin J Gastroenterol.* (2016) 9:302–5. doi: 10.1007/s12328-016-0675-2

149. Dias de Castro E, Leblanc A, Sarmento A, Cernadas JR. An unusual case of delayed-type hypersensitivity to ceftriaxone and meropenem. *Eur Ann Allergy Clin Immunol.* (2015) 47:225–7.

150. Sun Q, Sha W, Gui XW, Xiao YJ, Zeng WH, Sun WW, et al. Drug-induced lymphocyte stimulation test in the prediction of drug-induced hypersensitivity to antituberculosis drugs. *Diagn Microbiol Infect Dis.* (2015) 82:172–6. doi: 10.1016/j.diagmicrobio.2015.03.008

151. Khalil G, El-Sabban M, Al-Ghadban S, Azzi S, Shamra S, Khalife S, et al. Cytokine expression profile of sensitized human T lymphocytes following in vitro stimulation with amoxicillin. *Eur Cytokine Netw.* (2008) 19:131–41.

152. Bensaid B, Rozieres A, Nosbaum A, Nicolas JF, Berard F. Amikacin-induced drug reaction with eosinophilia and systemic symptoms syndrome: delayed skin test and ELISPOT assay results allow the identification of the culprit drug. *J Allergy Clin Immunol.* (2012) 130:1413–4. doi: 10.1016/j.jaci.2012.05.042

153. Copaescu A, Rose M, Mouhtouris E, Chua KY, Holmes NE, Phillips EJ, et al. Delayed hypersensitivity associated with amoxicillin-clavulanate. *Allergy.* (2020) 75:2700–2. doi: 10.1111/all.14359

154. Copaescu A, Gibson A, Li Y, Trubiano J, Phillips E. An updated review of the diagnostic methods in delayed drug hypersensitivity. *Front Pharmacol.* (2020) 11:573573. doi: 10.3389/fphar.2020.573573

155. Suthumchai N, Srinoulprasert Y, Thantiworasit P, Rerknimitr P, Tuchinda P, Chularojanamontri L, et al. The measurement of drug-induced interferon gamma-releasing cells and lymphocyte proliferation in severe cutaneous adverse reactions. *J Eur Acad Dermatol Venereol.* (2018) 32:992–8. doi: 10.1111/jdv.14890

156. Copaescu A, Choshi P, Pedretti S, Mouhtouris E, Peter J, Trubiano JA. Dose dependent antimicrobial cellular cytotoxicity-implications for ex vivo diagnostics. *Front Pharmacol.* (2021) 12:640012. doi: 10.3389/fphar.2021.758192

157. Trubiano JA, Chua KYL, Holmes NE, Douglas AP, Mouhtouris E, Goh M, et al. Safety of cephalosporins in penicillin class severe delayed hypersensitivity reactions. *J Allergy Clin Immunol Pract.* (2020) 8:1142–46.e4. doi: 10.1016/j.jaip.2019.10.005

158. Klaewsongkram J, Sukasem C, Thantiworasit P, Suthumchai N, Rerknimitr P, Tuchinda P, et al. Analysis of HLA-B allelic variation and IFN-gamma ELISpot responses in patients with severe cutaneous adverse reactions associated with drugs. *J Allergy Clin Immunol Pract.* (2019) 7:219–27.e4. doi: 10.1016/j.jaip.2018.05.004

159. Haw WY, Polak ME, McGuire C, Erlewyn-Lajeunesse M, Ardern-Jones MR. In vitro rapid diagnostic tests for severe drug hypersensitivity reactions in children. *Ann Allergy Asthma Immunol.* (2016) 117:61–6. doi: 10.1016/j.anai.2016.04.017

160. El-Ghaiesh S, Monshi MM, Whitaker P, Jenkins R, Meng X, Farrell J, et al. Characterization of the antigen specificity of T-cell clones from piperacillin-hypersensitive patients with cystic fibrosis. *J Pharmacol Exp Ther.* (2012) 341:597–610. doi: 10.1124/jpet.111.190900

161. Wang F, Cai R, He D, Zhao Y, Ye Y, Zhang X. Serum IFN-gamma-inducible chemokines CXCL9 and CXCL10 are elevated in non-immediate drug hypersensitivity reactions. *Asian Pac J Allergy Immunol.* (2016) 34:236–41.

162. Schaerli P, Britschgi M, Keller M, Steiner UC, Steinmann LS, Moser B, et al. Characterization of human T cells that regulate neutrophilic skin inflammation. *J Immunol.* (2004) 173:2151–8. doi: 10.4049/jimmunol.173.3.2151

163. Padial MA, Alvarez-Ferreira J, Tapia B, Blanco R, Manas C, Blanca M, et al. Acute generalized exanthematous pustulosis associated with pseudoephedrine. *Br J Dermatol.* (2004) 150:139–42. doi: 10.1111/j.1365-2133.2004.05717.x

164. Kabashima R, Sugita K, Sawada Y, Hino R, Nakamura M, Tokura Y. Increased circulating Th17 frequencies and serum IL-22 levels in patients with acute generalized exanthematous pustulosis. *J Eur Acad Dermatol Venereol.* (2011) 25:485–8. doi: 10.1111/j.1468-3083.2010.03771.x

165. Beeler A, Engler O, Gerber BO, Pichler WJ. Long-lasting reactivity and high frequency of drug-specific T cells after severe systemic drug hypersensitivity reactions. *J Allergy Clin Immunol.* (2006) 117:455–62. doi: 10.1016/j.jaci.2005.10.030

166. Ogawa K, Morito H, Hasegawa A, Daikoku N, Miyagawa F, Okazaki A, et al. Identification of thymus and activation-regulated chemokine (TARC/CCL17) as a potential marker for early indication of disease and prediction of disease activity in drug-induced hypersensitivity syndrome (DIHS)/drug rash with eosinophilia and systemic symptoms (DRESS). *J Dermatol Sci.* (2013) 69:38–43. doi: 10.1016/j.jdermsci.2012.10.002

167. Chung WH, Hung SI. Recent advances in the genetics and immunology of Stevens-Johnson syndrome and toxic epidermal necrosis. *J Dermatol Sci.* (2012) 66:190–6. doi: 10.1016/j.jdermsci.2012.04.002

168. Su SC, Mockenhaupt M, Wolkenstein P, Dunant A, Le Gouvello S, Chen CB, et al. Interleukin-15 is associated with severity and mortality in Stevens-Johnson syndrome/toxic epidermal necrolysis. *J Invest Dermatol.* (2017) 137:1065–73. doi: 10.1016/j.jid.2016.11.034

169. Norcross MA, Luo S, Lu L, Boyne MT, Gomarteli M, Rennels AD, et al. Abacavir induces loading of novel self-peptides into HLA-B∗57: 01: an autoimmune model for HLA-associated drug hypersensitivity. *AIDS.* (2012) 26:F21–9. doi: 10.1097/QAD.0b013e328355fe8f

170. Thomson PJ, Illing PT, Farrell J, Alhaidari M, Bell CC, Berry N, et al. Modification of the cyclopropyl moiety of abacavir provides insight into the structure activity relationship between HLA-B∗57:01 binding and T-cell activation. *Allergy.* (2020) 75:636–47. doi: 10.1111/all.14057

171. De Spiegelaere W, Philippe J, Vervisch K, Verhofstede C, Malatinkova E, Kiselinova M, et al. Comparison of methods for in-house screening of HLA-B*57:01 to prevent abacavir hypersensitivity in HIV-1 care. *PLoS One.* (2015) 10:e0123525. doi: 10.1371/journal.pone.0123525

172. Shen M, Lim JME, Chia C, Ren EC. CD39(+) regulatory T cells modulate the immune response to carbamazepine in HLA-B*15:02 carriers. *Immunobiology.* (2020) 225:151868. doi: 10.1016/j.imbio.2019.11.003

173. Zhou P, Zhang S, Wang Y, Yang C, Huang J. Structural modeling of HLA-B∗1502/peptide/carbamazepine/T-cell receptor complex architecture:

implication for the molecular mechanism of carbamazepine-induced Stevens-Johnson syndrome/toxic epidermal necrolysis. *J Biomol Struct Dyn.* (2016) 34:1806–17. doi: 10.1080/07391102.2015.1092476

174. Cheng L, Sun B, Xiong Y, Hu L, Gao L, Li J, et al. WGCNA-based DNA methylation profiling analysis on allopurinol-induced severe cutaneous adverse reactions: a DNA methylation signature for predisposing drug hypersensitivity. *J Pers Med.* (2022) 12:1–13. doi: 10.3390/jpm12040525

175. Yun J, Mattsson J, Schnyder K, Fontana S, Largiader CR, Pichler WJ, et al. Allopurinol hypersensitivity is primarily mediated by dose-dependent oxypurinol-specific T cell response. *Clin Exp Allergy.* (2013) 43:1246–55. doi: 10.1111/cea.12184

176. Ogese MO, Lister A, Gardner J, Meng X, Alfirevic A, Pirmohamed M, et al. Deciphering adverse drug reactions: in vitro priming and characterization of vancomycin-specific T cells from healthy donors expressing HLA-A∗32:01. *Toxicol Sci.* (2021) 183:139–53. doi: 10.1093/toxsci/kfab084

177. Kongpan T, Mahasirimongkol S, Konyoung P, Kanjanawart S, Chumworathayi P, Wichukchinda N, et al. Candidate HLA genes for prediction of co-trimoxazole-induced severe cutaneous reactions. *Pharmacogenet Genomics.* (2015) 25:402–11. doi: 10.1097/FPC.0000000000000153

178. Pratoomwun J, Thomson P, Jaruthamsophon K, Tiyasirichokchai R, Jinda P, Rerkpattanapipat T, et al. Characterization of T-Cell Responses to SMX and SMX-NO in Co-Trimoxazole Hypersensitivity Patients Expressing HLA-B∗13:01. *Front Immunol.* (2021) 12:658593. doi: 10.3389/fimmu.2021.658593

179. Zhao Q, Alhilali K, Alzahrani A, Almutairi M, Amjad J, Liu H, et al. Dapsone- and nitroso dapsone-specific activation of T cells from hypersensitive patients expressing the risk allele HLA-B∗13:01. *Allergy.* (2019) 74:1533–48. doi: 10.1111/all.13769

180. Chen WT, Wang CW, Lu CW, Chen CB, Lee HE, Hung SI, et al. The function of HLA-B∗13:01 involved in the pathomechanism of dapsone-induced severe cutaneous adverse reactions. *J Invest Dermatol.* (2018) 138:1546–54. doi: 10.1016/j.jid.2018.02.004

181. Niihara H, Kakamu T, Fujita Y, Kaneko S, Morita E. HLA-A31 strongly associates with carbamazepine-induced adverse drug reactions but not with carbamazepine-induced lymphocyte proliferation in a Japanese population. *J Dermatol.* (2012) 39:594–601. doi: 10.1111/j.1346-8138.2011.01457.x

182. Nicoletti P, Aithal GP, Chamberlain TC, Coulthard S, Alshabeeb M, Grove JI, et al. Drug-induced liver injury due to flucloxacillin: relevance of multiple human leukocyte antigen alleles. *Clin Pharmacol Ther.* (2019) 106:245–53. doi: 10.1002/cpt.1375

183. Puig M, Ananthula S, Venna R, Kumar Polumuri S, Mattson E, Walker LM, et al. Alterations in the HLA-B∗57:01 immunopeptidome by flucloxacillin and immunogenicity of drug-haptenated peptides. *Front Immunol.* (2020) 11:629399. doi: 10.3389/fimmu.2020.629399

184. Hirasawa M, Hagihara K, Abe K, Ando O, Hirayama N. Interaction of nevirapine with the peptide binding groove of HLA-DRB1∗01:01 and its effect on the conformation of HLA-peptide complex. *Int J Mol Sci.* (2018) 19:1660. doi: 10.3390/ijms19061660

185. Chen CB, Chen YE, Chu MT, Wang CW, Hui RC, Lu CW, et al. The risk of anti-osteoporotic agent-induced severe cutaneous adverse drug reactions and their association with HLA. *J Eur Acad Dermatol Venereol.* (2021) 35:712–20. doi: 10.1111/jdv.16924

186. Steiner R, King M, Byrne D, Rose L. Inappropriate use of aztreonam. *Am J Ther.* (2021) 28:e14–8. doi: 10.1097/MJT.0000000000001058

187. Ariza A, Mayorga C, Fernandez TD, Barbero N, Martin-Serrano A, Perez-Sala D, et al. Hypersensitivity reactions to beta-lactams: relevance of hapten-protein conjugates. *J Investig Allergol Clin Immunol.* (2015) 25:12–25.

188. Muller P, Dubreil P, Mahé A, Lamaury I, Salzer B, Deloumeaux J, et al. Drug hypersensitivity syndrome in a west-Indian population. *Eur J Dermatol.* (2003) 13:478–81.

189. Chiou CC, Yang LC, Hung SI, Chang YC, Kuo TT, Ho HC, et al. Clinicopathological features and prognosis of drug rash with eosinophilia and systemic symptoms: a study of 30 cases in Taiwan. *J Eur Acad Dermatol Venereol.* (2008) 22:1044–9. doi: 10.1111/j.1468-3083.2008.02585.x

190. Hung SI, Chung WH, Liou LB, Chu CC, Lin M, Huang HP, et al. HLA-B∗5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. *Proc Natl Acad Sci USA.* (2005) 102:4134–9. doi: 10.1073/pnas.0409500102

191. Zhang FR, Liu H, Irwanto A, Fu XA, Li Y, Yu GQ, et al. HLA-B∗13:01 and the dapsone hypersensitivity syndrome. *N Engl J Med.* (2013) 369:1620–8.

192. Nakkam N, Gibson A, Mouhtouris E, Konvinse KC, Holmes NE, Chua KY, et al. Cross-reactivity between vancomycin, teicoplanin and telavancin in HLA-A∗32:01 positive vancomycin DRESS patients sharing an HLA-Class II haplotype. *J Allergy Clin Immunol.* (2020) 147:403–5. doi: 10.1016/j.jaci.2020.04.056

193. Romano A, Gaeta F, Valluzzi RL, Maggioletti M, Caruso C, Quaratino D. Cross-reactivity and tolerability of aztreonam and cephalosporins in subjects with a T cell-mediated hypersensitivity to penicillins. *J Allergy Clin Immunol.* (2016) 138:179–86. doi: 10.1016/j.jaci.2016.01.025

194. Buonomo A, Nucera E, Pecora V, Rizzi A, Aruanno A, Pascolini L, et al. Cross-reactivity and tolerability of cephalosporins in patients with cell-mediated allergy to penicillins. *J Investig Allergol Clin Immunol.* (2014) 24:331–7.

195. Prasertvit P, Chareonyingwattana A, Wattanakrai P. Nevirapine patch testing in Thai human immunodeficiency virus infected patients with nevirapine drug hypersensitivity. *Contact Dermatitis.* (2017) 77:379–84. doi: 10.1111/cod.12849

196. Ye YM, Hur GY, Kim SH, Ban GY, Jee YK, Naisbitt DJ, et al. Drug-specific $CD4^{(+)}$ T-cell immune responses are responsible for antituberculosis drug-induced maculopapular exanthema and drug reaction with eosinophilia and systemic symptoms syndrome. *Br J Dermatol.* (2017) 176:378–86. doi: 10.1111/bjd.14839

197. Meller S, Gerber PA, Kislat A, Hevezi P, Göbel T, Wiesner U, et al. Allergic sensitization to pegylated interferon-alpha results in drug eruptions. *Allergy.* (2015) 70:775–83. doi: 10.1111/all.12618

198. Xiong H, Chen S, Luo X. Salazosulphapyridine-related Stevens-Johnson Syndrome Caused by Sulphapyridine and Confirmed by Enzyme-linked Immunospot Assay. *J Crohns Colitis.* (2018) 12:381–2. doi: 10.1093/ecco-jcc/jjx148

199. Trubiano JA, Redwood A, Strautins K, Pavlos R, Woolnough E, Chang CC, et al. Drug-specific upregulation of CD137 on CD8+ T cells aids in the diagnosis of multiple antibiotic toxic epidermal necrolysis. *J Allergy Clin Immunol Pract.* (2017) 5:823–6. doi: 10.1016/j.jaip.2016.09.043

200. Kato K, Kawase A, Azukizawa H, Hanafusa T, Nakagawa Y, Murota H, et al. Novel interferon-gamma enzyme-linked immunoSpot assay using activated cells for identifying hypersensitivity-inducing drug culprits. *J Dermatol Sci.* (2017) 86:222–9. doi: 10.1016/j.jdermsci.2017.03.007

201. Klaewsongkram J, Thantiworasit P, Suthumchai N, Rerknimitr P, Sukasem C, Tuchinda P, et al. In vitro test to confirm diagnosis of allopurinol-induced severe cutaneous adverse reactions. *Br J Dermatol.* (2016) 175:994–1002. doi: 10.1111/bjd.14701

202. Lucas A, Lucas M, Strhyn A, Keane NM, McKinnon E, Pavlos R, et al. Abacavir-reactive memory T cells are present in drug naive individuals. *PLoS One.* (2015) 10:e0117160. doi: 10.1371/journal.pone.0117160

203. Keane NM, Pavlos RK, McKinnon E, Lucas A, Rive C, Blyth CC, et al. HLA Class I restricted CD8+ and Class II restricted CD4+ T cells are implicated in the pathogenesis of nevirapine hypersensitivity. *AIDS.* (2014) 28:1891–901. doi: 10.1097/QAD.0000000000000345

204. Tanvarasethee B, Buranapraditkun S, Klaewsongkram J. The potential of using enzyme-linked immunospot to diagnose cephalosporin-induced maculopapular exanthems. *Acta Derm Venereol.* (2013) 93:66–9. doi: 10.2340/00015555-1386

205. Phatharacharukul P, Klaewsongkram J. A case of sulfasalazine-induced hypersensitivity syndrome confirmed by enzyme-linked immunospot assay. *Allergy Asthma Immunol Res.* (2013) 5:415–7. doi: 10.4168/aair.2013.5.6.415

206. Mallal S, Nolan D, Witt C, Masel G, Martin AM, Moore C, et al. Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. *Lancet.* (2002) 359:727–32. doi: 10.1016/S0140-6736(02)07873-X

207. Khanna D, Fitzgerald JD, Khanna PP, Bae S, Singh MK, Neogi T, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. *Arthritis Care Res (Hoboken).* (2012) 64:1431–46. doi: 10.1002/acr.21772

frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 08 December 2022
DOI 10.3389/fmed.2022.935408



OPEN ACCESS

EDITED BY
Poonkiat Suchonwanit,
Mahidol University, Thailand

REVIEWED BY
Chuang-Wei Wang,
Linkou Chang Gung Memorial Hospital, Taiwan
George Golovko,
University of Texas Medical Branch at Galveston, United States

*CORRESPONDENCE
Hajirah N. Saeed
hnsaeed@uic.edu

SPECIALTY SECTION
This article was submitted to Dermatology, a section of the journal Frontiers in Medicine

RECEIVED 03 May 2022
ACCEPTED 23 November 2022
PUBLISHED 08 December 2022

CITATION
Shareef O, Kwan JT, Lau S, Tahboub MA and Saeed HN (2022) An alternative model for assessing mortality risk in Stevens Johnson syndrome/toxic epidermal necrolysis using a random forests classifier: A pilot study.
*Front. Med.* 9:935408.
doi: 10.3389/fmed.2022.935408



# An alternative model for assessing mortality risk in Stevens Johnson syndrome/toxic epidermal necrolysis using a random forests classifier: A pilot study

Omar Shareef[1,2], James T. Kwan[2,3], Sarina Lau[2,4], Mohammad Ali Tahboub[2] and Hajirah N. Saeed[2,5]*

[1]Harvard College, Cambridge, MA, United States, [2]Department of Ophthalmology, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, MA, United States, [3]Tufts University School of Medicine, Boston, MA, United States, [4]Department of Biology, Simmons University, Boston, MA, United States, [5]Department of Ophthalmology, Illinois Eye and Ear Infirmary, University of Illinois Chicago, Chicago, IL, United States

**Introduction:** Mortality risk prediction is an important part of the clinical assessment in the Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN) patient. The SCORTEN and ABCD-10 scoring systems have been used as predictive clinical tools for assessing this risk. However, some of the metrics required in calculating these scores, such as the total body surface area (TBSA) involvement, are difficult to calculate. In addition, TBSA involvement is calculated in a variety of ways and is observer dependent and subjective. The goal of this study was to develop an alternative method to predict mortality in patients with SJS/TEN.

**Methods:** Data was split into training and test datasets and preprocessed. Models were trained using five-fold cross validation. Out of several possible candidates, a random forests model was evaluated as being the most robust in predictive power for this dataset. Upon feature selection, a final random forests model was developed which was used for comparison against SCORTEN.

**Results:** The differences in both accuracy ($p$ = 0.324) and area under the receiver operating characteristic curve (AUROC) ($p$ = 0.318) between the final random forests model and the SCORTEN and ABCD-10 models were not statistically significant. As such, this alternative method performs similarly to SCORTEN while only requiring simple laboratory tests from the day of admission.

**Discussion:** This new alternative can make the mortality prediction process more efficient, along with providing a seamless implementation of the patient laboratory tests directly into the model from existing electronic health record (EHR) systems. Once the model was developed, a web application was built to deploy the model which integrates with the Epic EHR system on the

Fast Healthcare Interoperability Resources (FHIR) Application Programming Interface (API); this only requires the patient medical record number and a date of the lab tests as parameters. This model ultimately allows clinicians to calculate patient mortality risk with only a few clicks. Further studies are needed for validation of this tool.

KEYWORDS

**Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (SJS/TEN), machine learning, random forest (bagging) and machine learning, SCORTEN score, mortality risk, ABCD**

# Introduction

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are both mucocutaneous diseases that result in blistering and desquamation of the skin and mucous membranes (1, 2). The distinction between SJS and TEN is based upon the amount of skin involvement. Epidermal detachment less than 10% is considered SJS, while that between 10–30% is considered SJS-TEN overlap, and skin involvement greater than 30% is classified as TEN (3). While the exact etiology of SJS/TEN is not well understood, most cases occur as hypersensitivity reactions from the use of certain medications and can be life-threatening (4, 5).

The SCORTEN scoring system was developed in 2000 as a severity-of-illness score for SJS/TEN and has since been used for predicting mortality for individuals with SJS/TEN. The model uses seven independent risk factors to predict mortality. These include age > 40 years, heart rate > 120 beats per minute, cancer/hematologic malignancy, TBSA involvement (TBSAI) at day 1 > 10%, serum urea level > 28 mmol/L, serum bicarbonate level < 20 mmol/L, and serum glucose levels > 14 mmol/L. Presence of these risk factors indicates a higher mortality risk for the patient (6). While still an important parameter clinically, predictors such as TBSAI can be difficult to assess accurately for various reasons including the subjectivity in calculating TBSAI, the various methods that are used to calculate it, and delays in transfer to a burn unit or hospital which manages SJS/TEN patients.

In addition to the SCORTEN scoring system, another risk prediction model known as ABCD-10 has been developed recently for assessing mortality risk in patients with SJS/TEN (7). This model uses five independent risk factors for mortality prediction: age > 50 years, epidermal detachment > 10% TBSA, serum bicarbonate level < 20 mmol/L, cancer malignancy, and ongoing dialysis (7). Cancer malignancy and ongoing dialysis are associated with greater degrees of risk according to the model (7). The ABCD-10 model still requires further validation; however, preliminary studies seem to show that SCORTEN performs similarly or better than the ABCD-10 model (8, 9).

Due to the vast amount of clinical data that can now be collected through electronic health record (EHR) systems, machine learning (ML), and artificial intelligence (AI) techniques have come into greater use recently to improve clinical decision making (10). The random forests classifier is a ML technique that was developed in 2001 and employs a combination of decision tree classifiers to allow for greater generalization and reduced noise (11). The algorithm has been validated in a number of studies including those on early glaucoma detection with spectral-domain optical coherence tomography (12), classification of melanocytic lesions using dermoscopic images (13), breast cancer diagnosis (14), and prediction of stroke outcome (15).

The purpose of this study was to develop an alternative model to SCORTEN which uses laboratory results to serve as a simpler way to predict mortality and that can be easily incorporated into existing EHR systems. Since the random forest classifier has proven useful in other medical contexts, it was a natural choice when seeking to build an alternative to the SCORTEN model.

# Materials and methods

## Obtaining the data

Access to a database of individuals diagnosed with SJS/TEN was obtained ($n$ = 452). All data were collected and managed using Research Electronic Data Capture (REDCap). Data collected included demographics (**Table 1**) and lab values. Lab values relevant to the SCORTEN and ABCD-10 scoring systems (**Table 2**) were collected as well as 96 labs values unique to this study. Data samples were taken from patients who had an acute SJS/TEN episode that required admission to a Mass General Brigham hospital. All laboratory tests used for training the model were taken upon admission. Patients who did not have laboratory tests upon admission were not included in the study. There were a total of 192 patients who met these criteria. Laboratory test data were collected for these patients which included 96 unique values. The laboratory test data for these

156 patients were then split into training ($n$ = 156) and test ($n$ = 36) datasets to be used for building and validating the model. Demographic data of both the training and test dataset can be found in **Table 1**.

## Data pre-processing

Categorical data were split using one-hot encoding, and missing values for categorical data were imputed with the mode. The remaining missing values in the training dataset were handled using $k$-nearest neighbors imputation ($k$ = 3).

