Grand Rounds Review

Blistering Drug Eruptions: Diagnostic Challenges and Management in Clinical Practice: Unmasking the Cause: A Grand Rounds Review of Blistering Drug Eruption

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Blistering drug eruptions represent a spectrum of severe cutaneous adverse reactions characterized by epidermal and mucosal detachment, which present clinically as vesiculobullous lesions. These conditions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous fixed drug eruptions, and other blistering mimickers, are rare but potentially life-threatening. Prompt recognition and management are critical to improving outcomes. This Grand Rounds Review describes two clinical cases of patients presenting with a blistering eruption, guiding the reader through the diagnostic approach, including differential diagnosis and acute management. The differential diagnosis and evaluation of blistering drug eruptions are central, with a focus on distinguishing among drug-, infection-, and autoimmune-induced diseases. A structured, clinical-based approach to these complex reactions can significantly improve patient safety and long-term outcomes. **(J Allergy Clin Immunol Pract 2026;■:■-■)**

Key words: *Blistering drug eruption; Severe cutaneous adverse reactions; Stevens-Johnson syndrome; Toxic epidermal necrolysis*

INTRODUCTION

Blistering drug eruptions represent a spectrum of severe cutaneous adverse reactions (SCAR) characterized by the development of vesicles and bullae on the skin and mucous membranes. These reactions are rare but potentially life-threatening, necessitating prompt recognition and intervention. Among the most clinically significant forms are Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which are defined by the extent of epidermal detachment and mucosal involvement.[1-3] Stevens-Johnson syndrome involves less than 10% of the body surface area whereas TEN affects more than 30%, with 10% to 30% of the body surface area detached classified as SJS/TEN overlap.[2] Other potentially deadly drug-induced blistering eruptions, such as generalized bullous fixed eruption and linear IgA disease, will also be discussed. Medications or infections often trigger these conditions and can lead to serious complications, including sepsis, multiple-organ failure, and long-term sequelae such as ocular damage and scarring.[4,5] Early identification is critical, because timely withdrawal of the offending agent and initiation of supportive care can significantly improve outcomes.[6,7] Given the complexity and severity of blistering drug eruptions, multidisciplinary management is essential.[1,4] Collaboration among dermatology, ophthalmology, and critical care teams, as well as potentially other specialists, ensures a comprehensive evaluation and treatment.[4]

This Grand Rounds Review will describe two clinical cases presenting with blistering eruptions. These cases highlight the importance of understanding the clinical features and differential diagnosis of blistering drug eruptions to guide appropriate and timely management.

CASE A: CLASSIC CASE OF DRUG-INDUCED TEN

A 35-year-old woman living with HIV, who had defaulted from antiretroviral therapy, presented with extrapulmonary tuberculosis (TB) confirmed by abdominal ultrasound and Xpert *Mycobacterium tuberculosis* complex and rifampin resistance sputum positivity. She was given first-line anti-TB

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Conflicts of interest: A. Copaescu receives support from the Montreal General Hospital Foundation and the Research Institute of the McGill University Health Center (RI-MUHC). The rest of the authors declare that they have no relevant conflicts of interest.
Received for publication October 31, 2025; revised December 13, 2025; accepted for publication December 22, 2025.
Available online ■■
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2213-2198

https://doi.org/10.1016/j.jaip.2025.12.029

Abbreviations used
PV- Pemphigus vulgaris
SCAR- Severe cutaneous adverse reactions
SJS- Stevens-Johnson syndrome
SSSS- Staphylococcal scalded skin syndrome
TB- Tuberculosis
TEN- Toxic epidermal necrolysis
TMP/SMX- Trimethoprim/sulfamethoxazole

treatment (rifampicin, isoniazid, pyrazinamide, and ethambutol) and trimethoprim/sulfamethoxazole (TMP/SMX) as prophylaxis for pneumocystis because of the CD4 T-cell count of 61 cells/mm^3. Three-drug antiretroviral therapy (emtricitabine/tenofovir/efavirenz) was commenced 24 days after the patient started the TB treatment (Figure 1).

Five days later, she presented with a fever of 39.2°C, facial edema, and a rapidly progressive, painful, erythematous, diffuse, blistering rash. Examination revealed that 40% of the body surface area was involved, with dusky erythema and darker areas suspected to be epidermal necrosis, accompanied by a positive Nikolsky sign (Figure 1). Oral, nasal and genital mucosae were involved, whereas ophthalmology documented minimal ocular involvement. She was admitted to our specialized dermatology service and received supportive care, including investigation for active infections. Serologies for hepatitis B and C, as well as rapid plasma reagin test to detect syphilis and cryptococcal antigen test, were negative.