## Model training

A number of different types of classifiers were initially tested on the dataset using five-fold cross validation. The implementation of all classifiers was carried out using the sci-kit learn Python library. These included support-vector machine (SVM), logistic regression, ridge regression, decision tree, and random forest classifiers (RFC) models. The laboratory data were fed into the model, and the ground truth corresponded to whether the patient had died during the acute SJS/TEN episode or survived. Upon cross validation, it was found that an RFC was the most robust in predictive power and was then used for the remainder of the study. Cross validation was then performed again to find the best hyperparameter set for an RFC model that was trained on the full set of predictors. The top five predictors on the training set of this model were found, and the remaining RFCs were trained using only this subset of predictors. This subset of predictors in order of importance were: nucleated red blood cell (NRBC) number, total bilirubin, prothrombin time (PT), white blood cells (WBC), and red blood cells (RBC). The data were pre-processed again in the same manner as the full dataset with this subset of predictors to ensure past predictors were not affecting the newer model. Because the dataset was quite imbalanced, with there being fewer deceased patients than living patients due to the mortality rate of SJS/TEN, various techniques were used to account for this. RFC models were trained on a dataset with no imbalance correction, upsampling of the data, and downsampling of the data. Imbalance correction was carried out using the imblearn library. Upsampling yielded the RFC model with the greatest accuracy when trained on the subset of predictors.

## Deploying the application

Once the model was trained, it was deployed into a clinician facing web app using Flask and Python along with Epic on FHIR API. By integrating Epic on FHIR API, clinicians can enter the MRN of the patient and the date for the lab tests that they wish to use to input into the model. If relevant lab tests were collected on that date, the model will output a mortality score. The deployment of the model in a web app paired with integration of the Epic on FHIR API makes the use of this mortality prediction system extremely simple.

$$95\%\ \mathrm{CI} = A \pm 1.96\mathrm{SE}(A)$$

## Statistical analysis

Accuracy between the SCORTEN and RFC models were compared using a paired $t$-test. Area under the receiver operating curve (AUROC) were compared using the method outlined by Hanley and McNeil (16). The 95% confidence interval was calculated as follows:

$$95\%\ \mathrm{CI} = A \pm 1.96\mathrm{SE}(A)$$

Where $A$ is the AUROC and SE is the standard error of the AUROC. The SE was determined as follows:

$$\mathrm{SE\ (AUROC)} = \sqrt{\frac{A\,(1-A) + (n_p - 1)\,(Q1 - A^2) + (n_n - 1)\,(Q2 - A^2)}{Np * Nn}}$$

Where $n_p$ is the number of positive cases in the test set (which corresponds to individuals who were deceased after the acute SJS/TEN episode) and $n_n$ is the number of negative test cases in the test set (which denotes the individuals who remained alive).

Q1 and Q2 were determined as follows:

$$Q1 = \frac{A}{2-A},\ Q2 = \frac{2 * A^2}{1+A}$$

Where Q1 is the probability that two randomly chosen samples of deceased individuals will both be ranked with greater suspicion than a randomly chosen living individual and Q2 is the probability that one randomly chosen deceased individual will be ranked with greater suspicion than two randomly chosen living individuals.

# Results

SCORTEN and ABCD score breakdowns can be found in **Table 2**. For the testing data, the accuracy, AUROC, specificity, and sensitivity for the SCORTEN model were 0.833, 0.688 (95% CI, 0.45–0.92), 0.931, and 0.429, respectively. For the RFC model, the accuracy, AUROC, specificity, and sensitivity were 0.889, 0.842 (95% CI, 0.65–1.03), 1.0, and 0.429, respectively. For the ABCD model, the accuracy, AUROC, specificity, and sensitivity were 0.778, 0.574 (95% CI, 0.33–0.82), 0.966, and 0.0. These results have been summarized in **Tables 3**, **4**. The differences in both accuracy ($p$ = 0.324) and AUROC ($p$ = 0.318)

TABLE 1 Demographics of training and test datasets.

| Demographics | Training dataset | | Testing dataset | |
|---|---|---|---|---|
| | Survived to discharge ($n$ = 129) | Died in the hospital ($n$ = 27) | Survived to discharge ($n$ = 29) | Died in the hospital ($n$ = 7) |
| Female, no. | 71 | 9 | 14 | 5 |
| Age (mean) | 46 | 60 | 44 | 66 |
| Hispanic or Latino | 6 | 0 | 4 | 0 |
| ***Race*** | | | | |
| White | 83 | 15 | 16 | 6 |
| Black | 18 | 6 | 3 | 0 |
| Asian | 10 | 2 | 2 | 0 |
| Other | 1 | 0 | 0 | 0 |
| Unknown/Not reported | 17 | 4 | 8 | 1 |

were not statistically significant when comparing SCORTEN to the RFC model. Differences in accuracy (0.083) and AUROC (0.091) were not statistically significant for ABCD-10 versus the RFC model as well. The five features used to train this algorithm in order of importance were: NRBC count, total bilirubin, PT, WBC count, and RBC count (LOINC codes: 771-6, 42,719-5, 5,902-2, 6,690-2, and 789-8, respectively). The ROC curves can be seen in **Figure 1**.

The model was then deployed on a web server using the Epic on FHIR API. An example of an integrated SJS/TEN Mortality Predictor is shown in **Figure 2**.

## Discussion

The medical community has progressed significantly in its understanding of SJS/TEN but mortality rates continue to remain high at 10–34% (3). Accurate assessment of mortality risk is important in disease prognostication, management, and patient/family provider discussions. It is unclear whether systemic treatments beyond supportive care improve mortality, but there has been recent interest in various immunomodulatory therapies in reducing mortality risk (3). Determining the effectiveness of these potential treatments for different risk cohorts requires accurate and precise mortality risk measurement. Patient and family counseling also heavily relies on mortality risk assessment.

This mortality risk is traditionally calculated with the SCORTEN, a prognostic score which predicts in-hospital mortality during acute SJS/TEN. A high SCORTEN score may also be a risk factor for death after discharge (17). SCORTEN is also often used as a benchmark against which mortality after treatments and interventions are compared.

The SCORTEN model uses seven independent risk factors upon admission to predict mortality: age > 40 years, heart rate > 120 beats per minute, cancer/hematologic malignancy, TBSA involvement > 10%, serum urea level > 28 mmol/L,

TABLE 2 SCORTEN and ABCD scores for testing data.

| Testing data | Survived ($n$ = 29) | Died ($n$ = 7) |
|---|---|---|
| **SCORTEN at admission** | | |
| Age > 40 | 17 | 6 |
| HR > 120 | 5 | 1 |
| BSA > 10% | 10 | 4 |
| Cancer | 4 | 2 |
| Serum BUN > 28 mg/dL | 4 | 3 |
| Serum glucose > 252 mg/dL | 1 | 0 |
| Serum bicarbonate < 20 mmol/L | 10 | 2 |
| Mean SCORTEN score | 1.76 | 2.57 |
| **ABCD at admission** | | |
| Age > 50 | 14 | 4 |
| BSA > 10% | 10 | 4 |
| Cancer | 4 | 2 |
| Serum bicarbonate < 20 mmol/L | 10 | 2 |
| Dialysis | 1 | 0 |
| Mean ABCD-10 score | 1.55 | 2.00 |

TABLE 3 SCORTEN versus random forest performance.

| | SCORTEN | Random forest | $P$-value |
|---|---|---|---|
| Accuracy | 0.833 | 0.889 | 0.324 |
| AUROC | 0.688 | 0.842 | 0.318 |
| Specificity | 0.931 | 1.000 | |
| Sensitivity | 0.429 | 0.429 | |

TABLE 4 ABCD versus random forest performance.

| | ABCD | Random forest | $P$-value |
|---|---|---|---|
| Accuracy | 0.778 | 0.889 | 0.083 |
| AUROC | 0.574 | 0.842 | 0.091 |
| Specificity | 0.966 | 1.000 | |
| Sensitivity | 0.000 | 0.429 | |

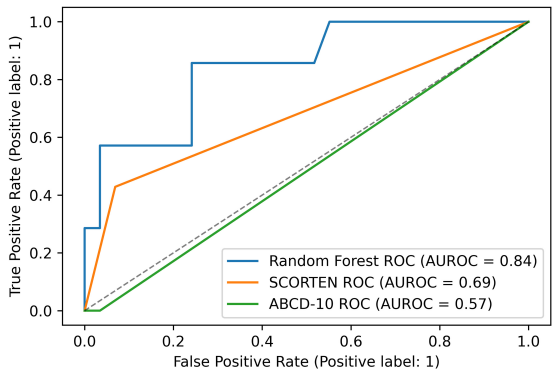


FIGURE 1
A graph depicting receiver operating characteristic (ROC) curves for random forest, SCORTEN, and ABCD-10 scoring systems.

serum bicarbonate level < 20 mmol/L, and serum glucose levels > 14 mmol/L. The most difficult to calculate of these is the TBSA. For SCORTEN, an exact degree of TBSA involvement isn't required, but rather, an assessment of TBSA involvement as less than or greater than 10%. Values significantly lower or higher than 10% are easily calculated and categorized, but those closer to 10% are difficult to categorize as measurement of TBSAI is highly observer dependent and subjective, and there are a variety of methods used to determine the TBSA involved. Furthermore, a single TBSAI measurement does not take into account progressive epidermal loss and TBSAI may be more sensitive to change over time as compared to other risk variables (17). Other alternatives to SCORTEN have been proposed; the most popular being ABCD-10 which stands for age, bicarbonate, cancer, dialysis, 10% BSA. Studies comparing the accuracy of SCORTEN and ABCD-10 have largely found SCORTEN to be superior or equivalent to ABCD-10 (18–20). ABCD-10, like SCORTEN, also requires calculation of TBSAI.

While TBSAI remains a clinically important tool, particularly in determining fluid resuscitation and management, it may not need to be used as a variable in a mortality risk prediction model as demonstrated by this pilot study. Another model of mortality risk prediction, described in 2021, uses the red cell distribution width to hemoglobin ratio as categorical measurements and found this alone to be comparable to the SCORTEN scoring system (21).

In addition to the difficulty in calculating TBSAI, a common criticism of both the SCORTEN and ABCD-10, is that they simplify continuous and dynamic biologic measurements into dichotomous variables, losing a significant amount of information, particularly in the skin assessment which does not take morphology or location into account (18).

While our proposed RFC model does not account for dynamic biologic measurements over time, the use of several continuous variables that are automatically pulled may allow for greater accuracy in mortality risk prediction, better prognostication over time, and may prove useful as a daily monitoring tool. None of the current scoring systems takes into account the time point after disease onset when a patient was admitted, as all variables are collected within 24 h of admission, with no regard to disease onset. It is unclear how much of an effect admission delay has on the accuracy of scoring systems. A 2006 study found that delay-adjusted SCORTEN scores were comparable to crude scores but that there was significant difference in score between days 1 and 4 (19). Another study showed that SCORTEN and ABCD-10 performed differently depending on when after admission data were collected (20). Our model also does not take time point into account; however, we believe that the use of only lab values as continuous variables may allow for stability over time. We plan to study this in the near future.

In our model, the top five predictors in order of importance were NRBC count, total bilirubin, PT, WBC count, and RBC count. These values from day of admission were the only ones used in the RFC model and are easily calculated and standard of care. The deployment of the model using a web server demonstrates the ease of use when implementing this alternative method. Using the Epic on FHIR API for pulling EHR data from patients in existing healthcare systems, a web app was built that allows clinicians to log in with their Epic credentials. By inputting the MRN of the patient in question and the date of the laboratory tests which they would like to use, the web app is able to use the Epic on FHIR API to pull the necessary laboratory tests and output a predicted probability score for the mortality of the patient using the RFC trained above. Such an application can prove useful in a clinical setting by allowing clinicians to easily, accurately, and quickly predict mortality for patients with SJS/TEN and decide on a course of action for the patient's treatment. These objective measures can also prove useful in both prospective and retrospective research studying the effect of treatments on mortality. Furthermore, interobserver discrepancies in TBSAI would not affect the calculated mortality risk.

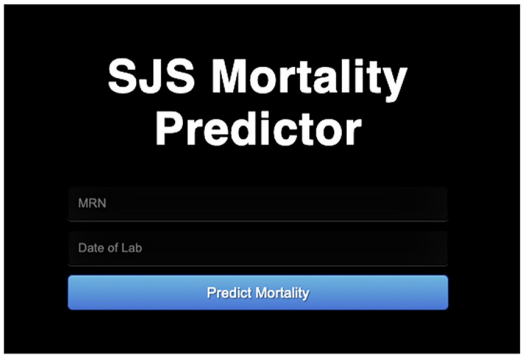


FIGURE 2
Deployment interface for web application.

While further validation of this model needs to be done on larger datasets and in a prospective manner, the similar performance between the SCORTEN and our RFC model indicates that the RFC model may be utilized as an alternative to SCORTEN in the future. Furthermore, given that the RFC model relies only on objective data that can be gleaned from patient laboratory tests, the RFC model may be put into use more simply than other methods.

## Limitations

The main limitation in this study was the sample size. The sample size in this study is significant given how rare SJS/TEN is and the single-center nature of this study, but ML models perform best with larger datasets. This pilot study demonstrates the potential utility of this RFC model as a proof of concept but should be tested on larger datasets with multicenter involvement. We plan to conduct these larger studies in the future to further validate and improve the model before implementing it in any clinical settings.

Furthermore, due to disease progression for some SJS/TEN patients, mortality predictions may change as time progresses. Due to the retroactive nature of the data collection, the time points of mortality risk calculation were not standardized. However, most patients had the necessary data to calculate risk at the day of admission so this was the only time point used in this study. Future improvements to the model include factoring in various time points during the patient's treatment period in a prospective fashion for predicting patient mortality over a longer period of time, including after discharge.

## Data availability statement

The datasets presented in this article are not readily available because they include confidential patient data. Requests to access the datasets should be directed to HS, hnsaeed@uic.edu.

## Author contributions

OS and HS contributed to the conception and design of the study. JK, SL, and MT organized the database. OS performed the statistical analysis. OS wrote the first draft of the manuscript. OS, JK, and HS wrote the sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

## Funding

The project described was supported by the National Eye Institute, National Institutes of Health, Award Number K23EY028230. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

## References

1. Mockenhaupt M. The current understanding of Stevens-Johnson syndrome and toxic epidermal necrolysis. *Expert Rev Clin Immunol.* (2011) 7:803–13; quiz 814–5. doi: 10.1586/eci.11.66

2. Hazin R, Ibrahimi O, Hazin M, Kimyai-Asadi A. Stevens-Johnson syndrome: pathogenesis, diagnosis, and management. *Ann Med.* (2008) 40:129–38. doi: 10.1080/07853890701753664

3. Lerch M, Mainetti C, Terziroli Beretta-Piccoli B, Harr T. Current perspectives on Stevens-Johnson syndrome and toxic epidermal necrolysis. *Clin Rev Allergy Immunol.* (2018) 54:147–76. doi: 10.1007/s12016-017-8654-z

4. Bohigian G. *The history of Stevens-Johnson Syndrome and A Case Study*. St Louis: Center for History of Medicine at Washington University School of Medicine (2015). 10 p.

5. University of Utah Burn Center. *Toxic Epidermal Necrolysis Syndrome (TEN) & Stevens-Johnson Syndrome (SJS)*. (2021). Available online at: https://healthcare.utah.edu/burncenter/conditions-treatment/epidermal-necrolysis-syndrome-stevens-johnson-syndrome.php (accessed January 23, 2022).

6. Bastuji-Garin S, Fouchard N, Bertocchi M, Roujeau J, Revuz J, Wolkenstein P. SCORTEN: a severity-of-illness score for toxic epidermal necrolysis.

*J Invest Dermatol.* (2000) 115:149–53. doi: 10.1046/j.1523-1747.2000.00061.x

7. Noe M, Rosenbach M, Hubbard R, Mostaghimi A, Cardones A, Chen J, et al. Development and validation of a risk prediction model for in-hospital mortality among patients with stevens-johnson syndrome/toxic epidermal necrolysis—ABCD-10. *JAMA Dermatol.* (2019) 155:448–54. doi: 10.1001/jamadermatol.2019.0998

8. Duplisea M, Roberson M, Chrisco L, Strassle P, Williams F, Ziemer C. Performance of ABCD-10 and SCORTEN mortality prediction models in a cohort of patients with Stevens-Johnson syndrome/toxic epidermal necrolysis. *J Am Acad Dermatol.* (2021) 85:873–7. doi: 10.1016/j.jaad.2021.04.082

9. Koh H, Fook-Chong S, Lee H. Assessment and comparison of performance of ABCD-10 and SCORTEN in prognostication of epidermal necrolysis. *JAMA Dermatol.* (2020) 156:1294–9. doi: 10.1001/jamadermatol.2020.3654

10. Jiang F, Jiang Y, Zhi H, Dong Y, Li H, Ma S, et al. Artificial intelligence in healthcare: past, present and future. *Stroke Vasc Neurol.* (2017) 2:230–43. doi: 10.1136/svn-2017-000101

11. Breiman L. *Random Forests*. Berkeley, CA: Statistics Department University of California (2001).

12. Asaoka R, Hirasawa K, Iwase A, Fujino Y, Murata H, Shoji N, et al. Validating the usefulness of the "Random Forests" classifier to diagnose early glaucoma with optical coherence tomography. *Am J Ophthalmol.* (2017) 174:95–103. doi: 10.1016/j.ajo.2016.11.001

13. Ferris L, Harkes J, Gilbert B, Winger D, Golubets K, Akilov O, et al. Computer-aided classification of melanocytic lesions using dermoscopic images. *J Am Acad Dermatol.* (2015) 73:769–76. doi: 10.1016/j.jaad.2015.07.028

14. Dai B, Chen R, Zhu S, Zhang W. Using random forest algorithm for breast cancer diagnosis. *Proceedings of the 2018 International Symposium on Computer, Consumer and Control (IS3C)*. Taichung: IEEE (2018). p. 449–52. doi: 10.1109/IS3C.2018.00119

15. Fernandez-Lozano C, Hervella P, Mato-Abad V, Rodríguez-Yáñez M, Suárez-Garaboa S, López-Dequidt I, et al. Random forest-based prediction of stroke outcome. *Sci Rep.* (2021) 11:10071. doi: 10.1038/s41598-021-89434-7

16. Hanley J, McNeil B. The meaning and use of the area under a receiver operating characteristic (ROC) Curve. *Radiology.* (1982) 143:29–36. *edit. doi: 10.1148/radiology.143.1.7063747

17. Retrouvey H, Chan J, Shahrokhi S. Comparison of two-dimensional methods versus three-dimensional scanning systems in the assessment of total body surface area estimation in burn patients. *Burns.* (2018) 44:195–200. doi: 10.1016/j.burns.2017.07.003

18. Dobry A, Himed S, Waters M, Kaffenberger B. Scoring assessments in Stevens-Johnson syndrome and toxic epidermal necrolysis. *Front Med.* (2022) 9:883121. doi: 10.3389/fmed.2022.883121

19. Guégan S, Bastuji-Garin S, Poszepczynska-Guigné E, Roujeau J, Revuz J. Performance of the SCORTEN during the first five days of hospitalization to predict the prognosis of epidermal necrolysis. *J Invest Dermatol.* (2006) 126:272–6. doi: 10.1038/sj.jid.5700068

20. Suo H, Jiang B, Sun X, Dong J, Alamgir M, Guan X, et al. Comparing the accuracy of ABCD-10 and SCORTEN in predicting the in-hospital mortality of Stevens-Johnson Syndrome/Toxic epidermal necrolysis: a multi-institutional study from Central China. *Dermatology.* (2022) 238:736–44. doi: 10.1159/000520494

21. Koh H, Fook-Chong S, Lee H. Improvement of mortality prognostication in patients with epidermal necrolysis: the role of novel inflammatory markers and proposed revision of SCORTEN (Re-SCORTEN). *JAMA Dermatol.* (2022) 158:160–6. doi: 10.1001/jamadermatol.2021.5119

frontiers | Frontiers in Medicine

TYPE Review
PUBLISHED 11 October 2023
DOI 10.3389/fmed.2023.1213889



OPEN ACCESS

EDITED BY
Je-Ho Mun,
Seoul National University, Republic of Korea

REVIEWED BY
David Andrew Fulcher,
Australian National University, Australia
Omer Iqbal,
Loyola University Chicago, United States

*CORRESPONDENCE
Elizabeth J. Phillips
✉ elizabeth.j.phillips@vumc.org

†These authors have contributed equally to this work and share first authorship

RECEIVED 28 April 2023
ACCEPTED 31 July 2023
PUBLISHED 11 October 2023

CITATION
Marks ME, Botta RK, Abe R, Beachkofsky TM, Boothman I, Carleton BC, Chung W-H, Cibotti RR, Dodiuk-Gad RP, Grimstein C, Hasegawa A, Hoofnagle JH, Hung S-I, Kaffenberger B, Kroshinsky D, Lehloenya RJ, Martin-Pozo M, Micheletti RG, Mockenhaupt M, Nagao K, Pakala S, Palubinsky A, Pasieka HB, Peter J, Pirmohamed M, Reyes M, Saeed HN, Shupp J, Sukasem C, Syu JY, Ueta M, Zhou L, Chang W-C, Becker P, Bellon T, Bonnet K, Cavalleri G, Chodosh J, Dewan AK, Dominguez A, Dong X, Ezhkova E, Fuchs E, Goldman J, Himed S, Mallal S, Markova A, McCawley K, Norton AE, Ostrov D, Phan M, Sanford A, Schlundt D, Schneider D, Shear N, Shinkai K, Tkaczyk E, Trubiano JA, Volpi S, Bouchard CS, Divito SJ and Phillips EJ (2023) Updates in SJS/TEN: collaboration, innovation, and community.
*Front. Med.* 10:1213889.
doi: 10.3389/fmed.2023.1213889



# Updates in SJS/TEN: collaboration, innovation, and community

Madeline E. Marks[1†], Ramya Krishna Botta[1†], Riichiro Abe[2], Thomas M. Beachkofsky[3], Isabelle Boothman[4], Bruce C. Carleton[5], Wen-Hung Chung[6], Ricardo R. Cibotti[7], Roni P. Dodiuk-Gad[8,9,10], Christian Grimstein[11], Akito Hasegawa[2], Jay H. Hoofnagle[12], Shuen-Iu Hung[13], Benjamin Kaffenberger[14], Daniela Kroshinsky[15], Rannakoe J. Lehloenya[16], Michelle Martin-Pozo[1], Robert G. Micheletti[17], Maja Mockenhaupt[18], Keisuke Nagao[7], Suman Pakala[1], Amy Palubinsky[1], Helena B. Pasieka[3,19,20], Jonathan Peter[21], Munir Pirmohamed[22], Melissa Reyes[23], Hajirah N. Saeed[24], Jeffery Shupp[25], Chonlaphat Sukasem[26], Jhih Yu Syu[27], Mayumi Ueta[28], Li Zhou[29], Wan-Chun Chang[5], Patrice Becker[30], Teresa Bellon[31], Kemberlee Bonnet[32], Gianpiero Cavalleri[4], James Chodosh[33], Anna K. Dewan[34], Arturo Dominguez[35], Xinzhong Dong[36], Elena Ezhkova[37], Esther Fuchs[38], Jennifer Goldman[39], Sonia Himed[40], Simon Mallal[41], Alina Markova[42], Kerry McCawley[43], Allison E. Norton[44], David Ostrov[45], Michael Phan[46], Arthur Sanford[47], David Schlundt[32], Daniel Schneider[48], Neil Shear[8], Kanade Shinkai[49], Eric Tkaczyk[50], Jason A. Trubiano[51], Simona Volpi[52], Charles S. Bouchard[53], Sherrie J. Divito[15] and Elizabeth J. Phillips[1*]

[1]Center for Drug Interactions and Immunology, Division of Infectious Disease, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, United States, [2]Division of Dermatology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan, [3]Departments of Dermatology and Medicine, Uniformed Services University, Bethesda, MD, United States, [4]The SFI Centre for Research Training in Genomics Data Science, Dublin, Ireland, [5]Division of Translational Therapeutics, Department of Pediatrics, Faculty of Medicine, University of British Columbia and the British Columbia Children's Hospital Research Institute, Vancouver, BC, Canada, [6]Department of Dermatology, Drug Hypersensitivity Clinical and Research Center, Chang Gung Memorial Hospital, Taoyuan, Taiwan, [7]National Institute of Arthritis and Musculoskeletal and Skin (NIAMS), National Institutes of Health (NIH), Bethesda, MD, United States, [8]Department of Dermatology, Emek Medical Center, Afula, Israel, [9]Division of Dermatology, Department of Medicine, University of Toronto, Toronto, ON, Canada, [10]Department of Dermatology, Bruce Rappaport Faculty of Medicine, Technion Institute of Technology, Haifa, Israel, [11]Office of Clinical Pharmacology, Office of Translational Sciences, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD, United States, [12]Liver Disease Research Branch, Division of Digestive Diseases and Nutrition of NIDDK, National Institutes of Health (NIH), Bethesda, MD, United States, [13]Cancer Vaccine and Immune Cell Therapy Core Laboratory, Department of Medical Research, Chang Gung Memorial Hospital, Taoyuan, Taiwan, [14]Department of Dermatology, Ohio State University Wexner Medical Center, Columbus, OH, United States, [15]Department of Dermatology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States, [16]Division of Dermatology, Department of Medicine, University of Cape Town, Cape Town, South Africa, [17]Department of Dermatology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, United States, [18]Dokumentationszentrum schwerer Hautreaktionen (dZh), Department of Dermatology, Medical Center and Medical Faculty, University of Freiburg, Freiburg, Germany, [19]The Burn Center, MedStar Washington Hospital Center, Washington, D.C., DC, United States, [20]Department of Dermatology, MedStar Health/Georgetown University, Washington, D.C., DC,

United States, [21]Division of Allergy and Clinical Immunology, Department of Medicine, University of Cape Town, Cape Town, South Africa, [22]Department of Pharmacology and Therapeutics, University of Liverpool, Liverpool, United Kingdom, [23]Center for Drug Evaluation and Research, United States Food and Drug Administration, Silver Spring, MD, United States, [24]Massachusetts Eye and Ear, Harvard Medical School, Boston, MA, United States, [25]Department of Surgery, Plastic and Reconstructive Surgery, Biochemistry, and Molecular and Cellular Biology, MedStar Washington Hospital Center, Georgetown University School of Medicine, Washington, D.C., DC, United States, [26]Department of Pathology, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand, [27]Department of Cell Biology and Anatomy, College of Medicine, National Cheng Kung University, Tainan, Taiwan, [28]Department of Frontier Medical Science and Technology for Ophthalmology, Kyoto Prefectural University of Medicine, Kyoto, Japan, [29]Division of General Internal Medicine and Primary Care, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States, [30]Division of Allergy, Immunology, and Transplantation, National Institute of Allergy and Infectious Disease, Bethesda, MD, United States, [31]Drug Hypersensitivity Laboratory, La Paz Health Research Institute (IdiPAZ), Madrid, Spain, [32]Department of Psychology, Vanderbilt University, Nashville, TN, United States, [33]University of New Mexico School of Medicine, Albuquerque, NM, United States, [34]Department of Dermatology, Vanderbilt University Medical Center, Nashville, TN, United States, [35]Department of Dermatology and Internal Medicine, UT Southwestern Medical Center, Dallas, TX, United States, [36]Department of Neuroscience, Johns Hopkins University School of Medicine, Baltimore, MD, United States, [37]Department of Cell, Developmental, and Regenerative Biology and Dermatology, Black Family Stem Cell Institute, Mount Sinai School of Medicine, New York, NY, United States, [38]Department of Obstetrics and Gynecology, University of Washington, Seattle, WA, United States, [39]Division of Pediatric Infectious Diseases and Clinical Pharmacology, Children's Mercy, Kansas City, MO, United States, [40]College of Medicine, University of Cincinnati, Cincinnati, OH, United States, [41]Division of Infectious Diseases, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, United States, [42]Department of Dermatology, Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, New York, NY, United States, [43]Stevens-Johnson Syndrome Foundation, Westminster, CO, United States, [44]Division of Pediatric Allergy, Immunology, and Pulmonary Medicine, Department of Pediatrics, Vanderbilt University Medical Center, Nashville, TN, United States, [45]Department of Pathology, Immunology and Laboratory Medicine, University of Florida, Gainesville, FL, United States, [46]Division of Pharmacovigilance-I, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD, United States, [47]Division of Trauma, Surgical Critical Care, and Burns, Loyola University Medical Center, Chicago, IL, United States, [48]Department of Psychiatry and Surgery, MedStar Washington Hospital Center, Georgetown University School of Medicine, Washington, D.C., DC, United States, [49]Department of Dermatology, University of California, San Francisco, San Francisco, CA, United States, [50]Department of Veterans Affairs, Vanderbilt Dermatology Translational Research Clinic (VDTRC.org), Nashville, TN, United States, [51]Department of Infectious Diseases and Medicine, Austin Health, University of Melbourne, Melbourne, VIC, Australia, [52]National Human Genome Research Institute (NHGRI), National Institutes of Health (NIH), Bethesda, MD, United States, [53]Department of Opthalmology, Loyola University Medical Center, Chicago, IL, United States

Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN) is a predominantly drug-induced disease, with a mortality rate of 15–20%, that engages the expertise of multiple disciplines: dermatology, allergy, immunology, clinical pharmacology, burn surgery, ophthalmology, urogynecology, and psychiatry. SJS/TEN has an incidence of 1–5/million persons per year in the United States, with even higher rates globally. One of the challenges of SJS/TEN has been developing the research infrastructure and coordination to answer questions capable of transforming clinical care and leading to improved patient outcomes. SJS/TEN 2021, the third research meeting of its kind, was held as a virtual meeting on August 28–29, 2021. The meeting brought together 428 international scientists, in addition to a community of 140 SJS/TEN survivors and family members. The goal of the meeting was to brainstorm strategies to support the continued growth of an international SJS/TEN research network, bridging science and the community. The community workshop section of the meeting focused on eight primary themes: mental health, eye care, SJS/TEN in children, non-drug induced SJS/TEN, long-term health complications, new advances in mechanisms and basic science, managing long-term scarring, considerations for skin of color, and COVID-19 vaccines. The meeting featured several important updates and identified areas of unmet research and clinical need that will be highlighted in this white paper.

KEYWORDS

**Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, severe adverse cutaneous drug reactions, HLA genotyping, pharmacogenomics, body surface area, electronic medical record, SCORTEN**

# 1. Introduction

Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are life-threatening, immunologically-mediated, severe, cutaneous adverse drug reactions (IM-ADRs) (1). They are thought to be clinically and mechanistically one illness defined across a spectrum of severity and classified according to the extent of body surface area (BSA) detached: SJS (<10% BSA detached), SJS/TEN (10–30% BSA detached), and TEN (>30% BSA detached) (2). SJS/TEN has an overall mortality of 15–20% but can be more than 50% in the elderly and immunocompromised (2). The incidence rate for SJS/TEN is 1–5 cases per million persons annually in the developed world (3). These rates are likely even higher in the developing world, where many infectious diseases are endemic, and corresponding treatments include drugs that are commonly associated with SJS/TEN. Although SJS/TEN can have an underlying infectious etiology, it is more commonly related to small-molecule drug therapies in more than 80% of adults (4). Drug therapies with the highest risks include aromatic antiepileptic drugs, sulfonamide antibiotics, and allopurinol (1). A causality assessment tool, known as the algorithm of drug causality for EN (ALDEN), defines drugs with a score of 4 or higher as being at higher risk of being associated with SJS/TEN (5). Over the last two decades, research has revealed that drug-induced SJS/TEN is an HLA class I-restricted CD8+ T-cell mediated disease (6). Yet, most drugs still lack known HLA risk alleles and other genetic associations. For some drugs, an HLA risk allele defined in one population will not actually be the main HLA risk association generalizable across all populations. If a known risk HLA allele is present, however, the risk of developing SJS/TEN is thought to be equal across different races and ethnicities. More research is needed to gain a more comprehensive understanding of the genetic risk factors associated with SJS/TEN. Stereotyping and race-based testing for HLA risk is discouraged (6, 7).

Several conferences have furthered goals of increased mentoring and networking in the field of SJS/TEN. In 2021, a two-day virtual meeting titled "SJS/TEN 2021: Collaboration, Innovation, and Community" brought together scientists and community members (Figure 1) to promote awareness, review recent progress, and set priorities for improving patient outcomes (4, 6, 8). At this meeting, we were saddened to acknowledge the loss of a great leader in SJS/TEN: Professor Jean-Claude Roujeau (9) (Supplementary Figure). This international meeting was built on the success of previous conferences in 2017 (8) and 2019 (4) highlighting the cutting-edge research on the prediction, prevention, early diagnosis, and treatment of SJS/TEN. In this paper we review the current state of knowledge in the field, along with the future priorities for patients, providers, and researchers.

Improving outcomes and raising awareness for SJS/TEN requires community engagement and is extremely important for moving the field forward. Awareness among physicians and broad healthcare constituencies is essential to facilitating early identification, diagnosis, and accurate documentation of high-risk medications in the electronic health records (EHR) for SJS/TEN. Patients perceive that most providers are not appropriately trained in the recognition, early diagnosis, triage, or treatment of SJS/TEN. Part of the challenge is the lack of high-level evidence to support specific therapeutic interventions. However, across critical care, the implementation of supportive care has made the most difference in patient outcomes, which stands true today (10). Additionally, the development and distribution of standardized care plans for SJS/TEN would also be beneficial for mending this gap. Delphi-based consensus exercises have both supported a consensus on the best supportive care practice (11) for SJS/TEN. A survey of SJS survivors attending SJS/TEN 2021 identified several barriers to receiving the post-discharge information and care they need (12).

SJS/TEN patients have also stressed the need for a standardized care protocol for improving patient outcomes (Table 1). SJS/TEN patients and survivors are concerned with the provision of standardized guidelines, a multidisciplinary team, and universal protocols for eye care during the acute stage of SJS/TEN. Patients would benefit from a standardized evidence-based protocol for early transfer to specialized facilities, that include both dermatologic and intensive care, for diagnosis and treatment (6). Additionally, the development of take-home care guidelines, and the distribution of educational materials to medical teams, patients, and caregivers would help improve post-discharge outcomes (12).

Decreasing the time to diagnosis and immediate cessation of the most likely implicated drug(s) is critical (6). Additionally, documenting all potentially implicated drugs in the EHR is imperative to ensure future drug safety. Optimization of specialized protocols, such as eye care, is necessary to reduce long-term ocular complications like blindness. Early engagement of a multidisciplinary team comprised of dermatology, ophthalmology, gynecology, urology, pulmonology, gastroenterology, psychology and/or psychiatry, and pharmacy is also essential to the creation of an effective rehabilitation plan. Such a plan should be decided directly upon admission to preserve a patient's quality of life.

Another key issue for SJS/TEN is the lack of appropriate follow-up post-discharge. Patients need guidance on proper follow-up care from knowledgeable professionals to ensure physical, mental, and emotional recovery. Follow-ups with specialists and discharge materials, like a list of low versus high-risk drugs, are vital. Another priority voiced by SJS/TEN survivors and their families were referrals, by providers, to community and psychosocial support groups. These groups, whether face-to-face or online, would help to facilitate continued engagement and education following discharge from acute care (12).

# 2. Preventive efforts

## 2.1. Advances in SJS/TEN pharmacogenomics

Clinical implementation and assessment for pharmacogenetic risk markers before initiating drugs suspected of causing severe cutaneous adverse reactions (SCARs) has added significantly to prevention and diagnosis. Several medical centers worldwide have implemented clinical pharmacogenetic services with an aim to prevent SCARs, including SJS/TEN, and have reported on this experience (13–18). The preliminary results of large-scale prospective pharmacogenetic screenings conducted in Southeast Asia have substantially reduced rates of SCARs (19). HLA-B*15:02 genotyping prior to carbamazepine administration was found to be a cost-effective means to preventing carbamazepine-induced SJS/TEN. This has been shown in several, but not all, Asian countries (20), like Southeast and South Asian countries where the population has a higher HLA-B*15:02 allele frequency (5–20%), and a strong association between HLA-B*15:02 and SJS/

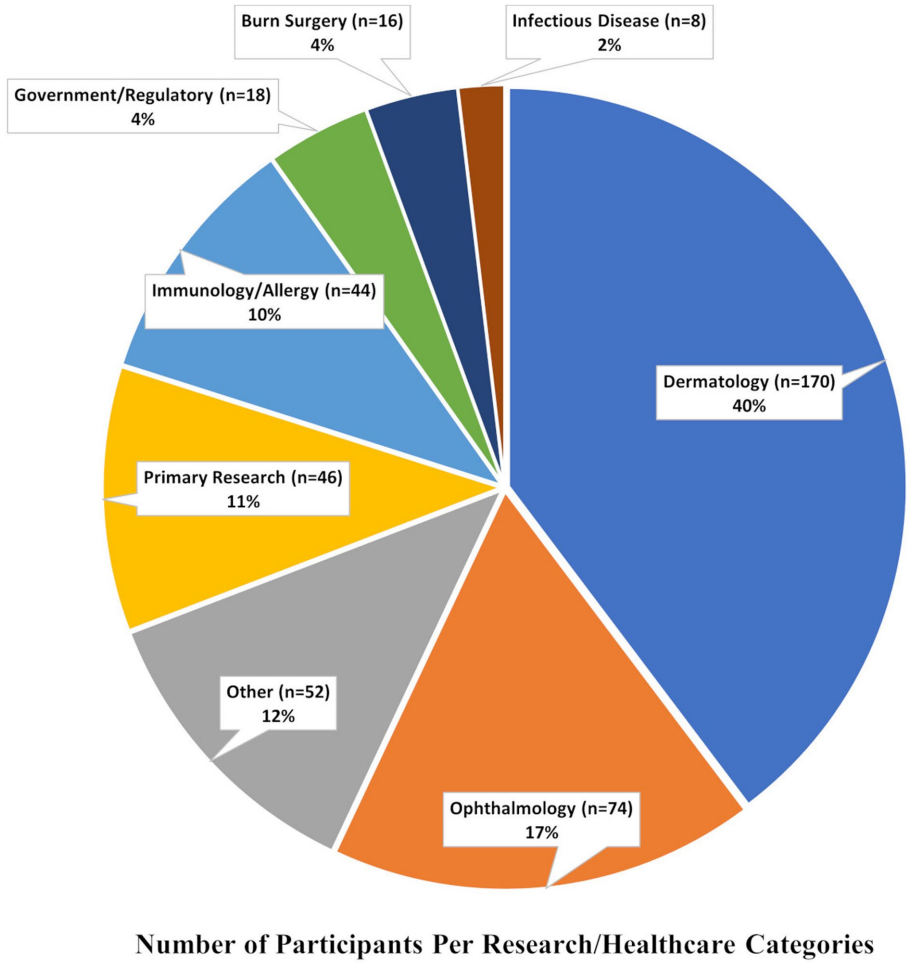


FIGURE 1
Pie chart representing the percentage of participants per research/healthcare categories.

TEN (21). The cost of HLA-B*15:02 screening is paid by national health insurance (Figure 2) in Hong Kong, Taiwan, Singapore (Chinese and Malay ethnicity), Thailand, and China (20). Caveats have been raised to the fact that the B75 serotype of HLA (which includes not only HLA-B*15:02 but HLA-B*15:21, HLA-B*15:08, HLA-B*15:11, HLA-B*15:30 and HLA-B*15:3) has been associated with carbamazepine SJS/TEN, however, the cost-effective single allele assays have been largely set-up to detect only HLA-B*15:02. Reports of carbamazepine SJS/TEN in patients carrying these other B75 HLA serotypes have been a primary reason in Southeast Asian countries for HLA-B*15:02 not detecting all patients at risk of developing carbamazepine SJS/TEN (22–25). Not all HLA alleles are associated with multiple clinical phenotypes of SCAR. For instance, HLA-B*58:01 is associated with both allopurinol SJS/TEN and drug reaction with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome (DRESS/DIHS), however, HLA-B*15:02 is only associated with carbamazepine SJS/TEN. Therefore, even in Southeast Asia if an individual was negative for HLA-B*15:02 and other B75 HLA serotypes, they would still be at risk for carbamazepine DRESS/DIHS (Table 2) (26, 27) which has been associated with HLA-A*31:01.

A model for precision medicine for the prediction and prevention of severe cutaneous adverse drug reactions (SCARs) including SJS/TEN has been the integration of pharmacogenetics into electronic health records (EHR) in Southeast Asian countries such as Thailand and Taiwan. The EHR-linked clinical decision support system (CDSS) improves the value of evidence-based pharmacogenetic screening through automated pop-up alerts that warn the prescriber if a high-risk allele is present (Figure 3). Diagnostic considerations and optimal treatment strategies are further offered so that clinicians are guided to choose lower-risk medications based on a patient's genetic profile, without being overwhelmed by large amounts of clinical and genetic information (28). This approach has significantly reduced the incidence of specific drug-induced SJS/TEN in Taiwan and Thailand (20, 28).

The training curriculum for certification of proficiency in pharmacogenetics and precision medicine has gradually received greater attention and is now being incorporated into many medical schools and relevant postgraduate training programs. This curriculum has helped healthcare providers and trainees understand the importance of the clinical implementation of pharmacogenetics for the prediction and prevention of SJS/TEN (29). The pharmacogenetics course contains fundamental principles to provide knowledge on pharmacology (e.g., drug metabolism and pharmacokinetics) and human genetics/genomics (e.g., pathogenesis and polymorphism

TABLE 1 SJS survivorship and patient perspectives.

| Themes | Community perspective | Physician perspective |
|---|---|---|
| Mental health | -Follow up care<br>-Bridge between hospital care and follow-up care<br>-Increase healthcare provider education for SJS/TEN PTSD<br>-Address mental health and changes immediately after SJS/TEN<br>-Assist through the recovery process<br>-Implement mandatory mental wellness checks before discharge from the hospital and beyond<br>-Address survivor's guilt<br>-Improve mental health/grief counseling for loved ones who lost an SJS/TEN patients<br>-Provide grief counseling for your "lost life" and changed life<br>-Discuss financial burden<br>-Address low self-esteem | -Understand the psychological impact, and related long term health complications<br>-Conduct qualitative and quantitative research to implicate in clinical care<br>-Understand how the disease condition affects the individual (psychologically, interpersonally, vocationally, and overall quality of life)<br>-Provide realistic expectations about challenges during hospitalization and after discharge<br>-Provide a multidisciplinary support team (social work, psychiatry, psychology)<br>-Provide proper discharge document with a list of medications<br>-Ensure post-discharge follow-ups and counseling with survivors |
| Long-term health complications | -Improve education for healthcare professionals on residual side effects<br>-Recognize SJS/TEN side effects<br>-Improve treatment for all side effects (more than only eye care, esophageal care, skin care, live care, reproductive care, oral care, dental care)<br>-Increase access to healthcare professionals who specialize with SJS/TEN patients (both in-person and telehealth appointments)<br>-Increase/improve physician response time<br>-Ease transfer of patient records<br>-Develop and utilize an SJS/TEN identification checklist<br>-Implement the use of educational materials by doctors (flyers, brochures, posters) | -Understand the various long-term health-related complications and their effects<br>-Understand complications vary based on the severity of cases<br>-Recognize that treatment options will change according to the case presentation<br>-Increase collaborative research projects to study cases post SJS/TEN<br>-Prioritize long-term follow-up of cases<br>-Provide advice on referral centers<br>-Standardize health checkups to identify complications<br>-Increase collaborative and coordinative work among clinicians<br>-Provide proper documentation for future referrals |
| Eye care | -Treatment during the acute stage<br>-Treatment post SJS/TEN<br>-Prompt treatment and diagnosis<br>-Education on eye care treatment<br>-Contact an eye care specialist<br>-Aftercare and follow-up appointments | -Understanding treatment during acute stage is critical<br>-Provide proper examination and care by specialists<br>-Recognize treatment options should not be limited to topical steroids. Surgical procedures need to be considered when appropriate<br>-Plan on decreasing the risk of infection and vision loss<br>-Increase knowledge of advanced surgical and sutureless procedures |
| Long-term scarring | -Awareness of how scarring impacts SJS/TEN survivors (skin, eyes, organs)<br>-How scarring changes over time (thickening)<br>-Improved education for healthcare professionals<br>-Eliminate the use of "Rare" to classify SJS/TEN<br>-Educate patients post SJS/TEN about scarring<br>-Prioritize early diagnosis<br>-Provide second opinions from healthcare providers who have treated SJS/TEN<br>-Implement mandatory certification on SJS/TEN and retraining<br>-Provide examples of SJS/TEN scaring (at all stages from early identification) | -Research best practices to identify, early diagnose and treat SJS/TEN<br>-Implement standard treatment protocols<br>-Confirm diagnosis through histology<br>-Determine specific signs that occur in the presence of certain medications<br>-Have evidence-based studies to determine the casual drugs and treatment options |
| Children with no identifiable drug cause | -Bring awareness that over-the-counter products are medications<br>-Create awareness about infections causing SJS/TEN and avoid accusing medications used to treat the first symptoms of SJS/TEN<br>-Provide for mental health concerns<br>-Look at genetic factors (HLA-b1502)<br>-Create screenings | -Awareness and documentation of the causal factors<br>-Knowledge of the possibility of life-threatening GI tract involvement when treating cases of SJS/TEN<br>-Consider the usage of steroids and enteric feeding |
| Special considerations in skin of color | -Identify SJS/TEN in the acute stage<br>-Acknowledge the difference between the appearance of SJS/TEN in the skin of color<br>-Awareness of hyperpigmentation<br>-Lack of visible blisters at the acute stage<br>-Consider low visibility (lack of redness) of SJS/TEN presentation<br>-Improve time to diagnosis<br>-Improve education for healthcare providers of SJS/TEN in the skin of color<br>-Implement a specific checklist for skin of color (purple-looking skin vs. red-looking skin) for identification | -Educate on dyspigmentation, skin changes, and different types of scarring<br>-Understand disease effect on all types of skin cells<br>-Change of practice: start counseling at the bedside<br>-Improve interactions with patients, survivors, and families<br>-Improve pharmacist education on common drug allergies<br>-Improve response to queries or concerns of survivors<br>-Provide detailed discharge instructions with frequent concerns (what products to use on skin, etc.) |
| Scientific advances in SJS/TEN | -Genetic testing<br>-More research studies and increased patient/survivor participation<br>-Gaining the patient perspective<br>-Spread knowledge/awareness of new SJS/TEN treatments<br>-Get more funding for SJS/TEN research<br>-Bring more awareness of SJS/TEN<br>-Eliminate the use of the word RARE<br>-Increase box warnings<br>-Increase funding to assist patients with SJS/TEN who are not financially stable | -Strengthen experimental models<br>-Predict possible risks and validate signals<br>-Capture cases, specimens, interoperable repositories<br>-Promote consistency and quality in research methods<br>-Use pharmacogenomics for drug safety<br>-Integrate distributed databases/biobanks could enable biomarker discovery/validation, test monitoring/utility<br>-Implement multicenter investigations to further understand management and treatment |

*(Continued)*

TABLE 1 (Continued)

| Themes | Community perspective | Physician perspective |
|---|---|---|
| Safety of COVID-19 vaccines | -Ensure that patients/survivors understand that COVID-19 vaccines are safe, including risks of COVID-19 vs. risk of vaccine<br>-Develop education on potential complications of COVID-19 as an SJS/TEN survivor | -Answer vaccine-related queries-Educate on different responses to the vaccine<br>-Ensure patients it is safe to get the COVID-19 vaccine<br>-Address the misconceptions, hesitancy, and fear of getting the vaccine |

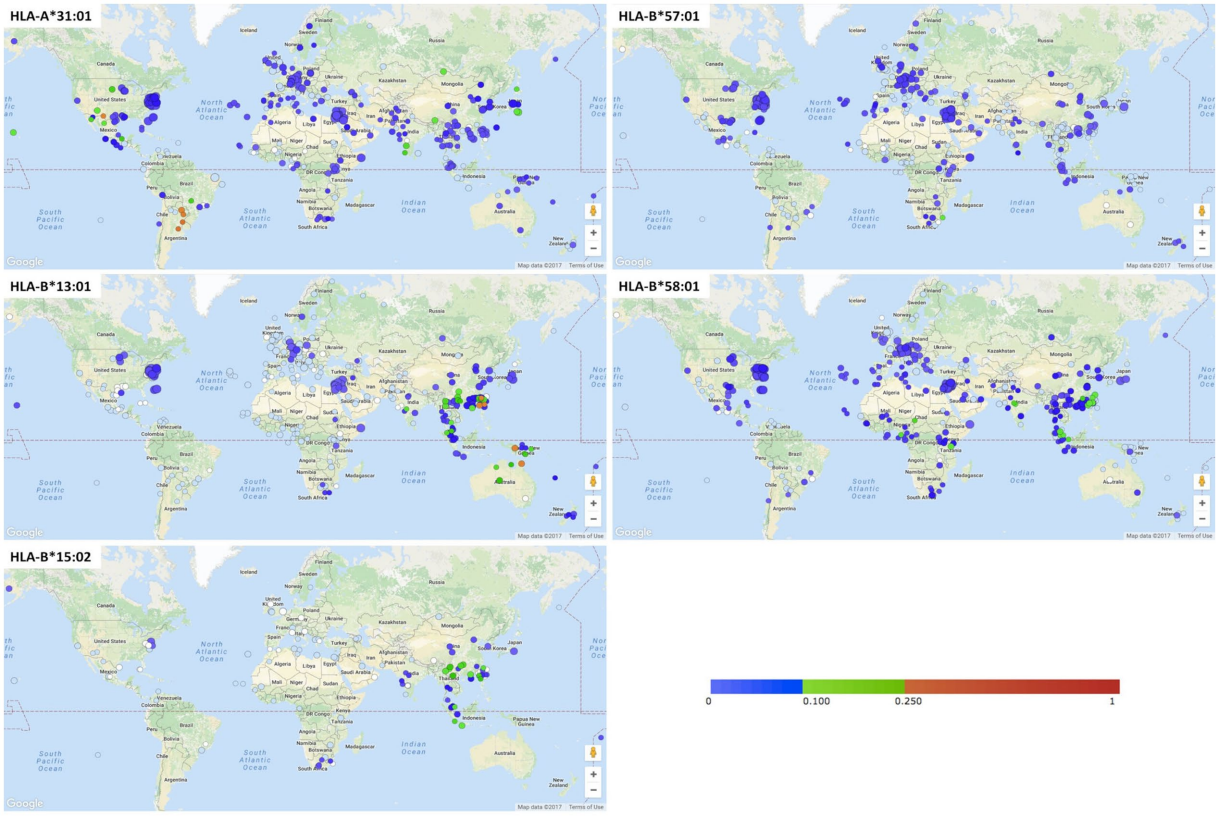


FIGURE 2
HLA risk alleles associated with SCAR in different ethnic populations.

TABLE 2 HLA class I risk alleles are shared amongst some but not all drugs & phenotypes.

| Drug | HLA risk allele | MDE | DRESS/DIHS | SJS/TEN | DILI | HSS |
|---|---|---|---|---|---|---|
| Allopurinol | HLA-B*58:01 | | | | | |
| Carbamazepine | HLA-B*15:02/B75 serotype | | | | | |
| Carbamazepine | HLA-A*31:01 | | | | | |
| Dapsone | HLA-B*13:01 | | | | | |
| TMP-SMX/Sulfapyridine | HLA-B*13:01 | | | | | |
| Vancomycin | HLA-A*32:01 | | | | | |
| Abacavir | HLA-B*57:01 | | | | | |
| Flucloxacillin | HLA-B*57:01<br>HLA-B*57:03 | | | | | |

MDE, maculopapular drug eruption; DRESS/DIHS, drug reaction with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome; SJS/TEN, stevens-johnson syndrome/toxic epidermal necrolysis; DILI, drug-induced liver injury; HSS, hypersensitivity syndrome.

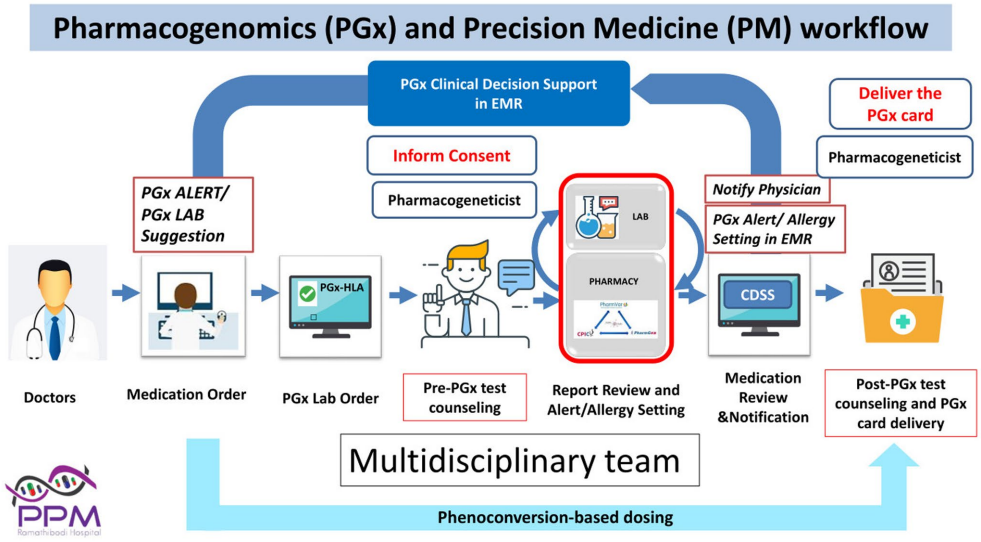


FIGURE 3
Pharmacogenomics test clinical workflow to alert physicians for drug prescriptions.

analysis). A practical approach is taken whereupon clinical decision-making strategies are built upon robust scientific evidence, clinical practice guidelines, and recommendations. Learning through case studies helps prescribers to become familiar with pharmacogenetic test interpretation and have confidence in incorporating the results into each patient's healthcare management plan (30).

There are a growing number of clinical recommendations for pharmacogenetic tests used in clinical practice (31). Compared with a single test for a particular variant, the utilization of multiple-variant panels are considered beneficial since multiple risk variants can be screened for simultaneously. A pharmacogenetic panel containing multiple genetic variants that are significantly associated with an increased risk for developing SJS/TEN, or other SCAR, has been proposed and separately developed by research groups in Taiwan, Thailand, the UK, and Canada (19, 20, 30, 32). In a prospective observational study conducted in Southeast Asians (e.g., Taiwanese, Chinese, Thai, and Malaysian), the sensitivity and specificity of a multiple-variant panel for specific antiepileptic drugs (e.g., carbamazepine, oxcarbazepine, and phenytoin) was 75 and 90%, respectively (20). Although the less than 100% negative predictive value (NPV) means this would not be the perfect screening test, the results from the panel contribute to drug causality assessment. The panel is also helpful for identifying drugs with increased risk of SCARs to which the patient has not yet been exposed and making shared medical and therapeutic decisions with the patient. Therefore, the development of such multiple-variant pharmacogenetic panels is a dynamic and ongoing process, allowing for cost-efficient additions of newly discovered variants as the evidence base grows.

Given the low incidence of SJS/TEN, several international collaborations are underway to increase statistical power for identifying genetic variants and novel, but clinically relevant, pharmacogenetic associations across diverse ancestries. The latest scientific methods and technologies (e.g., GWAS meta-analysis, polygenic risk scoring, low-pass whole-genome sequencing) have the potential to make significant contributions to the field by uncovering increased genetic information, particularly for rare variants. More reliable evidence generated from real-world data, especially for under-served populations like First Nations, LatinX, and other diverse populations globally, remains an urgent need to advance the science of SJS/TEN research with regards to all ancestries.

To improve public health and drug safety, regulators update drug labeling and mandate boxed warnings to guide prescribers on the use of SJS/TEN suspect drugs. The U.S. Food and Drug Administration (FDA) has been proactive in incorporating pharmacogenetic risk factors in labeling. As of December 2020, 453 drug-biomarker pairs, including 311 drugs and 133 biomarkers, have been documented by the FDA, while 252 pairs are considered clinically actionable in SCAR. In the past, the recommendation for pharmacogenetic testing has varied based on the likelihood that SCAR, related to a specific drug, will occur in a specific population, and is largely based on the frequency of the HLA risk allele. As highlighted above to avoid structural racism and pharmacogenetic screening approaches that would disadvantage specific populations, a targeted approach based on provider stereotyped patient race is inaccurate. In addition, there has been widespread population admixture and the implications of a specific risk allele when present is the same regardless of the population (6). Other regulatory actions that have been taken by the Taiwanese FDA include collaboration with advisory committees, drug reporting centers that collect necessary safety data, and consultant experts who provide suggestions. A search for drugs which have a warning for SJS/TEN in the label can be done using the FDA label tool[1].

1 https://www.fda.gov/science-research/bioinformatics-tools/fdalabel-full-text-search-drug-product-labeling

# 3. Updates in diagnosis, assessment, and causality

## 3.1. General principles

The mainstay of SJS/TEN management is early clinical diagnosis and triage into a critical care setting with a high standard of supportive care, as discussed above. Histopathology aids in the clinical diagnosis and direct immunofluorescence helps identify autoimmune bullous disorders which can be confused with SJS/TEN particularly early in disease. All new drugs, and particularly those initiated within 4 days to 6 weeks, are suspect and should be discontinued (33). Early recognition is key. Although biological markers, such as granulysin, appear quite sensitive and specific for early identification of SJS/TEN, they lack widespread validation (34–36). An HLA risk allele, in addition to being a pre-prescription strategy that prevents SJS/TEN to specific drugs, may also add to the causality assessment that a specific drug is the culprit. Skin and patch testing generally have low sensitivity but high specificity for SJS/TEN with the exception of aromatic anticonvulsants which have a sensitivity of >50%. However, there is a range of sensitivity across different drugs from 0% (allopurinol) to >50% (aromatic anticonvulsants) (37, 38). *Ex vivo* and *in vitro* testing has had lower sensitivity than other severe cutaneous adverse drug reactions and needs more widespread validation and optimization (34, 39, 40). Rechallenge is contraindicated for all suspected culprit drugs and potentially cross-reactive drugs. The exception to this is the treatment of tuberculosis in low and middle-income countries where progress has been made using combinations of *ex vivo* testing and sequential additive challenges with methylprednisolone rescue (41, 42). Integrated approaches combining HLA typing, *in vivo* and *ex vivo*/*in vitro* testing have been advocated as having higher positive and negative predictive values than any one test alone (27, 42, 43).

## 3.2. Photography and artificial intelligence to improve SJS/TEN assessment

The SJS/TEN-specific severity-of-illness score (SCORTEN) has been the mainstay of measurements to define mortality risk of SJS/TEN in both clinical practice and research (44). The ABCD-10 (age, bicarbonate, cancer, dialysis, 10% BSA) is another cross-sectional severity scoring system that incorporated end-stage renal disease and was shown to perform slightly inferior to SCORTEN by underestimating mortality (45, 46). Another study proposed adding inflammatory markers to the SCORTEN to improve predictive accuracy. The only marker that was shown to improve predictive accuracy was the red cell width over hemoglobin ratio (47). More recently the CRISTEN (clinical risk score for TEN) was developed as a clinical risk score that does not require laboratory values and this initial study was validated across 416 patients multinationally (48). However, it must be realized that all of these scoring systems are cross-sectional tools weighed toward patient co-morbidities that measure severity at one point in time and are not useful for longitudinal assessments that measure changes in disease severity over time or the specific course of the disease. Due to the difficulties of undertaking randomized controlled trials in an uncommon and unpredictable disease, studies typically draw their primary outcome from a comparison of survival on therapy to the SCORTEN-predicted survival – the standardized mortality ratio for the therapy (49). Six of the seven SCORTEN prognostic factors are completely objective, drawing from irrefutable patient demography or quantitative physiologic or laboratory measurements. Coupled with these is a single subjective measure known as body surface area (BSA) of epidermal detachment, which was found to have a remarkable mortality association upon crossing a threshold of 10% BSA on the first day of hospitalization.

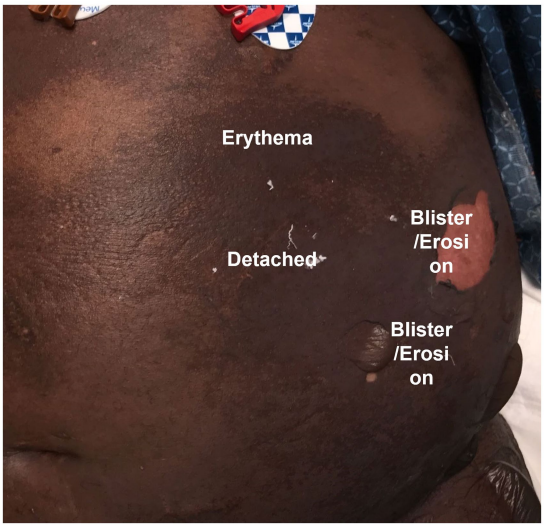


FIGURE 4
Example photograph of Vanderbilt Drug Safety patient (with permission) to guide standardized SJS/TEN scoring by illustrating the categorization of different appearances of skin into different terminology. Photo by Madeline Marks and Austin Cronin, VDTRC.org.

All clinical methods to estimate BSA have been shown to suffer major errors and inter-observer variations. For example, dermatology providers applying the rule of 9 s overestimated psoriatic plaque area by more than a factor of two in 49/80 patient assessments (50). Similarly, a meta-analysis of 26 studies in the burn literature found an average BSA estimation error of 70% across nearly 3,000 patients and concluded that neither the rule of 9 s nor palmar surface area are reliable estimates (51). Errors were significantly greater when under 20% BSA was affected. Notably, the rule of 9 s and more accurate Lund-Browder charts are both derived from paper-mâché molds from only 12 individuals (52). Very recently, our understanding of the human skin surface has been substantially advanced by high-resolution surface anthropometry laser body scans of 3,047 adults in the Civilian American and European Surface Anthropometry Resource (53), which proved that there is an enormous variability between individuals as to how much each body region contributes to the total BSA. Thus, regardless of evaluation by a dermatologist or in the burn unit, knowing the true BSA of an individual SJS/TEN patient is challenging. This represents a major barrier to the successful application of decades of clinical experience in SJS/TEN.

Collection and analysis of SJS/TEN patient photos could serve an important role in addressing the gap presented by clinical BSA estimation variation. The development of standardized SJS/TEN-specific scoresheets with accompanying training and photos, including preferred terminology for different skin appearances (e.g., Figure 4), could be a major step forward in comparing the outcomes of individual patients and the results of different studies. For

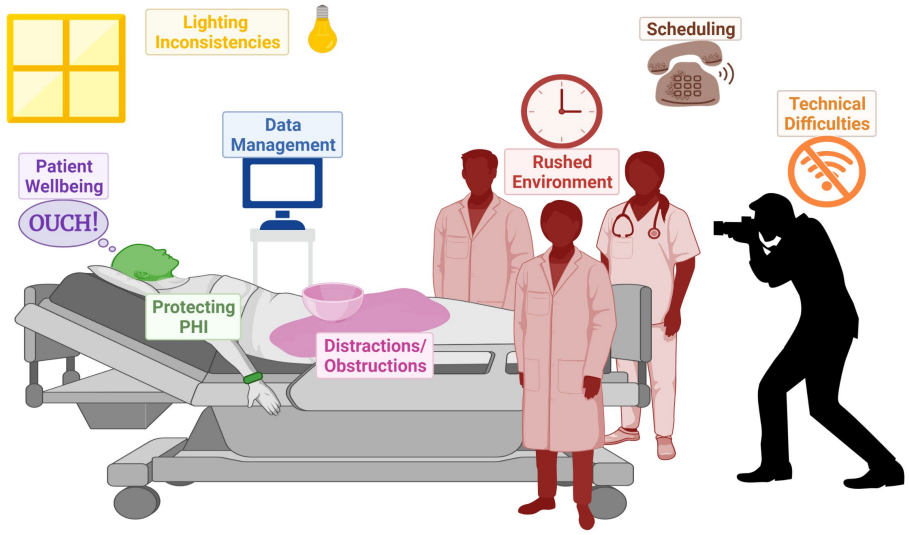


FIGURE 5
Infographic to illustrate the challenges of photographing in burn ICU.

example, clinicians vary widely in whether they perform a Nikolsky sign or refer to dusky areas of erythema as detached skin. Photography-based adjudication that follows patient bedside BSA assessments, whether by the rater or another trained adjudicator, could further improve data quality. However, standardizing critically ill patient photography presents several challenges illustrated in Figure 5 and Table 3 and so may not be practical for all research groups. In this case, we recommend that future publications of SJS/TEN studies specify the primary data collection sheet used as well as detailed methods on how BSA was estimated. For example, the Lund-Browder method is more reliable than the rule of 9 s but may take more time (54). Ideally, the study would retain marked avatars and note the corresponding rater's (or raters') experience and specific training in BSA estimation.

Provided that high-quality photographs are collected, several computer, web-based, and smartphone options for image analysis have been shown to add significant accuracy to BSA assessment (55), enabling completely untrained individuals to outperform experienced providers (56). The application of these technologies could revolutionize the way SJS/TEN studies are conducted by removing time and space constraints in the burn ICU, permitting centralized and standardized quality assurance, and adjudication by off-site experts. A limitation remains the amount of time necessary for a human user to mark borders and otherwise manipulate the photographs in these software interfaces, which can exceed the amount of time to do clinical scoring. One approach is leveraging crowdsourcing of multiple non-expert raters to achieve expert-level accuracy (57), but this would raise issues of patient privacy and data security.

In the future, the application of artificial intelligence (AI) image analysis to standardized photographs could offer practical, rapid, and standardized solutions to the critical gap in SJS/TEN BSA assessments. While there is currently a paucity of literature on this direct application, the SJS/TEN research community can take the following steps to advance:

1. Collating large numbers of standardized SJS/TEN patient photographs, ideally together with clinical variables and patient outcomes
2. Annotating the images with markings of different types of affected skin
3. Connecting these data sets to experts, for example, through global challenges like the melanoma challenge driven by the International Skin Imaging Collaboration (58)

Numerous FDA approvals for medical AI use and even specific guidelines for AI dermatology development (59) and validation lend promise that the combination of photography and AI will eventually lead to substantial advances in SJS/TEN research and patient care. In the near term, higher-quality skin surface assessment and standardized reporting of skin assessment in studies can improve personalized management, prognostic models, and understanding of SJS/TEN. Aside from the limitations stated above, there has been little consensus amongst dermatologists on SJS/TEN terminology, morphological terms and progression and consensus on the most affected sites. A recent study conducted a Delphi consensus exercise to establish a baseline consensus for the development of a standardized SJS/TEN instrument with consistent terminology (60).

## 4. Other considerations for clinical diagnosis and management

### 4.1. SJS mimickers and differential diagnosis

The early features of SJS/TEN are subtle and non-specific with a prodrome of low-grade fever, malaise, anorexia, and mucosal discomfort. It can then progress to include features such as skin pain, and development of bullae, even before the characteristic sloughing of the skin occurs (61). There are many illnesses including infections,

TABLE 3 Challenges in photographing SJS/TEN patients.

| Category | Challenge | Explanation | Solution |
|---|---|---|---|
| Room conditions | **Lighting inconsistency:** Variation in light tone and/or intensity, time of day, or weather. | Lighting inconsistencies increase the chance of shadowing, glare, and distorted skin tone in images. | • Document the light sources in the room during the photo session.<br>• Consistently utilize the same device between sessions.<br>• Capture both flash and non-flash photos.<br>• Use portable light devices. |
| | **Rushed environment:** A high-stress intensive care environment caused by time constraints, simultaneous performance of procedures, photographer inexperience, or patient discomfort. | A rushed environment negatively impacts attention to detail and photography session quality. | • Establish a relationship with the care team.<br>• Communicate with the care team.<br>• Get familiar with the hospital and the unit.<br>• Regularly conduct timed practice sessions with a volunteer. |
| | **Distractions/obstructions:** Objects, unrelated to the photography, which distract from or obstruct the patient's skin. | Objects may obstruct part of the skin, visually distract the viewer, and impact the consistency of daily images. | • Move items out of frame.<br>• Move items off patients' skin, if able.<br>• Drape distracting items. |
| Communication | **Scheduling:** A missed opportunity to capture uncovered patient's skin (e.g., dressing change, bath) due to miscommunication between the patient's care team and photographer or unavailability of the photographer. | Missed dressing changes or baths prevent a complete photograph of the entire skin surface across all body sites from being collected daily. | • Communicate daily with the patient's care team.<br>• Ideally, multiple trained photographers should be available.<br>• Photographers should have flexible schedules to allow time for sessions when needed. |
| Patients | Patient wellbeing: The physical or emotional comfort and discomfort of the patient. | Patient wellbeing determines if they are willing to fully participate in repeated photography sessions. | • Communicate with the patient and their caretaker.<br>• Ask permission to photograph at each session.<br>• Explain that the photography session can be stopped at any time.<br>• Limit the number of people in the room. |
| PHI | Protecting PHI & privacy: Photographs may contain sensitive and/or identifying information. | Protecting privacy and PHI helps to establish trust between the patient and photographer. | • Cover hospital bands with gauze or tape.<br>• Flag photos considered sensitive.<br>• Flag photos containing PHI.<br>• De-identify photos. |
| Data management | **Data management:** The organization of photos by establishing standard operating procedures for naming and storing files. | Standardized data management protocol ensures optimal organization, prevents data loss, and makes locating files easier. | • Develop a protocol for naming and storing photos.<br>• Ensure that filenames are consistent with the naming convention.<br>• Keep at least two copies of each photo (have a back-up). |
| Technical difficulties | **Technical difficulties:** Technological malfunctions due to a loss of power, Wi-Fi, or issues capturing images. | Technical difficulties can prevent data from being collected properly and affect its overall quality. | • Use newer-model devices.<br>• Fully charge the device before each session.<br>• Bring a backup photography device.<br>• Confirm all photos are submitted before exiting the photo capture app. |

autoimmune diseases, and other types of drug reactions that may mimic SJS/TEN (Table 4). Since treatments, prognosis, short and long-term complications, and outcomes vary, prompt and accurate diagnosis is important to guide early intervention and management.

Staphylococcal scalded skin syndrome (SSSS) is a condition with cutaneous involvement that can mimic SJS/TEN. It is a blistering skin condition caused by a toxin from staphylococcus seen either in healthy children with a bacterial focus or in adults with renal insufficiency. SSSS (62) usually presents with tissue-paper thin wrinkling of the epidermis concentrated in intertriginous areas; such as: inguinal folds, axillae, inframammary folds, and folds of the neck. Additionally, peri-oral radial fissures, as well as erythema of the eyes and ears is classic. The skin is red and tender before it sloughs. A very superficial layer of the skin is what sloughs off, revealing a moist, pink, and slightly matte surface at the base, underneath compared to the deep red and shiny exposed dermis that is seen at the base of desquamations in SJS/TEN (61, 62). The skin usually heals completely within 5–7 days after starting treatment with antibiotics and supportive care.

TABLE 4 Most common clinical mimickers of Stevens-Johnson Syndrome & Toxic Epidermal Necrolysis.

| Diagnosis | Context | Main clinical difference | Causes |
|---|---|---|---|
| RIME | Abrupt eruption of prominent mucositis triggered by infectious etiologies | Minimal to absent cutaneous eruption, mostly children and young adults | *Mycoplasma pneumoniae* and several other infections |
| EMM | Development of typical and atypical targetoid macules with central deeper purple or dusky coloration. | Typical, papular 3-zoned targetoid lesions in conjunction with atypical raised targets having only 2 zones, whereas SJS/TEN tends to be flat or flaccid bullous. | Herpes simplex virus most commonly, occasionally other infections, idiopathic, radiation |
| PNP | Smoldering onset of bullae and lichenoid dermatitis with mucositis, often mistaken for "chronic SJS/TEN" | 2 morphologies to eruption: there is both a B-cell mediated bullous morphology and a T-cell mediated lichenoid component | Non-Hodgkin lymphoma, chronic lymphocytic leukemia. Rarely, Castleman's disease, thymomas, sarcomas, and Waldenström's macroglobulinemia. |
| SSSS | Usually newborns, young children, adults with renal failure | Split is very superficial with a periocular, perioral, and intertriginous predilcition. Base of blisters have intact epidermis rather than beefy red dermal appearance. Often intense peri-oral involvement but spares mucous membranes. | Staphylococcal exotoxin (epidermolysin) targeting desmoglein 1 |
| AGEP | Explosive eruption of a brightly erythematous with moist slough | Primary morphology is innumerable, tiny, non-follicularly based pustules on a brightly erythematous base which coalesce to form "lakes of pus." Time to onset is shorter than SJS/TEN (<4 d), and split is superficial. Absence of mucosal involvement, generally. | Medications |
| aGVHD4 | Morbilliform exanthem that goes on to become blistering, usually within the first 3 months (but can occur later) after transplantation. | Predicliction for dorsal hands and feet, palms and soles, forearms, upper trunk, ears and postauricular areas. GI and hepatic signs/ symptoms may be concurrent. | Transplantation of bone marrow, sometimes with multivisceral or small bowel |

RIME, Reactive infectious mucocutaneous eruption; EMM, Erythema multiforme major; PNP, Paraneoplastic pemphigus; SSSS, Staphylococcus scalded skin syndrome; AGEP, acute generalized exanthematous pustulosis; aGVHD4, Acute Graft vs. Host Disease, grade IV.

Autoimmune and other immune-mediated disorders comprise an array of diseases that can mimic SJS/TEN. Lupus erythematosus can have many similarities to SJS/TEN. Important differences are photodistribution, and subacute presentation (weeks). Additionally, patients with lupus may have positive antinuclear and reflex-ENA antibodies, elevated anti-dsDNA levels, lymphopenia, and other cytopenia's and low complement levels which are not typically seen in patients with SJS/TEN (63). Hemophagocytic lymphohistiocytosis (HLH) is a very rare condition caused by natural killer cells and T lymphocytes. It differs from SJS/TEN in that it forms a reticuloform rash and is smoldering, with various stages of resolve although occasionally a positive Nikolsky sign can be seen. Bullous pemphigoid (BP) is a disease that involves the basement membrane. Unlike SJS/TEN, patients with BP will complain of pruritus instead of pain, and their lesions will show a positive Asboe-Hansen sign and a negative Nikolsky sign. Additionally, BP is more often seen in elderly patients without a drug ingestion history. Direct immunofluorescence (DIF) studies of skin reveal linear deposition of IgG and C3 at the basal membrane.

Reactive conditions such as erythema multiforme majus (EMM) are self-limited but occasionally recurrent and may be confused with SJS/TEN. It is hallmarked by typical and/or atypical raised target lesions predominantly on the extremities (acral) in adults and on the face and trunk in children. High fever and several swollen, painful, and erosive mucous membranes may lead to a severe condition in children, whose predominant cause is infection with Mycoplasma pneumonia (64, 65).

Acute graft vs. host disease (GVHD) is a major complication associated with bone marrow transplants. It is a multi-organ disorder that is most commonly due to foreign blood stem cells being transferred to a new host which in turn stimulates an immune reaction. The reaction can be seen following bone marrow transplants, non-irradiated blood transfusions, maternal-fetal transmission, and solid organ transplants. In its most severe form (Stage IV), acute skin disease can consist of generalized involvement with blister formation and skin sloughing resembling SJS/TEN (66).

Several other severe cutaneous adverse drug reactions can present with clinical features mimicking SJS/TEN. These include linear IgA bullous dermatosis, drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms (DiHS/DRESS) which can present with a wide range of skin morphologies, acute generalized exanthematous pustulosis (AGEP), generalized bullous fixed drug eruption (GBFDE), bullous lichenoid, and multiforme-like drug eruption caused by various medications, and more recently, by the immune checkpoint inhibitors and most commonly PD-1 and PDL-1 inhibitors used in lung cancer. Tumors have evolved to have several mechanisms to cloak themselves from the human immune system. Immune checkpoint inhibitors are used to unharness T and NK cell responses to improve the host tumor response. While this class of medication has been helpful in patient care, it can trigger reactions similar to SJS/TEN.

One last unusual severe cutaneous adverse drug reaction presentation is a delay in the development of a second mucosal site. It has been reported that greater than 85% of patients will present with involvement of two mucosal sites (1, 64). However, we are now becoming aware of a delay in the presentation of the second site in a subset of patients, which may provide initial confusion in the diagnosis.

## 4.2. SJS/TEN and drug-induced liver injury

Significant literature exists that describes the co-existence of drug-induced liver injury (DILI) and SJS/TEN. DILI is the most common cause of acute liver failure in the Western world and is associated with SCARs in 5% of cases. Although DILI most commonly occurs in the setting of DRESS/DIHS, a study looking at 1718 cases of validated DILI, found that 14 patients were diagnosed with concurrent SJS/TEN attributed to 9 different agents (67). The injury pattern in these cases was diverse. Seven presented with hepatocellular injury, while the other seven presented with cholestatic/mixed injury. Most patients presented with a rash and fever but were not jaundiced at the clinical onset but became jaundiced with disease progression. Two patients were classified with mild liver injury, five with moderate injury, and seven with severe injury. Compared with DILI cases, those with concurrent SJS/TEN were more often younger, more likely to be Black, had a shorter latency period from drug exposure to hepatic dysfunction, and ultimately developed a more severe liver injury. While genetic predisposition is suspected, HLA subtyping has not yet demonstrated any clear clinical patterns associated with SJS/TEN co-occurring with DILI. The experience with DILI in the setting of DRESS/DIHS suggests that the same HLA associations may be relevant (68, 69). Physicians diagnosing SJS/TEN should be aware of the possibility of drug-induced liver injury.

## 4.3. Cutaneous toxicities and management of immune checkpoint inhibitor toxicity and SJS/TEN

Immune checkpoint inhibitors (ICIs) such as PD-1, PD-L1, and CTLA-4 inhibitors often lead to non-specific immune activation, of which the skin is the most common target (70–72). Most patients treated with a PD-1 inhibitor will experience at least two or more adverse events (70); fortunately, patients with a cutaneous reaction also demonstrated improved survival rates (73). Common cutaneous adverse events can be classified into psoriasiform, morbilliform, lichenoid eruptions, and vitiligo-like depigmentation (74). Less common adverse events SCARs or blistering dermatoses (74) with the occurrence of an adverse event, the severity of the reaction is categorized utilizing the Common Terminology Criteria for Adverse Events (CTCAE) to communicate the severity of the rash, including total body surface area involved, as well as the safety of reinitiating immunotherapy.

The subtypes of cutaneous adverse events are associated with the type of immune checkpoint inhibitor. Psoriasiform eruptions generally occur with PD1/PD-L1 inhibitors and can be associated with inflammatory joint disease and uveitis. Flares of pre-existing psoriasis are commonly reported, and treatment should resemble a similar therapeutic ladder to classical psoriasis. Morbilliform reactions are the most common adverse event described with CTLA-4 inhibition (75–77). Histopathology typically demonstrates spongiosis, interface dermatitis, and/or perivascular dermatitis with a predominately lymphocytic infiltrate. Treatment is usually limited to the use of topical steroids and oral antihistamines. Lichenoid reactions have an unclear incidence but are more commonly reported with PD-1/PD-L1 inhibitors compared with CTLA-4 inhibitors (78). They are best treated with topical steroids, phototherapy, acitretin, hydroxychloroquine, or apremilast. Vitiligo-like depigmentation does not need therapy, but patients should be educated on the risk of photosensitivity in affected areas. Development of bullous dermatoses is rare, but also likely underreported and underdiagnosed (79, 80). These patients present with a median latency of 6–8 months after PD1/PD-L1 treatment initiation (79, 80). IgG and C3 linear deposits are typically demonstrated on immunofluorescence (80). Considerations for therapy include systemic corticosteroids, dupilumab, omalizumab, intravenous immunoglobulin (IVIG), or rituximab. Lastly, SJS/TEN-like reactions can begin as morbilliform eruptions that evolve into a lichenoid reaction with mucositis of oral, ocular, and genital regions (81, 82). It has recently been suggested that two types of SJS-like eruptions can occur following ICI. Bullous lichenoid reactions, which progress slowly and often occur in the presence of a small molecule drug associated with SCAR, and where rechallenge with ICI may not be contraindicated and reactions appear more like TEN (83, 84). The name progressive immunotherapy-related mucocutaneous eruption (PIRME) has been suggested to refer to these lower acuity reactions which may appear SJS-like but progress more slowly, may have a small molecule culprit drug, and where the pathology suggests a lichenoid bullous reaction (84). Patients then develop full-thickness epidermal necrosis. These patients are best managed in a burn ICU and systemic immunomodulating therapy should be considered.

Although complications of immune checkpoint inhibitor therapy are generally treated with immunosuppression, recent data has demonstrated a significant difference in the overall survival and time to treatment failure with either low or high-dose corticosteroids in patients (85), which sets a precautionary tone. Biomarkers such as IL-6, IgE, and elafin have been correlated with the severity of adverse events, as well as predicted six-month survival (86, 87). A future goal is for a combination of biomarkers and known pathophysiology of the eruption to guide the most judicious and targeted treatment options (87). In addition to corticosteroids, which have been the mainstay of treatment for ICI immune-related adverse events (iRAEs), more targeted therapies, such as etanercept and tocilizumab, are currently being studied and have demonstrated clinical benefit in treating cutaneous immune-related adverse events (88, 89). True severe cutaneous adverse events related to immunotherapy likely have a distinct immunopathogenesis when compared with SJS/TEN related to a small molecule. In addition, ICI may unmask or increase the risk of a SCAR related to a small molecule, such as those described above with lichenoid bullous reactions. Currently, rechallenge is still not recommended with severe cutaneous adverse events related to ICI that mimic and progress rapidly and are similar to SJS/TEN as case reports of fatalities have occurred even with ICI monotherapy rechallenge (90). However, case reports are emerging that may distinguish at least a subgroup of ICI SCAR that appear to tolerate rechallenge with a different ICI (e.g., distinct PD-1 inhibitor) or even the same drug in some instances (84, 91).

## 4.4. Updates on mechanisms

Current innovation in studying gene-protein and T-cell receptor expression at the site of tissue damage in SJS/TEN such as blister fluid

and sloughed skin has provided insights into the disease as a CD8-dependent class I HLA-restricted condition with upregulation of markers of cytotoxicity and proliferation. The expression of cytolytic peptides such as granulysin and granzyme B by CD8+ T cells, NK T cells, and NK cells has become the hallmark of SJS/TEN. Examples of how the tissue signatures can be utilized to provide the rationale for successful targeted therapy were exemplified by Kim et al. (92) in the case of a patient with a refractory DiHS/DRESS. Capabilities and the ability to deconvolute and analyze complex datasets are equally important (93, 94).

### 4.5. Cell death pathways and novel therapeutics

SJS/TEN is characterized by the death of keratinocytes. Previously, this epidermal damage in the skin lesions of SJS/TEN patients had been considered to be due to apoptosis. Apoptosis is induced by cytotoxic CD8+ T cells through the Fas–Fas ligand (FasL) pathway or the perforin/granzyme pathway. The cell surface of keratinocytes of TEN patients has revealed a high expression of FasL. In addition, high levels of soluble FasL (sFasL) have been found in the serum of SJS/TEN patients. Fas–FasL interactions mediated apoptosis in the skin lesion of SJS/TEN patients, and in addition, granulysin also demonstrated a cytotoxic effect in SJS/TEN (31). Granulysin, which is found in high levels in SJS/TEN blisters, is released from blister cells in skin lesions of SJS/TEN, including cytotoxic CD8+ T cells, NK T cells, and NK cells. Very recently it has been reported that the exosomal miRNA, miR-375-3p, was markedly upregulated in the plasma of SJS/TEN patients, where it induced mitochondria-dependent apoptosis via downregulation of the X-linked inhibitor of apoptosis protein (XIAP) (95). In 2014, Saito et al. (96) reported that necroptosis induced by annexin A1 – formyl peptide receptor 1 (FPR1) interaction contributes to keratinocyte death in SJS/TEN. In electron microscopic analysis, both necrotic cells and apoptotic cells were observed in the skin lesions of patients. Necroptotic (a type of programmed cell death that reveals morphological necrosis) cells release damage-associated molecular patterns (DAMPs), including a range of pro-inflammatory cytokines, resulting in inflammation, unlike apoptosis (97). The induction of necroptosis in the skin and gut provokes a strong inflammatory response, which might be triggered by the emission of DAMPs (98). In general, necroptosis occurs through the stimulation of TNF-α under conditions in which apoptosis is blocked (97). In TNF-α stimulation, receptor-interacting kinase 1 (RIP1) and receptor-interacting kinase 3 (RIP3) are phosphorylated and form a "necrosome" complex. Furthermore, the mixed lineage kinase domain-like (MLKL) pseudo kinase is recruited to the necrosome and phosphorylated by RIP3. The phosphorylated MLKL (pMLKL) is localized to the plasma membrane and induces cell death (97). Kinoshita et al. (99) discovered neutrophils associated with the mechanism of necroptosis in SJS/TEN. CD8+ T cells produced lipocalin-2, which triggered the formation of neutrophil extracellular traps (NETs) in early lesioned skin. Neutrophils undergoing NETosis released LL-37, and LL-37 induced the expression of FPR1 on keratinocytes through P2X7R stimulation. FPR1 expression caused necroptosis of keratinocytes that caused the further release of LL-37 and induced FPR1 expression on surrounding keratinocytes, which likely amplified the necroptotic response. Necroptosis plays an important role in the immunopathogenesis of SJS/TEN (99). Therefore, inhibition of necroptosis could be an effective therapeutic target. Several compounds, including a new FPR1 antagonist now in development, have been shown to inhibit TEN patient serum-mediated cytotoxicity and keratinocyte death.

Differential gene expression of matrix metalloproteinases (MMPs) and TIMP1 may also predict chronic eye disease in SJS/TEN. In one study, MMP9 was a prognostic predictor of poor best-corrected visual acuity (BCVA) post-cultivated oral mucosal epithelial transplantation (COMET) (100). Another study suggested that epidermal MMP9 expression was significantly higher in SJS/TEN skin than in healthy control skin and non-bullous skin reactions. Serum from SJS/TEN patients also induced MMP9 expression in healthy skin explants which were reduced by etanercept. Furthermore, etanercept reduced TNF-α induced MMP9 expression in cell lines providing additional support for the potential role of etanercept as an SJS/TEN therapeutic agent (101).

Other unexplored areas include the potential for innate triggers for SJS/TEN such as MRGPRX2, a mast cell-specific receptor crucial for pseudo-allergic drug reactions, and the application of novel areas of research such as the field of epigenomics.

Study of particular antigenic epitopes that generate an immune response to specific drugs is of significant interest. This approach has been championed by Kula et al. (102) who described the Tscan® methodology of epitope discovery. Tscan® uses a library screening strategy to validate epitopes of interest. For instance, T cells from an SJS/TEN patient could target cells engineered to carry the human peptidome or virus-specific libraries in addition to the suspected HLA risk allele. Granzyme B-producing cells are sorted and processed by deep sequencing to identify epitopes in conjunction with activated T cells (102).

## 5. Updates in acute care

### 5.1. Updates in supportive care management (Table 5)

#### 5.1.1. Burn and critical care management

Acute SJS/TEN is characterized initially by flat, atypical targets or purpuric macules predominantly on the trunk and by mucosal erosions in at least two mucosal sites, often including the ocular surface. Transfer and consultation for patients with SJS/TEN should happen early before advanced critical care is needed. Once progression to multi-organ failure occurs, the transfer of patients may be futile and often leads to a transition to comfort care once they arrive at the tertiary or quaternary hospital with a burn center. These delayed transfers can utilize already scarce resources, distract from the acute management of burn patients, and challenge future collaboration with referring hospitals.

The consensus on how to manage states of shock after burn injury continues to be debated (103). Nonetheless, hospitals with burn programs have extensive expertise in managing non-hemorrhagic hypovolemia. Additionally, some centers have reported that, like burn injury, SJS/TEN may be associated with multifactorial shock. This may include vasodilatory, cardiogenic, and distributive shock phenotypes, and may occur through a perturbed inflammatory stimulation which warrants further investigation. There remains variation by practice on

TABLE 5 Key points discussed during "updates for clinicians."

| |
|---|
| **Specialized units** |
| 1. Consideration should be made to transfer patients with suspected SJS/TEN to hospitals with dermatology inpatient wards or burn centers early in their presentation. The decision should be based on the extent of skin detachment and the need for intensive care. |
| 2. Acute and critical care needs for patients with SJS/TEN can be similar to those of patients suffering a thermal injury. |
| 3. Psychosocial, rehabilitation, and after care needs for patients with SJS/TEN might be better addressed at hospitals with established programs for patients recovering from thermal injury. |
| **Eye care** |
| 1. Early ocular involvement is highly variable and can result in chronic complications leading to severe ocular surface disease including corneal blindness. |
| 2. Patients who receive acute ophthalmic care based on an evidence-based treatment that involves the use of amniotic membrane may be more likely to retain >20/40 vision than those who do not. |
| 3. Customized scleral lenses provide a protective barrier, support the ocular surface, and can prevent corneal complications, improving visual acuity and comfort. |
| **Genitourinary issues** |
| 1. Gynecology was only consulted in half of the cases of possible vulvovaginal involvement. |
| 2. There appeared to be an assumption that there was no need for vulvovaginal care in patients presumably not sexually active. |
| 3. Obtaining consent in a sensitive matter is important in very young/older patients as to explain long-term sequelae. |
| **Unusual presentations** |
| 1. Recognition of SJS/TEN mimickers is critical as management and prognosis can be very different for each category. These include infectious, autoimmune, reactive, and other drug response etiologies. |
| 2. Autoimmune conditions and reactive conditions can produce cutaneous mimics of SJS/TEN but differences exist in presentation, chronicity, laboratory studies and histopathology. |
| 3. While greater than 85% of patients will present with involvement of two mucosal sites some patients have a delayed second mucosal site involvement. Often times this 2nd site includes ocular mucosa. |

how bullae (or blisters) are managed (104, 105). Some centers remove blisters, while others drain. Most dermatologists prefer to drain bullae that result from SJS/TEN, and therefore collaboration is required between teams to reach a consensus on wound management. Similarly, there is some variability in the selection of topical dressing, which should be a subject of future studies. An international team has just published a Delphi-based consensus paper and wound management was one item examined (11). Regardless of bullae management and dressing choice, wounds should be cleaned and examined for stigmata of infection. If infection concerns arise, topical or/and systemic antimicrobials should be initiated to prevent wound-related infection, and subsequent systemic sepsis. There have been studies examining the effects of grafting the wounds in SJS/TEN after mild wound bed preparation; however, these practices have not become standard in most burn centers (106–108). Re-epithelialization of large areas of skin, either primarily or assisted with grafting, requires significant energy expenditure. Although not studied formally, most burn centers will provide hyperalimentation for patients with SJS/TEN using similar formulae that they would use for patients with burns (109). Burn centers work closely with dieticians and most have them embedded within their teams. Protein calorie malnutrition must be prevented, and assessment of nutritional status should be performed either by indirect calorimetry or adjuncts such as urinary excretion of nitrogen if normal kidney function is maintained. Hypermetabolic states persist after wound closure and need to be monitored similarly to those receiving care for burns. Pharmacotherapies such as propranolol and oxandrolone are currently under study for patients with burns (110, 111), and further work in this area will be needed depending on the results.

## 5.2. Eye care in SJS/TEN

Early ocular involvement is highly variable and not proportionately related to the extent of body surface area detached. It ranges from conjunctival hyperemia to near-total sloughing of the ocular surface, including the tarsal conjunctiva and eyelid margins. Chronic complications can result in severe ocular surface disease including corneal blindness.

For survivors, ocular complications are among the most common and debilitating. In a recent survey conducted at 11 academic health centers in the US which evaluated 121 adults diagnosed with SJS/TEN by inpatient consultive dermatologists, 60% of SJS/TEN patients reported long-term eye problems (112). In another study evaluating 105 eyes of 66 patients, the ocular surface worsened during a follow-up of over 5 years, and more than 50% of eyes with partial conjunctivalization progressed toward total conjunctivalization. The severity of tarsal conjunctival or lid-margin scarring affected the worsening of the ocular surface (113).

All of this points to the critical importance of acute phase management. There is a window of opportunity in the first 7 days to alter visual outcomes. Intervention with the amniotic membrane (AM) is the most critical decision to be made to mitigate eyelid margin disease and prevent the long-term sequelae associated with eyelid microtrauma to the ocular surface (114, 115). Traditionally, AM transplantation (AMT) involved the use of bolsters and sutures to secure AM across the eyelid margin and a symblepharon ring to secure it onto the ocular surface. Recent advances in AMT techniques include using cyanoacrylate glue instead of sutures to secure the AM to the eyelids and allow for a painless and rapid procedure that does not require the use of sedation or general anesthesia. This may be of critical importance in acutely ill patients such as those with SJS/TEN (116).

According to a recent study, patients who receive acute ophthalmic care based on an evidence-based treatment that involves the use of AM were more likely to retain >20/40 vision than those who did not (92% vs.33%). Vision-threatening complications in the chronic phase were also significantly higher in the latter group (67% vs. 17%) (117). However, AMT is not a panacea and long-term complications do still occur, particularly eyelid-related complications and dry eye (118).

Systemic treatments for SJS/TEN have long shown equivocal outcomes in ocular disease. More recently, corticosteroid pulse therapy (CPT), systemic cyclosporine, and etanercept have been explored. In a retrospective case series study by Mieno et al. (119), 36 patients who received CPT within 4 days of disease onset were compared against 49 patients who did not receive such therapy. The percentage of patients with a best corrected visual acuity of 20/200 or greater in the worst eye was significantly different between the two groups, with 52.8% reaching ≥20/200 in those who received CPT vs. 14.3% in those who did not. Severe ocular complications were also significantly less in the group that received CPT. It is important to note that this study was not randomized, so more research may be needed to further validate these findings. Another study evaluated the effects of acute systemic cyclosporine in a small cohort of patients and found no association between the use of systemic cyclosporine therapy and chronic ocular complications (120). Etanercept, however, has been shown, along with concurrent use of AMT, to have a beneficial effect in reducing chronic ocular sequela in a small cohort, though the effects of etanercept vs. AMT may be difficult to separate (121). The question of whether specific acute therapies may be better than others for preventing chronic eye sequelae in SJS/TEN is still an open one.

A pivotal point in the care of chronic ocular disease in SJS/TEN was the introduction of customized scleral lenses known as prosthetic replacement of the ocular surface ecosystem (PROSE®). These provide both a protective barrier and support for the ocular surface and can prevent corneal complications, thus improving visual acuity and comfort. PROSE® is often thought of as an intervention that applies only to adults but recently, Wang et al. have shown that pediatric patients with SJS/TEN can also benefit from PROSE® treatment (122). Treatment was feasible in over two-thirds of pediatric patients with chronic ocular surface disease from SJS/TEN and resulted in significant improvements in vision. Other variations of scleral lenses have recently been explored, including a limbal-supported contact lens that led to improved vision compared to spectacles and reduced ocular pain in patients with ocular sequelae from SJS/TEN (123).

Significant advances in our understanding of ocular disease in SJS/TEN have fostered progress in management and outcomes. Though it remains a blinding disease, future advancements will continue to improve vision and visual function in patients with SJS/TEN (124).

## 5.3. Genitourinary disease in SJS/TEN

Although there is consensus on the need that standardized supportive measures should be instituted to prevent long-term genitourinary and reproductive complications in men and women, knowledge of what happens in real clinical practice is lacking. Strictures in the urogenital tract may be more common in women (125). A review of 55 female SJS/TEN survivors sheds light on this issue (126). The key findings from this retrospective review included that gynecology was consulted in <50% of cases and this was unimpacted by the severity of SJS/TEN disease. Furthermore, consultation and care were particularly neglected in girls and young women presumed to be sexually inactive, with no reporting of sexual activity and pregnancy. There was also underutilization of the operating room (OR) and times when sedation was applied to minimize pain and adverse symptoms associated with vulvovaginal exams.

In a subsequent long-term follow-up study involving the same 55 patients, nine patients were found to be deceased, and one patient had an unknown mailing address. Among the remaining 45 patients who were sent follow-up questionnaires, only five patients responded. Although responses were scarce, many noted persistent complaints of vaginal dryness (126).

The overall goal emphasized by this study is the need to standardize the clinical management of women experiencing vulvovaginal sloughing and men with a urogenital disease during the acute phase. It also highlights the importance of improving follow-up care in the gynecology and urology clinics, or alternatively, implementing a multidisciplinary follow-up plan for affected patients.

During the acute phase of SJS/TEN, it is strongly encouraged to consult with gynecology or urology and remain cognizant of potential long-term sequelae such as scarring, strictures, and vaginal dryness. A follow-up plan involving collaboration between different specialties involving gynecologists and urologists is imperative.

## 5.4. Considerations for rehabilitation therapy, hyperproliferative healing, and aftercare reintegration

Physical and occupational therapy is a keystone of burn care and benefits patients with SJS/TEN. Hospitals with burn programs have a higher density of therapists comfortable with managing patients in intensive care units with open wounds. Therapists are also poised to manage anti-deformity positioning and scar prevention. Although not always discussed, patients with SJS/TEN may develop hypertrophic scars that can be remarkably similar to those seen after burn injury (127). Burn therapists are specialists in scar management and employ adjuncts such as splints and compression garments. Acute stress and later post-traumatic stress disorders may develop and burn programs are poised to screen and treat these early. Community, school, and work reintegration are also areas where burn programs have unique expertise and can provide additional resources to patients with SJS/TEN.

## 5.5. Long-term physical and mental health complications of SJS/TEN

Long-term health complications following SJS/TEN are prevalent and underrecognized. SJS survivors have articulated in a recent survey their concerns for inadequacy of post-discharge physical and mental health care (12). Due to incomplete follow-up of SJS/TEN populations, many complications may not have been initially recognized as being associated with SJS/TEN. Recognized complications can include but are not limited to the eye, skin, mucous membrane, ear, internal organ stricture, reproductive, and mental health concerns. One study found that 88.2% of participants felt that their SJS/TEN diagnosis impacted their physical health. In that same study, 70.2% of participants felt that their physicians did not sufficiently address these complications (12).

The acute stage of SJS/TEN is characterized by mucosal membrane involvement (21). Such involvement may include erosion of the ocular

mucous membranes. The most feared long-term effects in SJS/TEN are chronic ocular complications. Approximately 50% of SJS survivors report long-term ocular complications (128). Ocular damage can include limbal stem cell deficiency and numerous side effects. Survivors with limbal stem cell deficiency often have epithelial defects, corneal scarring, lid entropion, vascularization, dry eye syndrome, photophobia, corneal abrasions, and erosions due to the corneal epithelium losing the ability to repair itself. Often corneal abrasions and erosions lead to visual impairment, including blindness. According to Gregory (114), "Interventions during the acute stage are crucial, as the long-term sequelae can be difficult, if not impossible, to repair." Additionally, 77% of SJS/TEN patients present with ocular involvement during the acute stage (129). Standard treatment for SJS/TEN patients can include but is not limited to topical medications, pulse corticosteroid therapy, systemic cyclosporine, symblepharon rings, amniotic membrane transplantation, PROKERA® ring, scleral contact lenses, PROSE® contact lenses, SynergEYES® contact lenses, and limbal supported contact lenses.

It is suggested that daily rinsing of the eyes with sterile saline helps combat inflammatory disease. When used in combination with prophylactic topical antibiotics that are bactericidal, rinsing may also decrease the risk of infection. According to Mieno et al. (119), if given within 4 days of symptom onset, pulse corticosteroid therapy led to significantly better vision and fewer corneal and conjunctival complications. Gregory (114) suggests that systemic cyclosporine may decrease ocular surface inflammation.

Symblepharon may still occur with the treatments above, which indicates the implementation of a symblepharon ring to prevent adhesion of the conjunctiva with the eyelid. In addition, amniotic membrane transplantation may be used for anti-inflammatory and anti-scarring purposes and to promote epithelial healing. Increasing evidence supports a combination of the two previously mentioned treatments, called the PROKERA® ring, which prevents symblepharon, and decreases inflammation and scarring risk while promoting epithelial healing.

Increasing evidence for treatment of chronic eye complications includes, but is not limited to topical medications, scleral contact lenses, PROSE® contact lenses, SynergEYES® contact lenses, and limbal supported contact lenses. SJS/TEN survivors frequently suffer from dry eye syndrome and therefore require constant use of artificial eye drops throughout the day and eye ointment during the night. In addition, some survivors opt to use blood serum tears during the day as they provide healing properties for healthy cell growth and may afford patients additional relief and comfort. Scleral contact lenses are gas-permeable contact lenses designed to cover the eye's cornea and help with dry eye syndrome. PROSE® contacts provide durable improvements in vision. SynergEYES® contact lenses consist of a stable, rigid center with high oxygen permeability that delivers clear vision and the comfort of a soft lens. Limbal-supported contact lenses are a type of scleral lens that can improve vision and reduce ocular pain. Itoi et al. (123) suggest that wearing limbal-supported lenses improved vision and reduced ocular pain compared to spectacles.

Outside of ocular complications, complications vary in severity as SJS/TEN cases and treatment courses differ among individuals. According to one study, 80% of patients reported skin sequelae from SJS/TEN (128). Skin damage can manifest as hyper-or hypopigmentation, fibrosis, scarring, sealed pores, hair follicle destruction, and nail bed and plate damage. Hyper-or hypopigmentation, fibrosis, and hypertrophic scars are more prevalent in people of color. Survivors with hypertrophic scars may experience sealed pores, leading to overheating in hot weather and the inability to sweat. Additionally, survivors may experience hair follicle destruction causing loss of hair, and many survivors experience damage to their nail beds and plates resulting in slow-growing, fragile, or missing nails.

SJS/TEN can affect the regenerative capacity of the mucosal surfaces. In severe cases, it manifests as scarring/fibrosis. Skin areas exposed to pressure and friction may show delayed healing and sometimes even failure to re-epithelialize. Deeper tissue involvement causes significant damage to progenitor and stem cell populations in affected tissues and can impact the surrounding cellular, immunological, and cytokine microenvironment (130). Hair follicle destruction has also been associated with secondary dermal microcalcifications, scarring, and sebaceous hyperplasia (131).

Many survivors also experience oral health complications, including dental growth abnormalities, low saliva volume (dry mouth), altered tongue, pain, burning sensation, numbness, and loss of taste and smell. Dental growth abnormalities, such as stunted root development, enamel damage, and loss of tooth buds have been observed in children, resulting in missing permanent teeth. SJS/TEN survivors may experience altered tongue, which appears smooth due to filiform and/or fungiform papillae damage. This damage can result in pain, burning sensation, numbness, and loss of taste. Closely related to loss of taste, there may be sinus damage from mucous membrane involvement, resulting in disordered smell perception.

Ear damage can occur which includes scarring and loss of cilia. This can result in complete occlusion of the external auditory canal. Loss of cilia can also lead to abnormal ear wax drainage and loss of hearing.

Urogenital complications most commonly include internal strictures. Female SJS/TEN survivors may experience vulvar, vaginal, and cervical adhesions and scarring, as well as vaginal and cervical stenosis (narrowing) due to damage to mucous membranes which can subsequently complicate childbirth.

Female survivors may also suffer from menstrual disturbances caused by obstruction of the outflow of menstrual blood manifesting as: cyclical abdominal pain, hematocolpos (blood accumulated in the vagina), and hematometra (blood accumulated in the uterine cavity). Both male and female survivors may experience urethral adhesions and scarring, urethral stenosis, hypogastric mass, recurrent painful urination, urinary tract infection, and sexual dysfunction.

Other internal organs can be involved largely from mechanical fractures (strictures) and other organ damage including to the esophagus, colon, liver, renal, gastrointestinal, and respiratory systems. Esophageal strictures commonly manifest as difficulty swallowing. Survivors may also have colon complications such as colitis. Ileal strictures can be associated with chronic diarrhea, intestinal ulcers, intussusception (intestinal inversion), ileal pseudodiverticula, and bleeding. Respiratory complications most commonly include asthma, chronic bronchitis, bronchiolitis obliterations, chronic obstructive pulmonary disease (COPD), interstitial lung disease, pulmonary air leak syndrome, and laryngeal obstruction.

Acute and chronic mental health issues are an important, and often overlooked complication of SJS/TEN that can be prevalent decades later and be a key factor impairing return to work and regular daily activities. Psychiatric damage among survivors can manifest as

TABLE 6 Future directions to move SJS/TEN forward.

| Unmet needs/gaps | Implementation/focus points |
|---|---|
| **Prevention, prediction, and regulation:** | |
| -Lack of knowledge on all casual factors<br>-Generalized genetic test findings<br>-Limited information on casual drugs and targets<br>-Genetic tests with low positive predictive value<br>-Need of evidence-based pre-prescription genetic tests<br>-Lack of real time information on SJS/TEN cases with any new casual drug | -Conduct studies across diverse population groups (age, race, gender, ethnicity)<br>-Low and cost-effective testing<br>-Networks and collaborations to study on multiple drugs, and risk factors<br>-Studies to include genetic and other risk factor identifications<br>-Advancement in pharmacovigilance for immediate updates and alerts on new adverse drug effects |
| **Early diagnosis and treatment:** | |
| -Unidentifiable/unreported cases<br>-Inadequate transfer specialized centers<br>-Lack of knowledge on biological markers that aid in early diagnosis<br>-Identify culprit drugs with testing methods (*in vivo/ex vivo/ in vitro*)<br>-Photographic data to assess risk and prognosis | -Clinical awareness and decision-making support<br>-Telehealth triage services<br>-Studies to provide genetic markers and point of care markers for early diagnosis and prognosis<br>-Validate drugs causes across different cohorts<br>-Introduce artificial intelligence algorithms into clinical care |
| **Clinical care and follow-up:** | |
| -Need for evidence-based studies to provide best supportive care<br>-Short term treatment plans<br>-Long term clinical/health complications<br>-Coordinated clinical care and support services | -Provide evidence-based study results for best clinical practices<br>-Introduce collaborative networks (domestic and international) in clinical trial studies<br>-Follow-up and long-term care for survivors and families<br>-Coordination among clinical specialties |
| **Understanding mechanisms and providing care:** | |
| -Mechanistic studies to identify cellular and molecular signals that act as a biological marker and novel targets for treatment | -Cohort studies on prospectively collected samples for long-term storage with collaborative effort from international networks |

anxiety and fear of new medicines, survivor guilt, flashbacks, insomnia, depression, and post-traumatic stress disorder. Survivors often feel frustrated due to a lack of providers versed in the disease and a lack of appropriate explanations of how to access specialty care and what to expect. They are particularly fearful of trying new medications and products such as vaccines due to the concern of recurrence.

## 6. Moving the field forward/future directions

SJS/TEN remains a life-threatening and a largely drug-induced disease in adults with high morbidity and mortality. Research into prevention, earlier diagnosis, and treatment of SJS/TEN is impacted by its overall rarity which challenges the ability to study large and diverse populations. The continued development of international networks to synergize efforts from researchers with expertise in different genres of research will be key to the overall success, advancement, and translation. Engagement with the community of SJS/TEN survivors and affected families remains key in this process. Particularly relevant is the fragmentation of healthcare and lack of information on long-term health outcomes for survivors of SJS/TEN. Notable recent advances in SJS/TEN have included insights into earlier diagnosis, mechanisms, risk identification, clinical implications, and pharmaco-surveillance, making risk prediction and prevention possible for some causative factors. As some of the main barriers remain unaddressed, and to truly understand the disease, this research effort requires the collaboration of experts, multidisciplinary leadership/approach, and coordination that includes a critical review of patient-centered clinical and research priorities and unmet evidence-based research needs.

Strengths and opportunities prevail, and in this paper, we have tried to summarize the updated literature on SJS/TEN while highlighting knowledge gaps and research opportunities. Although there have been many recent advances in SJS/TEN research that will improve SJS/TEN outcomes and care, ongoing global research collaboration is urgently needed to address the challenges of studying diverse SJS/TEN populations to include adequate representation of age, gender, race, and ethnicity. Several national and international projects have had small sample sizes that were not ancestrally diverse enough to identify risk alleles, generalized-based risk factors, or effective treatment strategies. These international collaboration networks grown over time will be a powerful vehicle to address unmet needs like developing affordable pharmacogenomic assays, piloting preemptive testing, and incorporating genotypic information that supports the decision-making directly into the medical record which will aid in drug prescription and dispensing systems (Table 6) (6). These networks can also facilitate genome-wide association research studies of other implicated drugs/agents for which robust genomic risk factors are yet to be identified as well as multiomic and mechanistic studies to facilitate the development of earlier diagnostic and prognostic markers and new targeted therapeutic agents.

## Author's note

This paper was written using the priority framework of content presented at the virtual meeting: SJS/TEN 2021: Collaboration, Innovation and Community (https://sjsten2021.vfairs.com/).

## Author contributions

MEM and RKB are the co-first-authors of this manuscript. CB, SD, and EJP are the last authors, with EJP as the corresponding author of this manuscript. RKB and MM contributed to the Supplementary Figure. SP, MEM, RKB and EJP contributed to Figure 1. W-HC and MEM contributed to Figure 2. W-CC and CS contributed to Figure 3. ET and MEM contributed to Figure 4. MEM contributed to Figure 5. RKB, MEM, HBP, and KM contributed to Table 1. SH, BK, MM, and RKB contributed to Table 2. MEM and ET contributed to Table 3. HBP contributed to Table 4. JS, TMB, HNS, AS, JC, EF, HBP, and MM contributed to Table 5. RKB contributed to Table 6. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

## Funding

This work was partially supported by Vanderbilt University Medical Center Department of Medicine, the University of Ottawa Department of Medicine, and the Canadian Dermatology Foundation. EP reports grants from National Institutes of Health (R01HG010863, R01AI152183, and U01AI154659) and from the National Health and Medical Research Council of Australia. The funder was not involved in the study design, collection, analysis, interpretation of data, the writing of this article, or the decision to submit it for publication.

## Acknowledgments

The authors would like to thank the patients and their medical care teams whose efforts and cooperation greatly contributed to the value of this work. We would like to thank all attendees, including Stephen Elledge for their presence at the virtual meeting. The contents of this paper are solely the responsibility of the authors and do not necessarily represent the views of the National Institutes of Health. The opinions and assertions expressed herein are those of the authors and do not reflect the official policy or position of the U.S. Food and Drug Administration. Eric Tkaczyk was supported by Career Development Award Number IK2 CX001785 from the United States Department of Veterans Affairs Clinical Science R&D Service.

## Conflict of interest

KM was employed by Stevens-Johnson Syndrome Foundation. EJP reports grants from National Institutes of Health (R01HG010863, R01AI152183, U01AI154659) and from the National Health and Medical Research Council of Australia. She receives Royalties and consulting fees from UpToDate and has received consulting fees from Janssen, Verve, Biocryst, Regeneron, AstraZeneca and Novavax.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer OI declared a shared affiliation with the author AS to the handling editor at the time of review.

## Publisher's note



## Author disclaimer

TB, MR, and HBP the opinions and assertions expressed herein are those of the authors and do not reflect the official policy or position of the U.S. Food and Drug Administration, Uniformed Services, University of the Health Sciences, or the Department of Defense. This work was prepared by a military or civilian employee of the US Government as part of the individual's official duties. Therefore, is in the public domain and does not possess copyright protection (public domain information may be freely distributed and copied; however, as a courtesy it is requested that the Uniformed Services University and the author be given an appropriate acknowledgement).

## Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2023.1213889/full#supplementary-material

## References

1. Peter JG, Lehloenya R, Dlamini S, Risma K, White KD, Konvinse KC, et al. Severe delayed cutaneous and systemic reactions to drugs: a global perspective on the science and art of current practice. *J Allergy Clin Immunol Pract*. (2017) 5:547–63. doi: 10.1016/j.jaip.2017.01.025

2. Dobry AS, Himed S, Waters M, Kaffenberger BH. Scoring assessments in Stevens-Johnson syndrome and toxic epidermal necrolysis. *Front Med (Lausanne)*. (2022) 9:883121. doi: 10.3389/fmed.2022.883121

3. Frantz R, Huang S, Are A, Motaparthi K. Stevens-Johnson syndrome and toxic epidermal necrolysis: A review of diagnosis and management. *Medicina*. (2021) 57:895. doi: 10.3390/medicina57090895

4. Chang WC, Abe R, Anderson P, Anderson W, Ardern-Jones MR, Beachkofsky TM, et al. SJS/TEN 2019: from science to translation. *J Dermatol Sci*. (2020) 98:2–12. doi: 10.1016/j.jdermsci.2020.02.003

5. Gronich N, Maman D, Stein N, Saliba W. Culprit medications and risk factors associated with Stevens-Johnson syndrome and toxic epidermal necrolysis: population-based nested case-control study. *Am J Clin Dermatol*. (2022) 23:257–66. doi: 10.1007/s40257-021-00661-0

6. Phillips EJ, Bouchard CS, Divito SJ. Stevens-Johnson syndrome and toxic epidermal necrolysis-coordinating research priorities to move the field forward. *JAMA Dermatol*. (2022) 158:607–8. doi: 10.1001/jamadermatol.2022.0484

7. Goodman CW, Brett AS. Race and pharmacogenomics-personalized medicine or misguided practice? *JAMA*. (2021) 325:625–6. doi: 10.1001/jama.2020.25473

8. White KD, Abe R, Ardern-Jones M, Beachkofsky T, Bouchard C, Carleton B, et al. SJS/TEN 2017: building multidisciplinary networks to drive science and translation. *J Allergy Clin Immunol Pract*. (2018) 6:38–69. doi: 10.1016/j.jaip.2017.11.023

9. Stern RS. Professor Jean-Claude Roujeau (1944-2021). *Br J Dermatol*. (2021) 185:470–1. doi: 10.1111/bjd.20076

10. Micheletti RG, Chiesa-Fuxench Z, Noe MH, Stephen S, Aleshin M, Agarwal A, et al. Stevens-Johnson syndrome/toxic epidermal necrolysis: a multicenter retrospective

study of 377 adult patients from the United States. *J Invest Dermatol*. (2018) 138:2315–21. doi: 10.1016/j.jid.2018.04.027

11. Bruggen MC, Le ST, Walsh S, Toussi A, de Prost N, Ranki A, et al. Supportive care in the acute phase of Stevens-Johnson syndrome and toxic epidermal necrolysis: an international, multidisciplinary Delphi-based consensus. *Br J Dermatol*. (2021) 185:616–26. doi: 10.1111/bjd.19893

12. Coromilas AJ, Divito SJ, Phillips EJ, Micheletti RG. Physical and mental health impact of Stevens-Johnson syndrome/toxic epidermal necrolysis and post–hospital discharge care: identifying practice gaps. *JAAD Int*. (2023) 11:88–9. doi: 10.1016/j.jdin.2023.01.012

13. Bousman CA, Bengesser SA, Aitchison KJ, Amare AT, Aschauer H, Baune BT, et al. Review and consensus on pharmacogenomic testing in psychiatry. *Pharmacopsychiatry*. (2021) 54:5–17. doi: 10.1055/a-1288-1061

14. Chang CJ, Chen CB, Hung SI, Ji C, Chung WH. Pharmacogenetic testing for prevention of severe cutaneous adverse drug reactions. *Front Pharmacol*. (2020) 11:969. doi: 10.3389/fphar.2020.00969

15. Liu H, Wang Z, Bao F, Wang C, Sun L, Zhang H, et al. Evaluation of prospective HLA-B*13: 01 screening to prevent dapsone hypersensitivity syndrome in patients with leprosy. *JAMA Dermatol*. (2019) 155:666–72. doi: 10.1001/jamadermatol.2018.5360

16. Sung C, Tan L, Limenta M, Ganesan G, Toh D, Chan CL. Usage pattern of carbamazepine and associated severe cutaneous adverse reactions in Singapore following implementation of HLA-B*15:02 genotyping as standard-of-care. *Front Pharmacol*. (2020) 11:527. doi: 10.3389/fphar.2020.00527

17. Tang MM, Fok JS, Thong BY, Yun J, Li PH, Kang HR, et al. Diagnostic procedures & practices in drug allergy/hypersensitivity: a survey of 13 Asian countries. *Asia Pac Allergy*. (2020) 10:e36. doi: 10.5415/apallergy.2020.10.e36

18. Thong BY, Lucas M, Kang HR, Chang YS, Li PH, Tang MM, et al. Drug hypersensitivity reactions in Asia: regional issues and challenges. *Asia Pac Allergy*. (2020) 10:e8. doi: 10.5415/apallergy.2020.10.e8

19. Su SC, Chen CB, Chang WC, Wang CW, Fan WL, Lu LY, et al. HLA alleles and CYP2C9*3 as predictors of phenytoin hypersensitivity in east Asians. *Clin Pharmacol Ther*. (2019) 105:476–85. doi: 10.1002/cpt.1190

20. Yang SC, Chen CB, Lin MY, Zhang ZY, Jia XY, Huang M, et al. Genetics of severe cutaneous adverse reactions. *Front Med*. (2021) 8:652091. doi: 10.3389/fmed.2021.759559

21. Tempark T, John S, Rerknimitr P, Satapornpong P, Sukasem C. Drug-induced severe cutaneous adverse reactions: insights into clinical presentation, immunopathogenesis, diagnostic methods, treatment, and pharmacogenomics. *Front Pharmacol*. (2022) 13:832048. doi: 10.3389/fphar.2022.832048

22. Capule F, Tragulpiankit P, Mahasirimongkol S, Jittikoon J, Wichukchinda N, Theresa Alentajan-Aleta L, et al. Association of carbamazepine-induced Stevens-Johnson syndrome/toxic epidermal necrolysis with the HLA-B75 serotype or HLA-B*15:21 allele in Filipino patients. *Pharmacogenomics J*. (2020) 20:533–41. doi: 10.1038/s41397-019-0143-8

23. Pan RY, Chu MT, Wang CW, Lee YS, Lemonnier F, Michels AW, et al. Identification of drug-specific public TCR driving severe cutaneous adverse reactions. *Nat Commun*. (2019) 10:3569. doi: 10.1038/s41467-019-11396-2

24. Phillips EJ, Sukasem C, Whirl-Carrillo M, Muller DJ, Dunnenberger HM, Chantratita W, et al. Clinical pharmacogenetics implementation consortium guideline for HLA genotype and use of carbamazepine and oxcarbazepine: 2017 update. *Clin Pharmacol Ther*. (2018) 103:574–81. doi: 10.1002/cpt.1004

25. Wong CSM, Yap DYH, Ip P, Wong WHS, Chua GT, Yeung CK, et al. HLA-B*15:11 status and carbamazepine-induced severe cutaneous adverse drug reactions in HLA-B*15:02 negative Chinese. *Int J Dermatol*. (2022) 61:184–90. doi: 10.1111/ijd.15792

26. Deshpande P, Hertzman RJ, Palubinsky AM, Giles JB, Karnes JH, Gibson A, et al. Immunopharmacogenomics: mechanisms of HLA-associated drug reactions. *Clin Pharmacol Ther*. (2021) 110:607–15. doi: 10.1002/cpt.2343

27. Gibson A, Deshpande P, Campbell CN, Krantz MS, Mukherjee E, Mockenhaupt M, et al. Updates on the immunopathology and genomics of severe cutaneous adverse drug reactions. *J Allergy Clin Immunol*. (2023) 151:289–300.e4. doi: 10.1016/j.jaci.2022.12.005

28. Jantararoungtong T, Tempark T, Koomdee N, Medhasi S, Sukasem C. Genotyping HLA alleles to predict the development of severe cutaneous adverse drug reactions (SCARs): state-of-the-art. *Expert Opin Drug Metab Toxicol*. (2021) 17:1049–64. doi: 10.1080/17425255.2021.1946514

29. Guy JW, Patel I, Oestreich JH. Clinical application and educational training for pharmacogenomics. *Pharmacy*. (2020) 8:163. doi: 10.3390/pharmacy8030163

30. Sukasem C, Jantararoungtong T, Koomdee N. Pharmacogenomics research and its clinical implementation in Thailand: lessons learned from the resource-limited settings. *Drug Metab Pharmacokinet*. (2021) 39:100399. doi: 10.1016/j.dmpk.2021.100399

31. Relling MV, Klein TE, Gammal RS, Whirl-Carrillo M, Hoffman JM, Caudle KE. The clinical pharmacogenetics implementation consortium: 10 years later. *Clin Pharmacol Ther*. (2020) 107:171–5. doi: 10.1002/cpt.1651

32. Plumpton CO, Pirmohamed M, Hughes DA. Cost-effectiveness of panel tests for multiple pharmacogenes associated with adverse drug reactions: an evaluation framework. *Clin Pharmacol Ther*. (2019) 105:1429–38. doi: 10.1002/cpt.1312

33. Yoo HW, Kim HY, Shin K, Kim SH. Clinical characteristics of drug-induced Stevens-Johnson syndrome and toxic epidermal necrolysis: a single-center study. *Asia Pac Allergy*. (2022) 12:e17. doi: 10.5415/apallergy.2022.12.e17

34. Porebski G. In vitro assays in severe cutaneous adverse drug reactions: are they still research tools or diagnostic tests already? *Int J Mol Sci*. (2017) 18:1737. doi: 10.3390/ijms18081737

35. Sadek M, Iqbal O, Siddiqui F, Till S, Mazariegos M, Campbell E, et al. The role of IL-13, IL-15 and granulysin in the pathogenesis of Stevens-Johnson syndrome/toxic epidermal necrolysis. *Clin Appl Thromb Hemost*. (2021) 27:1076029620950831. doi: 10.1177/1076029620950831

36. Schwartz RA, McDonough PH, Lee BW. Toxic epidermal necrolysis: Part II. Prognosis, sequelae, diagnosis, differential diagnosis, prevention, and treatment. *J Am Acad Dermatol*. (2013) 69:187.e1–187.e16; Quiz 203-4. doi: 10.1016/j.jaad.2013.05.002

37. Barbaud A, Romano A. Skin testing approaches for immediate and delayed hypersensitivity reactions. *Immunol Allergy Clin N Am*. (2022) 42:307–22. doi: 10.1016/j.iac.2022.01.003

38. Phillips EJ, Bigliardi P, Bircher AJ, Broyles A, Chang YS, Chung WH, et al. Controversies in drug allergy: testing for delayed reactions. *J Allergy Clin Immunol*. (2019) 143:66–73. doi: 10.1016/j.jaci.2018.10.030

39. Copaescu A, Gibson A, Li Y, Trubiano JA, Phillips EJ. An updated review of the diagnostic methods in delayed drug hypersensitivity. *Front Pharmacol*. (2020) 11:573573. doi: 10.3389/fphar.2020.573573

40. Copaescu AM, Ben-Shoshan M, Trubiano JA. Tools to improve the diagnosis and management of T-cell mediated adverse drug reactions. *Front Med*. (2022) 9:923991. doi: 10.3389/fmed.2022.923991

41. Lehloenya RJ, Isaacs T, Nyika T, Dhana A, Knight L, Veenstra S, et al. Early high-dose intravenous corticosteroids rapidly arrest Stevens Johnson syndrome and drug reaction with eosinophilia and systemic symptoms recurrence on drug re-exposure. *J Allergy Clin Immunol*. (2021) 9:582–584.e1. doi: 10.1016/j.jaip.2020.08.012

42. Lehloenya RJ, Peter JG, Copascu A, Trubiano JA, Phillips EJ. Delabeling delayed drug hypersensitivity: how far can you safely go? *J Allergy Clin Immunol Pract*. (2020) 8:2878–2895.e6. doi: 10.1016/j.jaip.2020.07.005

43. Copaescu AM, Trubiano JA. In vitro/ex vivo assays for severe cutaneous drug reactions. *J Allergy Clin Immunol*. (2023) 152:39–41. doi: 10.1016/j.jaci.2023.03.024

44. Bastuji-Garin S, Fouchard N, Bertocchi M, Roujeau JC, Revuz J, Wolkenstein P. SCORTEN: a severity-of-illness score for toxic epidermal necrolysis. *J Invest Dermatol*. (2000) 115:149–53. doi: 10.1046/j.1523-1747.2000.00061.x

45. Koh HK, Fook-Chong S, Lee HY. Assessment and comparison of performance of ABCD-10 and SCORTEN in prognostication of epidermal necrolysis. *JAMA Dermatol*. (2020) 156:1294–9. doi: 10.1001/jamadermatol.2020.3654

46. Suo H, Jiang B, Sun X, Dong J, Alamgir M, Guan X, et al. Comparing the accuracy of ABCD-10 and SCORTEN in predicting the in-hospital mortality of Stevens-Johnson syndrome/toxic epidermal necrolysis: a multi-institutional study from Central China. *Dermatology*. (2022) 238:736–44. doi: 10.1159/000520494

47. Koh HK, Fook-Chong SMC, Lee HY. Improvement of mortality prognostication in patients with epidermal necrolysis: the role of novel inflammatory markers and proposed revision of SCORTEN (Re-SCORTEN). *JAMA Dermatol*. (2022) 158:160–6. doi: 10.1001/jamadermatol.2021.5119

48. Hama N, Sunaga Y, Ochiai H, Kokaze A, Watanabe H, Kurosawa M, et al. Development and validation of a novel score to predict mortality in Stevens-Johnson syndrome and toxic epidermal necrolysis: CRISTEN. *J Allergy Clin Immunol Pract*. (2023). doi: 10.1016/j.jaip.2023.07.001

49. Ng QX, De Deyn M, Venkatanarayanan N, Ho CYX, Yeo WS. A meta-analysis of cyclosporine treatment for Stevens-Johnson syndrome/toxic epidermal necrolysis. *J Inflamm Res*. (2018) 11:135–42. doi: 10.2147/JIR.S160964

50. Ramsay B, Lawrence CM. Measurement of involved surface area in patients with psoriasis. *Br J Dermatol*. (1991) 124:565–70. doi: 10.1111/j.1365-2133.1991.tb04952.x

51. Pham C, Collier Z, Gillenwater J. Changing the way we think about burn size estimation. *J Burn Care Res*. (2019) 40:1–11. doi: 10.1093/jbcr/iry050

52. DuBOIS D, Dubois EF. Fifth paper the measurement of the surface area of man. *Arch Intern Med*. (1915) XV (5_2):868–81.

53. Choi J, Patil A, Vendrow E, Touponse G, Aboukhater L, Forrester JD, et al. Practical computer vision application to compute total body surface area burn: reappraising a fundamental burn injury formula in the modern era. *JAMA Surg*. (2022) 157:129–35. doi: 10.1001/jamasurg.2021.5848

54. Wachtel TL, Berry CC, Wachtel EE, Frank HA. The inter-rater reliability of estimating the size of burns from various burn area chart drawings. *Burns*. (2000) 26:156–70. doi: 10.1016/S0305-4179(99)00047-9

55. Chong HP, Quinn L, Jeeves A, Cooksey R, Lodge M, Carney B, et al. A comparison study of methods for estimation of a burn surface area: Lund and Browder, e-burn and Mersey burns. *Burns*. (2020) 46:483–9. doi: 10.1016/j.burns.2019.08.014

56. Tocco-Tussardi I, Presman B, Huss F. Want correct percentage of TBSA burned? Let a layman do the assessment. *J Burn Care Res*. (2018) 39:295–301. doi: 10.1097/BCR.0000000000000613

57. Tkaczyk ER, Coco JR, Wang J, Chen F, Ye C, Jagasia MH, et al. Crowdsourcing to delineate skin affected by chronic graft-vs-host disease. *Skin Res Technol*. (2019) 25:572–7. doi: 10.1111/srt.12688

58. Codella NCF, Gutman D, Celebi ME, Helba B, Marchetti MA, Dusza SW, et al. Skin lesion analysis toward melanoma detection: A challenge at the 2017 international symposium on biomedical imaging (ISBI), hosted by the international skin imaging collaboration (ISIC). Proceedings of the 2018 IEEE 15th International Symposium on Biomedical Imaging (ISBI 2018). Washington, DC, USA: IEEE. (2018): 168–172.

59. Daneshjou R, Barata C, Betz-Stablein B, Celebi ME, Codella N, Combalia M, et al. Checklist for evaluation of image-based artificial intelligence reports in dermatology: CLEAR Derm consensus guidelines from the international skin imaging collaboration artificial intelligence working group. *JAMA Dermatol*. (2022) 158:90–6. doi: 10.1001/jamadermatol.2021.4915

60. Waters M, Dobry A, Le ST, Shinkai K, Beachkofsky TM, Davis MDP, et al. Development of a skin-directed scoring system for Stevens-Johnson syndrome and epidermal necrolysis: a delphi consensus exercise. *JAMA Dermatol*. (2023) 159:772–7. doi: 10.1001/jamadermatol.2023.1347

61. Charlton OA, Harris V, Phan K, Mewton E, Jackson C, Cooper A. Toxic epidermal necrolysis and Steven-Johnson syndrome: a comprehensive review. *Adv Wound Care*. (2020) 9:426–39. doi: 10.1089/wound.2019.0977

62. Brazel M, Desai A, Are A, Motaparthi K. Staphylococcal scalded skin syndrome and bullous impetigo. *Medicina*. (2021) 57:1157. doi: 10.3390/medicina57111157

63. Tankunakorn J, Sawatwarakul S, Vachiramon V, Chanprapaph K. Stevens-Johnson syndrome and toxic epidermal necrolysis-like lupus erythematosus. *J Clin Rheumatol*. (2019) 25:224–31. doi: 10.1097/RHU.0000000000000830

64. Klimas N, Quintanilla-Dieck J, Vandergriff T. Stevens–Johnson syndrome and toxic epidermal necrolysis. *Cutaneous Drug Eruptions*. (2015):259–69. doi: 10.1007/978-1-4471-6729-7_24

65. Newkirk RE, Fomin DA, Braden MM. Erythema multiforme versus Stevens-Johnson syndrome/toxic epidermal necrolysis: subtle difference in presentation, major difference in management. *Mil Med*. (2020) 185:e1847–50. doi: 10.1093/milmed/usaa029

66. Hung YT, Chen YW, Huang Y, Lin YJ, Chen CB, Chung WH. Acute graft-versus-host disease presenting as Stevens-Johnson syndrome and toxic epidermal necrolysis: a retrospective cohort study. *J Am Acad Dermatol*. (2022) 88:792–801. doi: 10.1016/j.jaad.2022.10.035

67. Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, et al. Features and outcomes of 899 patients with drug-induced liver injury: the DILIN prospective study. *Gastroenterology*. (2015) 148:1340–1352.e7. doi: 10.1053/j.gastro.2015.03.006

68. Fontana RJ, Li Y-J, Phillips E, Saeed N, Barnhart H, Kleiner D, et al. Allopurinol hepatotoxicity is associated with human leukocyte antigen class I alleles. *Liver Int*. (2021) 41:1884–93. doi: 10.1111/liv.14903

69. Nicoletti P, Barrett S, McEvoy L, Daly AK, Aithal G, Lucena MI, et al. Shared genetic risk factors across carbamazepine-induced hypersensitivity reactions. *Clin Pharm Ther*. (2019) 106:1028–36. doi: 10.1002/cpt.1493

70. Hasan Ali O, Berner F, Bomze D, Fassler M, Diem S, Cozzio A, et al. Human leukocyte antigen variation is associated with adverse events of checkpoint inhibitors. *Eur J Cancer*. (2019) 107:8–14. doi: 10.1016/j.ejca.2018.11.009

71. Sznol M, Ferrucci PF, Hogg D, Atkins MB, Wolter P, Guidoboni M, et al. Pooled analysis safety profile of nivolumab and ipilimumab combination therapy in patients with advanced melanoma. *J Clin Oncol*. (2017) 35:3815–22. doi: 10.1200/JCO.2016.72.1167

72. Santini FC, Rizvi H, Plodkowski AJ, Ni A, Lacouture ME, Gambarin-Gelwan M, et al. Safety and efficacy of re-treating with immunotherapy after immune-related adverse events in patients with NSCLC. *Cancer Immunol Res*. (2018) 6:1093–9. doi: 10.1158/2326-6066.CIR-17-0755

73. Freeman-Keller M, Kim Y, Cronin H, Richards A, Gibney G, Weber JS. Nivolumab in resected and unresectable metastatic melanoma: characteristics of immune-related adverse events and association with outcomes. *Clin Cancer Res*. (2016) 22:886–94. doi: 10.1158/1078-0432.CCR-15-1136

74. Geisler AN, Phillips GS, Barrios DM, Wu J, Leung DYM, Moy AP, et al. Immune checkpoint inhibitor-related dermatologic adverse events. *J Am Acad Dermatol*. (2020) 83:1255–68. doi: 10.1016/j.jaad.2020.03.132

75. Belum VR, Benhuri B, Postow MA, Hellmann MD, Lesokhin AM, Segal NH, et al. Characterisation and management of dermatologic adverse events to agents targeting the PD-1 receptor. *Eur J Cancer*. (2016) 60:12–25. doi: 10.1016/j.ejca.2016.02.010

76. Powles T, O'Donnell PH, Massard C, Arkenau HT, Friedlander TW, Hoimes CJ, et al. Efficacy and safety of durvalumab in locally advanced or metastatic urothelial carcinoma: updated results from a phase 1/2 open-label study. *JAMA Oncol*. (2017) 3:e172411. doi: 10.1001/jamaoncol.2017.2411

77. Minkis K, Garden BC, Wu S, Pulitzer MP, Lacouture ME. The risk of rash associated with ipilimumab in patients with cancer: a systematic review of the literature and meta-analysis. *J Am Acad Dermatol*. (2013) 69:e121–8. doi: 10.1016/j.jaad.2012.12.963

78. Joseph RW, Millis SZ, Carballido EM, Bryant D, Gatalica Z, Reddy S, et al. PD-1 and PD-L1 expression in renal cell carcinoma with sarcomatoid differentiation. *Cancer Immunol Res*. (2015) 3:1303–7. doi: 10.1158/2326-6066.CIR-15-0150

79. Tsiogka A, Bauer JW, Patsatsi A. Bullous pemphigoid associated with anti-programmed cell death protein 1 and anti-programmed cell death ligand 1 therapy: a review of the literature. *Acta Derm Venereol*. (2021) 101:adv 00377. doi: 10.2340/00015555-3740

80. Siegel J, Totonchy M, Damsky W, Berk-Krauss J, Castiglione F Jr, Sznol M, et al. Bullous disorders associated with anti-PD-1 and anti-PD-L1 therapy: a retrospective analysis evaluating the clinical and histopathologic features, frequency, and impact on cancer therapy. *J Am Acad Dermatol*. (2018) 79:1081–8. doi: 10.1016/j.jaad.2018.07.008

81. Goldinger SM, Stieger P, Meier B, Micaletto S, Contassot E, French LE, et al. Cytotoxic cutaneous adverse drug reactions during anti-PD-1 therapy. *Clin Cancer Res*. (2016) 22:4023–9. doi: 10.1158/1078-0432.CCR-15-2872

82. Kwon CW, Murthy RK, Kudchadkar R, Stoff BK. Pembrolizumab-induced lichen planus pemphigoides in a patient with metastatic Merkel cell carcinoma. *JAAD Case Rep*. (2020) 6:1045–7. doi: 10.1016/j.jdcr.2020.03.007

83. Kuo AM, Markova A. High grade dermatologic adverse events associated with immune checkpoint blockade for cancer. *Front Med*. (2022) 9:898790. doi: 10.3389/fmed.2022.898790

84. Shi CR, Shaughnessy M, Sehgal K, Clark JR, Reynolds KL, Toyohara J, et al. Successful rechallenge with pembrolizumab after case of progressive immunotherapy-related mucocutaneous eruption (PIRME), a Stevens-Johnson syndrome-like reaction. *Int J Dermatol*. (2023). doi: 10.1111/ijd.16572

85. Faje AT, Lawrence D, Flaherty K, Freedman C, Fadden R, Rubin K, et al. High-dose glucocorticoids for the treatment of ipilimumab-induced hypophysitis is associated with reduced survival in patients with melanoma. *Cancer*. (2018) 124:3706–14. doi: 10.1002/cncr.31629

86. Mori S, Hickey A, Dusza SW, Lacouture ME, Markova A. Markers of systemic involvement and death in hospitalized cancer patients with severe cutaneous adverse reactions. *J Am Acad Dermatol*. (2019) 80:608–16. doi: 10.1016/j.jaad.2018.10.039

87. Phillips GS, Wu J, Hellmann MD, Postow MA, Rizvi NA, Freites-Martinez A, et al. Treatment outcomes of immune-related cutaneous adverse events. *J Clin Oncol*. (2019) 37:2746–58. doi: 10.1200/JCO.18.02141

88. Campochiaro C, Farina N, Tomelleri A, Ferrara R, Lazzari C, De Luca G, et al. Tocilizumab for the treatment of immune-related adverse events: a systematic literature review and a multicentre case series. *Eur J Intern Med*. (2021) 93:87–94. doi: 10.1016/j.ejim.2021.07.016

89. Hibler BP, Markova A. Treatment of severe cutaneous adverse reaction with tocilizumab. *Br J Dermatol*. (2020) 183:785–7. doi: 10.1111/bjd.19129

90. Pollack MH, Betof A, Dearden H, Rapazzo K, Valentine I, Brohl AS, et al. Safety of resuming anti-PD-1 in patients with immune-related adverse events (ir AEs) during combined anti-CTLA-4 and anti-PD1 in metastatic melanoma. *Ann Oncol*. (2018) 29:250–5. doi: 10.1093/annonc/mdx642

91. Ingen-Housz-Oro S, Milpied B, Bensaid B, Elshot Y, Bruggen MC, Starace M, et al. Drug reactions with eosinophilia and systemic symptoms induced by immune checkpoint inhibitors: an international cohort of 13 cases. *Melanoma Res*. (2023) 33:155–8. doi: 10.1097/CMR.0000000000000877

92. Kim D, Kobayashi T, Voisin B, Jo JH, Sakamoto K, Jin SP, et al. Targeted therapy guided by single-cell transcriptomic analysis in drug-induced hypersensitivity syndrome: a case report. *Nat Med*. (2020) 26:236–43. doi: 10.1038/s41591-019-0733-7

93. Deshpande P, Li Y, Thorne M, Palubinsky AM, Phillips EJ, Gibson A. Practical implementation of genetics: new concepts in immunogenomics to predict, prevent, and diagnose drug hypersensitivity. *J Allergy Clin Immunol Pract*. (2022) 10:1689–700. doi: 10.1016/j.jaip.2022.04.027

94. Hertzman RJ, Deshpande P, Leary S, Li Y, Ram R, Chopra A, et al. Visual genomics analysis studio as a tool to analyze multiomic data. *Front Genet*. (2021) 12:642012. doi: 10.3389/fgene.2021.642012

95. Zhang C, Zhu Z, Gao J, Yang L, Dang E, Fang H, et al. Plasma exosomal mi R-375-3p regulates mitochondria-dependent keratinocyte apoptosis by targeting XIAP in severe drug-induced skin reactions. *Sci Transl Med*. (2020) 12:eaaw6142. doi: 10.1126/scitranslmed.aaw6142

96. Saito N, Qiao H, Yanagi T, Shinkuma S, Nishimura K, Suto A, et al. An annexin A1-FPR1 interaction contributes to necroptosis of keratinocytes in severe cutaneous adverse drug reactions. *Sci Transl Med*. (2014) 6:245ra95. doi: 10.1126/scitranslmed.3008227

97. Shi FL, Yuan LS, Wong TS, Li Q, Li YP, Xu R, et al. Dimethyl fumarate inhibits necroptosis and alleviates systemic inflammatory response syndrome by blocking the RIPK1-RIPK3-MLKL axis. *Pharmacol Res*. (2023) 189:106697. doi: 10.1016/j.phrs.2023.106697

98. Kaczmarek A, Vandenabeele P, Krysko DV. Necroptosis: the release of damage-associated molecular patterns and its physiological relevance. *Immunity*. (2013) 38:209–23. doi: 10.1016/j.immuni.2013.02.003

99. Kinoshita M, Ogawa Y, Hama N, Ujiie I, Hasegawa A, Nakajima S, et al. Neutrophils initiate and exacerbate Stevens-Johnson syndrome and toxic epidermal necrolysis. *Sci Transl Med*. (2021) 13:eaax2398. doi: 10.1126/scitranslmed.aax2398

100. Venugopal R, Sharma N, Sen S, Mohanty S, Kashyap S, Agarwal T, et al. Prognostic significance of matrix metalloproteinase 9 in COMET operated chronic

ocular Stevens-Johnson syndrome. *Br J Ophthalmol*. (2023) 107:187–94. doi: 10.1136/bjophthalmol-2021-319302

101. Olsson-Brown A, Yip V, Ogiji ED, Jolly C, Ressel L, Sharma A, et al. TNF-alpha–mediated keratinocyte expression and release of matrix metalloproteinase 9: putative mechanism of pathogenesis in Stevens–Johnson syndrome/toxic epidermal necrolysis. *J Invest Dermatol*. (2022) 143:1023–1030.e7. doi: 10.1016/j.jid.2022.11.024

102. Kula T, Dezfulian MH, Wang CI, Abdelfattah NS, Hartman ZC, Wucherpfennig KW, et al. T-scan: a genome-wide method for the systematic discovery of T cell epitopes. *Cells*. (2019) 178:1016–1028.e13. doi: 10.1016/j.cell.2019.07.009

103. Burmeister DM, Smith SL, Muthumalaiappan K, Hill DM, Moffatt LT, Carlson DL, et al. An assessment of research priorities to dampen the pendulum swing of burn resuscitation. *J Burn Care Res*. (2021) 42:113–25. doi: 10.1093/jbcr/iraa214

104. Ro HS, Shin JY, Sabbagh MD, Roh SG, Chang SC, Lee NH. Effectiveness of aspiration or deroofing for blister management in patients with burns: a prospective randomized controlled trial. *Medicine*. (2018) 97:e0563. doi: 10.1097/MD.0000000000010563

105. Swain AH, Azadian BS, Wakeley CJ, Shakespeare PG. Management of blisters in minor burns. *Br Med J*. (1987) 295:181.

106. Bradley T, Brown RE, Kucan JO, Smoot EC 3rd, Hussmann J. Toxic epidermal necrolysis: a review and report of the successful use of biobrane for early wound coverage. *Ann Plast Surg*. (1995) 35:124–32. doi: 10.1097/00000637-199508000-00002

107. Marvin JA, Heimbach DM, Engrav LH, Harnar TJ. Improved treatment of the Stevens-Johnson syndrome. *Arch Surg*. (1984) 119:601–5. doi: 10.1001/archsurg.1984.01390170097019

108. Young JB, Gondek SP, Troche M, Summitt JB, Rae L, Thayer WP, et al. The use of porcine xenografts in patients with toxic epidermal necrolysis. *Burns*. (2016) 42:1728–33. doi: 10.1016/j.burns.2016.06.003

109. Graves C, Faraklas I, Maniatis K, Panter E, La Force J, Aleem R, et al. Nutrition in toxic epidermal necrolysis: a multicenter review. *Nutr Clin Pract*. (2016) 31:836–40. doi: 10.1177/0884533616642746

110. Knuth CM, Auger C, Jeschke MG. Burn-induced hypermetabolism and skeletal muscle dysfunction. *Am J Physiol Cell Physiol*. (2021) 321:C58–71. doi: 10.1152/ajpcell.00106.2021

111. Gus EI, Shahrokhi S, Jeschke MG. Anabolic and anticatabolic agents used in burn care: what is known and what is yet to be learned. *Burns*. (2020) 46:19–32. doi: 10.1016/j.burns.2018.03.009

112. Hoffman M, Chansky PB, Bashyam AR, Boettler MA, Challa N, Dominguez A, et al. Long-term physical and psychological outcomes of Stevens-Johnson syndrome/toxic epidermal necrolysis. *JAMA Dermatol*. (2021) 157:712–5. doi: 10.1001/jamadermatol.2021.1136

113. Yoshikawa Y, Ueta M, Fukuoka H, Inatomi T, Yokota I, Teramukai S, et al. Long-term progression of ocular surface disease in Stevens-Johnson syndrome and toxic epidermal necrolysis. *Cornea*. (2020) 39:745–53. doi: 10.1097/ICO.0000000000002263

114. Gregory DG. Treatment of acute Stevens-Johnson syndrome and toxic epidermal necrolysis using amniotic membrane: a review of 10 consecutive cases. *Ophthalmology*. (2011) 118:908–14. doi: 10.1016/j.ophtha.2011.01.046

115. Hsu M, Jayaram A, Verner R, Lin A, Bouchard C. Indications and outcomes of amniotic membrane transplantation in the management of acute Stevens-Johnson syndrome and toxic epidermal necrolysis: a case-control study. *Cornea*. (2012) 31:1394–402. doi: 10.1097/ICO.0b013e31823d02a8

116. Shanbhag SS, Chodosh J, Saeed HN. Sutureless amniotic membrane transplantation with cyanoacrylate glue for acute Stevens-Johnson syndrome/toxic epidermal necrolysis. *Ocul Surf*. (2019) 17:560–4. doi: 10.1016/j.jtos.2019.03.001

117. Shanbhag SS, Hall L, Chodosh J, Saeed HN. Long-term outcomes of amniotic membrane treatment in acute Stevens-Johnson syndrome/toxic epidermal necrolysis. *Ocul Surf*. (2020) 18:517–22. doi: 10.1016/j.jtos.2020.03.004

118. Shanbhag SS, Rashad R, Chodosh J, Saeed HN. Long-term effect of a treatment protocol for acute ocular involvement in Stevens-Johnson syndrome/toxic epidermal necrolysis. *Am J Ophthalmol*. (2019) 208:331–41. doi: 10.1016/j.ajo.2019.07.006

119. Mieno H, Ueta M, Kinoshita F, Teramukai S, Kinoshita S, Sotozono C. Corticosteroid pulse therapy for Stevens-Johnson syndrome and toxic epidermal necrolysis patients with acute ocular involvement. *Am J Ophthalmol*. (2021) 231:194–9. doi: 10.1016/j.ajo.2021.06.015

120. Hall LN, Shanbhag SS, Rashad R, Chodosh J, Saeed HN. The effects of systemic cyclosporine in acute Stevens-Johnson syndrome/toxic epidermal necrolysis on ocular disease. *Ocul Surf*. (2021) 19:128–32. doi: 10.1016/j.jtos.2020.05.003

121. Ma DH, Tsai TY, Pan LY, Chen SY, Hsiao CH, Yeh LK, et al. Clinical aspects of Stevens-Johnson syndrome/toxic epidermal necrolysis with severe ocular complications in Taiwan. *Front Med*. (2021) 8:661891. doi: 10.3389/fmed.2021.800685

122. Wang Y, Rao R, Jacobs DS, Saeed HN. Prosthetic replacement of the ocular surface ecosystem treatment for ocular surface disease in pediatric patients with Stevens-Johnson syndrome. *Am J Ophthalmol*. (2019) 201:1–8. doi: 10.1016/j.ajo.2019.01.006

123. Itoi M, Ueta M, Ogino K, Sumi E, Imai K, Teramukai S, et al. Clinical trial to evaluate the therapeutic benefits of limbal-supported contact lens wear for ocular sequelae due to Stevens-Johnson syndrome/toxic epidermal necrolysis. *Cont Lens Anterior Eye*. (2020) 43:535–42. doi: 10.1016/j.clae.2020.05.007

124. Toth G, Lukacs A, Schirra F, Sandor GL, Killik P, Maneschg OA, et al. Ophthalmic aspects of Stevens-Johnson syndrome and toxic epidermal necrolysis: a narrative review. *Ophthalmol Ther*. (2023) 12:1795–811. doi: 10.1007/s40123-023-00725-w

125. Gulanikar A, Abrol A, Sagar S. Study of genital manifestations of Stevens Johnson syndrome/toxic epidermal necrolysis. *Indian J Sex Transm Dis AIDS*. (2022) 43:39–42. doi: 10.4103/ijstd.IJSTD_61_19

126. Den Adel MA, Hendrickson SE, Fuchs E. Stevens Johnson syndrome: past, present, and future directions gynecologic manifestations and management in SJS/TEN. *Front Med*. (2022) 9:874445. doi: 10.3389/fmed.2022.874445

127. Olteanu C, Shear NH, Chew HF, Hashimoto R, Alhusayen R, Whyte-Croasdaile S, et al. Severe physical complications among survivors of Stevens-Johnson syndrome and toxic epidermal necrolysis. *Drug Saf*. (2018) 41:277–84. doi: 10.1007/s40264-017-0608-0

128. Oplatek A, Brown K, Sen S, Halerz M, Supple K, Gamelli RL. Long-term follow-up of patients treated for toxic epidermal necrolysis. *J Burn Care Res*. (2006) 27:26–33. doi: 10.1097/01.bcr.0000194268.01514.f8

129. Sotozono C, Ueta M, Yokoi N. Severe dry eye with combined mechanisms is involved in the ocular sequelae of SJS/TEN at the chronic stage. *Invest Ophthalmol Vis Sci*. (2018) 59:DES80–6. doi: 10.1167/iovs.18-24019

130. Lehloenya RJ, Esmail F, Christians SJ, Motsepe D, Todd G. Toxic epidermal necrolysis with failure of re-epithelialization. Could umbilical cord mesenchymal stem cell transplantation have a role? *J Eur Acad Dermatol Venereol*. (2013) 27:923–5. doi: 10.1111/j.1468-3083.2012.04667.x

131. Habre M, Ortonne N, Colin A, Meningaud JP, Chosidow O, Wolkenstein P, et al. Facial scars following toxic epidermal necrolysis: role of adnexal involvement? *Dermatology*. (2016) 232:220–3. doi: 10.1159/000443164

frontiers | Frontiers in Pharmacology

TYPE Case Report
PUBLISHED 14 November 2023
DOI 10.3389/fphar.2023.1131703



OPEN ACCESS

EDITED BY
Mounir Tilaoui,
Waterford Institute of Technology, Ireland

REVIEWED BY
Siu Fun Wong,
Chapman University, United States
Silvia Mendez-Flores,
Instituto Nacional de Ciencia y Nutrición "Salvador Zubirán", Mexico

*CORRESPONDENCE
Hao Tang,
tanghao_0921@126.com

†These authors have contributed equally to this work

RECEIVED 26 December 2022
ACCEPTED 25 October 2023
PUBLISHED 14 November 2023

CITATION
Chen Y, Hong H, Bao S and Tang H (2023), Stevens–Johnson syndrome induced by toripalimab in a previously EGFR-TKI-treated advanced lung adenocarcinoma patient harboring *EGFR* mutations 19 del/T790M/C797S in *trans* and *cis*: a case report.
*Front. Pharmacol.* 14:1131703.
doi: 10.3389/fphar.2023.1131703



# Stevens–Johnson syndrome induced by toripalimab in a previously EGFR-TKI-treated advanced lung adenocarcinoma patient harboring *EGFR* mutations 19 del/T790M/C797S in *trans* and *cis*: a case report

Yang Chen†, Hanhan Hong†, Shujun Bao† and Hao Tang*

Department of Respiratory and Critical Care Medicine, Changzheng Hospital, Naval Medical University, Shanghai, China

**Background:** The treatment paradigm for advanced non-small-cell lung cancer (NSCLC) is rapidly changing. Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) and anti-programmed death-1 (PD-1) antibodies have increasingly been incorporated into routine care for nearly all patients with NSCLC. Toripalimab was recently approved as the first-line treatment for advanced non-squamous NSCLC in combination with chemotherapy. Stevens–Johnson syndrome (SJS) is a rare but potentially fatal complication of TKI and anti-PD-1 therapy. We reported a case of SJS after sequential use of EGFR-TKIs and toripalimab in an NSCLC patient with *EGFR* mutations 19 del/T790M/C797S in *trans* and *cis*.

**Case presentation:** A 58-year-old man with stage IV NSCLC received gefitinib because next-generation sequencing (NGS) revealed an *EGFR* 19del, followed by osimertinib and pemetrexed with the emergence of *EGFR* T790M. Four *EGFR* mutations 19 del/T790M/C797S in *trans* and *cis* were detected after osimertinib resistance. The combination of toripalimab and docetaxel was administered as a third-line treatment. The patient developed SJS at 21 days, and toripalimab was discontinued. After treatment with methylprednisolone and prednisolone, the skin toxicity of the patient gradually decreased and eventually disappeared. The patient received osimertinib and anlotinib after recovery, and SJS has not recurred. The ongoing treatment is still effective and results in stable disease.

**Conclusion:** We reported the first case of SJS induced by toripalimab in a patient with lung adenocarcinoma harboring multiple *EGFR* mutations. The TKI treatment after SJS was well tolerated and effective.

KEYWORDS

**Stevens–Johnson syndrome, adverse reaction, toripalimab, non-small-cell lung cancer, EGFR tyrosine kinase inhibitor**

## Introduction

Lung adenocarcinoma is one of the most common types of non-small-cell lung cancer (NSCLC). The treatment paradigm for advanced NSCLC is rapidly changing. Epidermal growth factor receptor (EGFR) is the most common driver genes of lung cancer, and EGFR tyrosine kinase inhibitors (TKIs), such as gefitinib, osimertinib, and anlotinib, dramatically improve the clinical outcomes of *EGFR* mutant lung cancers (Han et al., 2018; Soria et al., 2018; Hosomi et al., 2020). At the same time, immune checkpoint inhibitors (ICIs), such as anti-programmed death-ligand-1 (PD-(L)1) monoclonal antibodies, have increasingly been incorporated into routine care for nearly all patients with NSCLC. Pembrolizumab was approved as the front-line therapy with or without chemotherapy in patients with metastatic NSCLC (Reck et al., 2016). Nivolumab plus ipilimumab was approved as a first-line treatment for NSCLC patients by the Food and Drug Administration (Hellmann et al., 2019). Toripalimab, an anti-PD-1 antibody, significantly improved both progression-free survival (PFS) and overall survival (OS) with chemotherapy in patients with advanced NSCLC with a manageable safety profile (Wang et al., 2023).

However, cutaneous eruptions are one of the most common immune-related adverse events, including lichenoid reactions, eczema, and vitiligo (Hwang et al., 2016), most of which are mild. Stevens–Johnson syndrome (SJS) is a rare but life-threatening cutaneous adverse reaction, mainly elicited by exposure to certain drugs including EGFR-TKIs and ICIs (Chen et al., 2018). There is growing concern that the combination of PD-(L)1 and EGFR-TKIs may be associated with an increased risk of toxicity. It is reported that PD-(L)1 blockade followed by osimertinib is associated with severe immune-related adverse events (Schoenfeld et al., 2019). There were no reports of SJS in a patient treated with toripalimab and EGFR-TKIs. Here, we reported the first case of SJS induced by toripalimab in a previously EGFR-TKI-treated advanced lung adenocarcinoma patient harboring multiple *EGFR* mutations.

## Case presentation

A 58-year-old male non-smoker presented to our hospital complaining of persistent pain in the lower back in January 2019. He had no existing physical health issues and no special underlying diseases. The family medical history was unremarkable. The enhanced computerized tomography (CT) scan of the chest and lumbar spine revealed multiple nodules in both the lungs and spinal lesions (Figure 1A). A CT-guided percutaneous needle biopsy was performed. The pathological examination showed lung adenocarcinoma. Together, these results suggested the clinical stage was classified as cT4N3M1, stage IV (TNM classification seventh edition). The patient performance status (PS) was 1. Next-generation sequencing (NGS) identified *EGFR* exon 19 deletion (19 del) with a mutant allele frequency (MAF) of 60.2%. The patient was begun on gefitinib 250 mg once daily in March 2019. Partial response (PR) was achieved with 3 months'

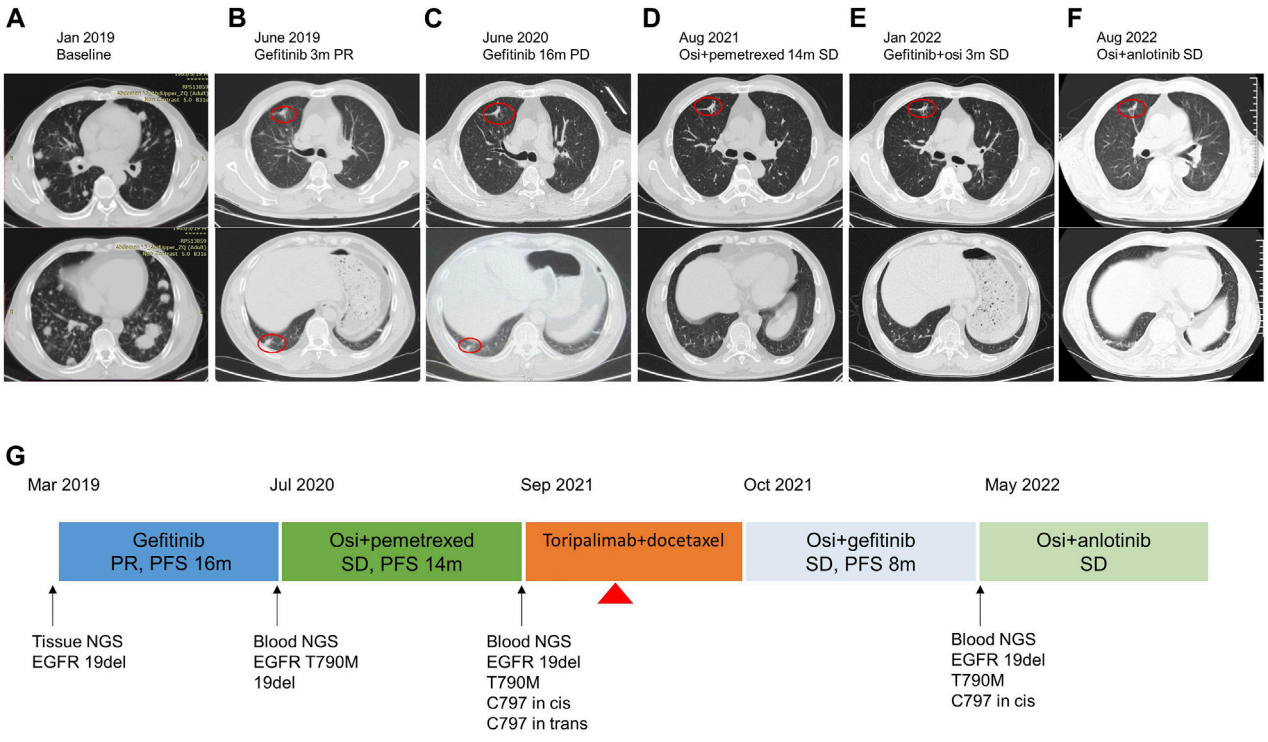


FIGURE 1
Treatment timeline of the patient. **(A–F)** The chest CT images at each time point. The red circle indicated the tumor lesion. **(G)** Flow diagram of the clinical course of the patient. Osi, osimertinib; PR, partial response; PD, progressive disease; SD, stable disease; PFS, progression-free survival. The red triangle indicates the SJS onset on day 12 since treatment with toripalimab plus docetaxel.

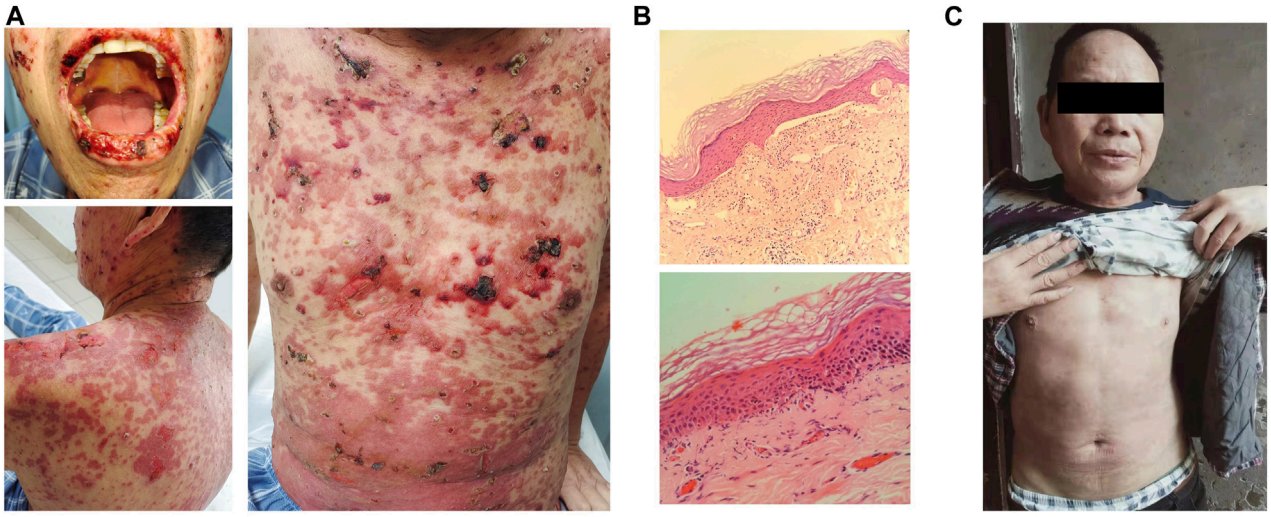


FIGURE 2
Diagnosis and treatment of Stevens–Johnson syndrome. **(A)** Erosions were seen on the mouth, face, and body trunk after 24 days of toripalimab treatment. **(B)** Hematoxylin and eosin staining of skin biopsy. Original magnifications, the upper panel × 40 and the lower panel × 100. **(C)** Reduction in diffuse erythema at 6 weeks of steroid therapy.

treatment based on the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (Figure 1B), and the PFS was 16 m. New lesions were seen in the left lower lobe (Figure 1C), and gefitinib was discontinued. Blood-based NGS detected *EGFR* T790M (MAF 3.4%) and the retention of *EGFR* 19 del (MAF 5.99%). Osimertinib (oral) and pemetrexed (0.9 g, iv, q3w) were administered in July 2020, and stable disease (SD) was achieved with a PFS of 14 m. The patient complained of pain in the lower back accompanied by numbness in the lower leg in August 2021. The spine magnetic resonance imaging (MRI) revealed more spinal lesions, and the chest CT scan showed the lung nodules were stable (Figure 1D).

NGS targeting eight core lung cancer driver genes (Lung Cure, Burning Rock Biotech, Guangzhou, China) was performed on blood samples. *EGFR* mutations 19 del/T790M/C797S in *trans* and *cis* were detected, with MAF of 1.7%, 0.44%, 0.16%, and 0.14%, respectively. In a phase-II trial, toripalimab plus chemotherapy showed promising anti-tumor activity as the second-line setting in patients with *EGFR*-mutant NSCLC (Jiang et al., 2021). In September 2021, the patient received toripalimab 240 mg and docetaxel 120 mg as the third-line therapy.

The patient began to develop oral ulcers and scattered rash on the 12th day since treatment with toripalimab plus docetaxel, and the rash gradually worsened. He had not received treatment for the skin reactions before visiting our hospital on day 24. He presented with multiple macules and vesicles, and detachment of the epidermis on the mucous membranes of the mouth, face, and body trunk (Figure 2A). He had no fever, and the PS was 1. Routine blood examinations were normal. Bacterial cultures from blood, urine, and sputum revealed no evidence of bacterial infection. Skin biopsy showed a sub-epidermal cell poor blister and perivascular infiltrate of lymphocytes (Figure 2B). Throughout the course of the disease, there were no other organ function abnormalities. He had normal levels of alanine aminotransferase, aspartate aminotransferase, creatinine, urea nitrogen, cardiac enzymes, or brain natriuretic peptide. The patient was diagnosed as SJS with a severity-of-illness score for toxic epidermal necrolysis (SCORTEN) as 4 (Supplementary Table S1). In terms of pharmacogenetic assessments, we performed human leukocyte antigen (HLA) typing using NGS, which revealed HLA-A*24:02, HLA-A*11:01, HLA-B*40:01, HLA-B*15:01, HLA-C*04:01, and HLA-C*03:04.

Toripalimab and docetaxel were discontinued immediately. A dermatologist was consulted for the diagnosis of skin symptoms. The patient presented with diffuse erythema, and vesicles and ulcerations on extremities, the trunk, oral cavity, throat, nose, eyelids, and genitalia, which were accompanied by skin detachment and tissue necrosis. These manifestations were consistent with SJS. We also checked serum levels of several autoantibodies, including anti-BM antibody, anti-AD antibody, and anti-EC antibody, all of which were negative. Taking into account the clinical and pathological manifestations and the medication history, we arrived at the diagnosis of SJS. The patient was treated with 100 mg/day of methylprednisolone on 10 October 2021 for 1 week, followed by 90 mg/day of prednisolone for 3 weeks. Prednisolone was tapered off and eventually discontinued after 2 months. The patient recovered from SJS after steroid therapy (Figure 2C). During this period, the patient took medicine at home, and the local broken surface was disinfected with iodine and covered with dry gauze to keep the wound dry. He did not experience any concurrent infection.

Afterward, the patient received spine stereotactic body radiotherapy (SBRT) to treat spinal metastases. The combination of gefitinib and osimertinib was administered between October 2021 and May 2022, and SD was achieved with a PFS of 8 m (Figure 1E). A follow-up CT scan revealed stable lung nodules but more spinal lesions, which led to pathological bone fracture and paraplegia. NGS targeting 520 cancer-related genes (OncoScreen Plus, Burning Rock Biotech, Guangzhou, China) was performed on blood samples in May 2022 and revealed

mutations of *EGFR* 19 del/T790M/C797S in *cis*, with MAF of 18.9%, 3.53%, and 3.06%. The patient received osimertinib 80 mg and anlotinib 12 mg in May 2022. A CT scan showed the shrinkage of the lung tumors (Figure 1F) and stable lesions of the spine after 2 months. The patient declined the surgery for spinal metastasis because of financial concerns. He is still treated with osimertinib and anlotinib, and SJS has not recurred. The clinical course is shown in Figure 1G.

## Discussion

Therapeutic anti-PD-1/PD-L1 monoclonal antibodies, such as toripalimab, are important in treatments for patients with advanced NSCLC (Wang et al., 2023). We found that the sequential use of toripalimab and osimertinib was associated with SJS. Importantly, the toxicity appeared associated with toripalimab, given the fact that SJS has not recurred after osimertinib was rechallenged. The patient recovered after steroid treatment and benefited from the EGFR-TKI treatment that was followed. His OS was more than 44 months at the time of preparation the manuscript.

Skin reaction is one of the common adverse reactions of immune checkpoint inhibitors, and once it occurs, it needs to be discontinued permanently. However, with prednisone pre-treatment before using docetaxel, the probability of severe skin adverse reactions is very low, and delayed skin reaction after 1 week of drug use is rare. Based on previous clinical experience and other case reports, it is considered that the patient's SJS is an adverse reaction to immune checkpoint inhibitors rather than to docetaxel. The incidence of SJS was low, but the lethality was extremely high. Although uncommon, SJS related to anti-PD1 in NSCLC has also been reported, such as pembrolizumab (Saw et al., 2017), atezolizumab (Chirasuthat and Chayavichitsilp, 2018), and ipilimumab (Dika et al., 2017). It has been reported that tumor tissues in NSCLC and skin shared similar antigens; thus, in patients treated with PD-1/PD-L1 antibodies, activated T cells may attack skin tissues as well, causing skin-related immune-related adverse events (irAEs) (Berner et al., 2019). The underlying mechanism of Stevens–Johnson syndrome/toxic epidermal necrolysis (TEN) associated with PD-1/PD-L1 and other drugs may be different. It is hypothesized that small-molecule drugs may bind to proteins in the serum, forming a complex that is recognized by certain HLA molecules and presented to T cells to generate an immune response (Frantz et al., 2021). However, in patients treated with PD-1/PD-L1 antibodies, the immune response is enhanced by the blockade of PD-1 and PD-L1 interaction instead of directly presenting PD-1/PD-L1 antibodies to T cells.

SJS could occur from 1 week to 5 months after the initiation of ICIs, which was usually 1–2 cycles of treatment (Chen et al., 2018). In our case, SJS started to manifest on day 12 since the start of toripalimab plus docetaxel administration. NGS detected HLA-A*24:02, HLA-A*11:01, HLA-B*40:01, HLA-B*15:01, HLA-C*04:01, and HLA-C*03:04 in this case. Because associations between SJS/TEN and certain human leukocyte antigen (HLA) variants have been identified, molecular diagnosis can help to confirm the diagnosis of SJS/TEN. A meta-analysis of Chinese, Korean, and Thai populations found HLA-A*24:02 associated with the susceptibility to SJS/TEN or mild maculopapular eruptions as lamotrigine-induced cutaneous adverse drug reactions (Deng et al., 2018). A study in the Japanese population also identified significant associations between HLA-A*24:02:01 and susceptibility to cold medicine-related SJS/TEN with severe ocular complications (Nakatani et al., 2019). It is possible that the HLA-A*24:02 allele in our patient conferred susceptibility to SJS upon treatment with toripalimab combined with docetaxel.

Toripalimab is a humanized monoclonal antibody and the first domestically approved anti-PD-1 monoclonal antibody in China. The pharmacokinetic (PK) characteristics of toripalimab within the dose range of 1–10 mg/kg showed that Cmax exhibited generally linear PK characteristics, and the increase in area under the curve was slightly greater than the increase in the dosage. The mean clearance rate of toripalimab was 0.18 mL/h/kg (co-efficient of variation%: 37%), and the geometric mean elimination half-life (t1/2) was 12.6 days (co-efficient of variation %: 29%). Toripalimab was degraded through non-specific pathways, and its metabolism was independent of clearance. As monoclonal antibodies are not metabolized by cytochrome P450 enzymes or other drug-metabolizing enzymes, the inhibition or induction of these enzymes by concomitant drugs is not expected to affect the PK of toripalimab. Docetaxel is a taxane that can form a stable, non-functional microtubule bundle by strengthening microtubule polymerization and inhibiting microtubule depolymerization, thereby breaking down tumor cell mitosis to achieve an antitumor effect. Clinical pharmacologic studies have confirmed that docetaxel's antitumor activity is stronger than that of paclitaxel, and there is no cross-resistance with paclitaxel. It is used for the treatment of advanced or metastatic NSCLC after first-line chemotherapy failure. Chemotherapy in combination with immunotherapy has become one of the standard treatment regimens for lung cancer. Many phase III clinical studies of immunotherapy checkpoint inhibitors in the field of lung cancer have adopted paclitaxel in combination with platinum as the basis of chemotherapy regimen. Therefore, there are high-level safety data and evidence-based medical evidence for the combination of docetaxel and PD-1 inhibitors. Considering the patient's economic burden, the relatively low-priced toripalimab was selected as the second-line treatment among the available immunotherapy checkpoint inhibitors.

Management principles of SJS include urgent inpatient evaluation/specialist support, prognostication with tools such as SCORTEN, withdrawal of culprit drug, and supportive care (Saw et al., 2017). The ideal management of severe anti-PD-1-related skin toxicities needs to be clarified. Intravenous prednisone/methylprednisolone 1–2 mg/kg/day and intravenous immunoglobulin are necessary.

The concomitant *EGFR* T790M/C797S in *trans* and *cis* is rare, with a poor prognosis (Liu et al., 2019). Previous studies showed that patients harboring EGFR C797S in *trans* with T790M are sensitive to a combination of first- and third-generation EGFR TKIs (Wang et al., 2017). However, patients harboring *EGFR* C797S in *cis* with T790M are resistant to combination therapy or every single reagent. In our case, the patient was sensitive to the combination of gefitinib and osimertinib, and the PFS was 8 m, indicating that gefitinib plus osimertinib might be an effective therapy for patients with *EGFR* T790M/C797S in *trans* and *cis*.

In the present case report, we provided timely treatment and discontinued the use of toripalimab when the diagnosis of SJS was made. However, we cannot fully exclude the possibility that SJS was caused by the administration of docetaxel. In the future, clinical usage of PD-1/PD-L1 antibodies in NSCLC patients harboring

EGFR mutations needs to be cautious, and close attention should be paid to identify potential severe adverse events.

## Conclusion

We reported the first case of SJS induced by toripalimab in a patient with lung adenocarcinoma harboring multiple *EGFR* mutations, and the TKI treatment after SJS was well tolerated and effective. Our case report gave additional cautions to observe possible life-threatening cutaneous reactions to toripalimab therapy in NSCLC patients with *EGFR* mutations.

## Data availability statement

The original contributions presented in the study are included in the article; further inquiries can be directed to the corresponding author.

## Ethics statement

The study was approved by The Ethics Committee of Changzheng Hospital, Naval Medical University. The study was conducted in accordance with the local legislation and institutional requirements. The participant provided his written informed consent to participate in this study. Written informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in this article.

## Author contributions

All authors participated in study conceptualization, data collection and analysis, and manuscript draft and revision. HT provided project supervision. All authors contributed to the article and approved the submitted version.

## Funding

This work was supported by grants from the General Program of the National Nature Science Foundation of China (No. 82070036).

## Acknowledgments

The authors thank the patient for agreeing to publish this report and thank Mr. Mingjun Zhu, and Drs. Chunxiao Pan and Xiao Zou from Burning Rock Biotech for their help in sequencing. The authors also thank Shanghai Municipal Hospital Respiratory and Critical Care Medicine Specialist Alliance.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors, and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2023.1131703/full#supplementary-material

## References

Berner, F., Bomze, D., Diem, S., Ali, O. H., Fassler, M., Ring, S., et al. (2019). Association of checkpoint inhibitor-induced toxic effects with shared cancer and tissue antigens in non-small cell lung cancer. *JAMA Oncol.* 5, 1043–1047. doi:10.1001/jamaoncol.2019.0402

Chen, C. B., Wu, M. Y., Ng, C. Y., Lu, C. W., Wu, J., Kao, P. H., et al. (2018). Severe cutaneous adverse reactions induced by targeted anticancer therapies and immunotherapies. *Cancer Manag. Res.* 10, 1259–1273. doi:10.2147/CMAR.S163391

Chirasuthat, P., and Chayavichitsilp, P. (2018). Atezolizumab-induced stevens-johnson syndrome in a patient with non-small cell lung carcinoma. *Case Rep. Dermatol* 10, 198–202. doi:10.1159/000492172

Deng, Y., Li, S., Zhang, L., Jin, H., and Zou, X. (2018). Association between HLA alleles and lamotrigine-induced cutaneous adverse drug reactions in Asian populations: a meta-analysis. *Seizure* 60, 163–171. doi:10.1016/j.seizure.2018.06.024

Dika, E., Ravaioli, G. M., Fanti, P. A., Piraccini, B. M., Lambertini, M., Chessa, M. A., et al. (2017). Cutaneous adverse effects during ipilimumab treatment for metastatic melanoma: a prospective study. *Eur. J. Dermatol* 27, 266–270. doi:10.1684/ejd.2017.3023

Frantz, R., Huang, S., Are, A., and Motaparthi, K. (2021). Stevens-johnson syndrome and toxic epidermal necrolysis: a review of diagnosis and management. *Med. Kaunas.* 57, 895. doi:10.3390/medicina57090895

Han, B., Li, K., Wang, Q., Zhang, L., Shi, J., Wang, Z., et al. (2018). Effect of anlotinib as a third-line or further treatment on overall survival of patients with advanced non-small cell lung cancer: the ALTER 0303 phase 3 randomized clinical trial. *JAMA Oncol.* 4, 1569–1575. doi:10.1001/jamaoncol.2018.3039

Hellmann, M. D., Paz-Ares, L., Bernabe Caro, R., Zurawski, B., Kim, S. W., Carcereny Costa, E., et al. (2019). Nivolumab plus ipilimumab in advanced non-small-cell lung cancer. *N. Engl. J. Med.* 381, 2020–2031. doi:10.1056/NEJMoa1910231

Hosomi, Y., Morita, S., Sugawara, S., Kato, T., Fukuhara, T., Gemma, A., et al. (2020). Gefitinib alone versus gefitinib plus chemotherapy for non-small-cell lung cancer with mutated epidermal growth factor receptor: NEJ009 study. *J. Clin. Oncol.* 38, 115–123. doi:10.1200/JCO.19.01488

Hwang, S. J., Carlos, G., Wakade, D., Byth, K., Kong, B. Y., Chou, S., et al. (2016). Cutaneous adverse events (AEs) of anti-programmed cell death (PD)-1 therapy in patients with metastatic melanoma: a single-institution cohort. *J. Am. Acad. Dermatol* 74, 455–461. doi:10.1016/j.jaad.2015.10.029

Jiang, T., Wang, P., Zhang, J., Zhao, Y., Zhou, J., Fan, Y., et al. (2021). Toripalimab plus chemotherapy as second-line treatment in previously EGFR-TKI treated patients with EGFR-mutant-advanced NSCLC: a multicenter phase-II trial. *Signal Transduct. Target Ther.* 6, 355. doi:10.1038/s41392-021-00751-9

Liu, C., Li, J., Liu, H., Du, R., Fang, N., Zhang, J., et al. (2019). The concomitant EGFR T790M/C797S in trans and cis in three osimertinib-resistant lung adenocarcinoma patients. *J. Clin. Oncol.* 37, e20105. doi:10.1200/jco.2019.37.15_suppl.e20105

Nakatani, K., Ueta, M., Khor, S.-S., Hitomi, Y., Okudaira, Y., Masuya, A., et al. (2019). Identification of HLA-A*02:06:01 as the primary disease susceptibility HLA allele in cold

medicine-related Stevens-Johnson syndrome with severe ocular complications by high-resolution NGS-based HLA typing. *Sci. Rep.* 9, 16240. doi:10.1038/s41598-019-52619-2

Reck, M., Rodríguez-Abreu, D., Robinson, A. G., Hui, R., Csőszi, T., Fülöp, A., et al. (2016). Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N. Engl. J. Med.* 375, 1823–1833. doi:10.1056/NEJMoa1606774

Saw, S., Lee, H. Y., and Ng, Q. S. (2017). Pembrolizumab-induced Stevens-Johnson syndrome in non-melanoma patients. *Eur. J. Cancer* 81, 237–239. doi:10.1016/j.ejca.2017.03.026

Schoenfeld, A. J., Arbour, K. C., Rizvi, H., Iqbal, A. N., Gadgeel, S. M., Girshman, J., et al. (2019). Severe immune-related adverse events are common with sequential PD-(L)1 blockade and osimertinib. *Ann. Oncol.* 30, 839–844. doi:10.1093/annonc/mdz077

Soria, J. C., Ohe, Y., Vansteenkiste, J., Reungwetwattana, T., Chewaskulyong, B., Lee, K. H., et al. (2018). Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N. Engl. J. Med.* 378, 113–125. doi:10.1056/NEJMoa1713137

Wang, Z., Wu, L., Li, B., Cheng, Y., Li, X., Wang, X., et al. (2023). Toripalimab plus chemotherapy for patients with treatment-naive advanced non–small-cell lung cancer: a multicenter randomized phase III trial (CHOICE-01). *J. Clin. Oncol.* 41, 651–663. doi:10.1200/JCO.22.00727

Wang, Z., Yang, J. J., Huang, J., Ye, J. Y., Zhang, X. C., Tu, H. Y., et al. (2017). Lung adenocarcinoma harboring EGFR T790M and in trans C797S responds to combination therapy of first- and third-generation EGFR TKIs and shifts allelic configuration at resistance. *J. Thorac. Oncol.* 12, 1723–1727. doi:10.1016/j.jtho.2017.06.017

# Frontiers in Medicine

**Translating medical research and innovation into improved patient care**

A multidisciplinary journal which advances our medical knowledge. It supports the translation of scientific advances into new therapies and diagnostic tools that will improve patient care.

## Discover the latest Research Topics

See more →


**Frontiers**

Avenue du Tribunal-Fédéral 34
1005 Lausanne, Switzerland
frontiersin.org

**Contact us**

+41 (0)21 510 17 00
frontiersin.org/about/contact