A skin biopsy performed 5 days after the onset of blistering demonstrated a subcorneal blister with numerous necrotic keratinocytes, parakeratosis, and spongiosis, as well as patchy basal vacuolar change, pigment incontinence, and colloid bodies. The skin histology was reported as consistent with TEN.

All potential offending agents were withdrawn 2 days after the rash appeared. Supportive care (including fluids, wound care, analgesia, and barrier protection) and high-potency topical corticosteroids were initiated. The algorithm of drug causality for epidermal necrolysis score was 6 for TMP/SMX (very likely).

We conducted *in vitro* IFN-γ enzyme-linked immunospot testing for first-line anti-TB drugs and TMP/SMX.[8-10] The assay showed a weak positive reaction to TMP/SMX. Because of the urgent need to resume life-saving anti-TB therapy in the context of advanced immunosuppression, a supervised sequential additive drug rechallenge was undertaken on day 15 after admission with intravenous methylprednisolone to abort positive rechallenge reactions, as described elsewhere.[11] In the context of possible hypersensitivity to TMP/SMX (as evidenced by a positive IFN-γ enzyme-linked immunospot result), rifampicin, isoniazid, pyrazinamide, and ethambutol were reintroduced together and were successfully tolerated. She was discharged on day 21 with good cutaneous reepithelization, resolved fever, and systemic parameters to complete the first-line anti-TB drug regimen. Subsequent HLA typing confirmed that she carried established class I HLA risk allele HLAB44:03 for TMP/SMX SJS/TEN.[12]

This presentation of TEN highlights the typical features and timing of SJS/TEN resulting from a common offending drug, TMP/SMX. However, this report also reflects the heterogeneity of the condition, as evidenced by minimal ocular involvement in this case despite extensive cutaneous necrolysis and multimucosal erosions. Notably, in deeply pigmented skin, early TEN may lack redness and can instead present with subtle violaceous or dusky hues, purpura-like macules, and tender indurated plaques before frank blistering or denudation.

CASE B: CLASSIC CASE OF VIRAL-INDUCED SJS/TEN

A previously healthy 5-year-old boy presented with an 11-day history of sore throat and fever before developing a widespread erythematous rash that became bullous within 24 hours. Subsequently, he developed 26% skin detachment, with marked oral mucosal ulceration and conjunctival injection (Figure 2). Histopathology confirmed full-thickness epidermal necrosis consistent with SJS/TEN, with negative direct immunofluorescence findings. Intravenous immunoglobulin (2.4 g/kg over 3 days) was commenced. Polymerase chain reaction testing of a nasopharyngeal aspirate identified adenovirus, implicating it as the probable trigger of SJS/TEN. The skin had re-epithelialized by day 26. Two weeks after discharge, the patient developed exertional dyspnea, and imaging demonstrated bronchiolitis obliterans. After 1 year of treatment with inhaled steroids and prophylactic antibiotics, significant recovery of pulmonary function was achieved.

DIFFERENTIAL DIAGNOSIS AND EVALUATION OF BLISTERING DRUG ERUPTIONS

Blistering skin rashes represent a heterogeneous group of disorders often with significant clinical overlap, ranging from benign self-limited to life-threatening.[4,13] Rapid recognition is essential because some conditions require urgent intervention. Clinical and histologic complexity, coupled with potential for high morbidity and mortality, necessitate a low threshold for dermatologic and potentially other specialist involvement early in presentation.

Complexity stems from several factors. First, the differential diagnosis for bullous eruptions is broad, encompassing not only drug-induced but also infectious, autoimmune, and paraneoplastic etiologies (Figure 3). Moreover, many individual diagnoses can have multiple etiologies. For example, SJS/TEN can be drug-induced, infection-induced, alloantigen-induced, or possibly autoimmune-induced, or potentially arise from a combination of these factors.[14] Second, many drugs can cause multiple types of reactions. For example, vancomycin can cause SJS/TEN, linear IgA bullous dermatosis, DRESS, and other conditions. Third, although common or distinctive features are often taught, presentation can vary, with considerable overlap, and evolve after the initial disease onset. This is further complicated by the proposed new diagnoses and classification schema (for example, reactive infectious mucocutaneous eruption vs *Mycoplasma pneumoniae*-induced rash and mucositis)[15] and terminology such as TEN-like, which have not yet reached full consensus. Consequently, arriving at the correct diagnosis and management plan requires a systematic approach, including a thorough physical examination, a comprehensive history and review of systems, and, when available, pathology with or without additional testing, along with a low threshold for specialist input.

Clinical findings are described below and are presented in Figure 3. For visual reference, VisualDx.com (Dr Art Papier and Lowell Goldsmith, Rochester, NY; subscription required) provides an excellent, vetted resource with images and relevant information. DermNet (https://dermnetnz.org/; DermNet NZ,

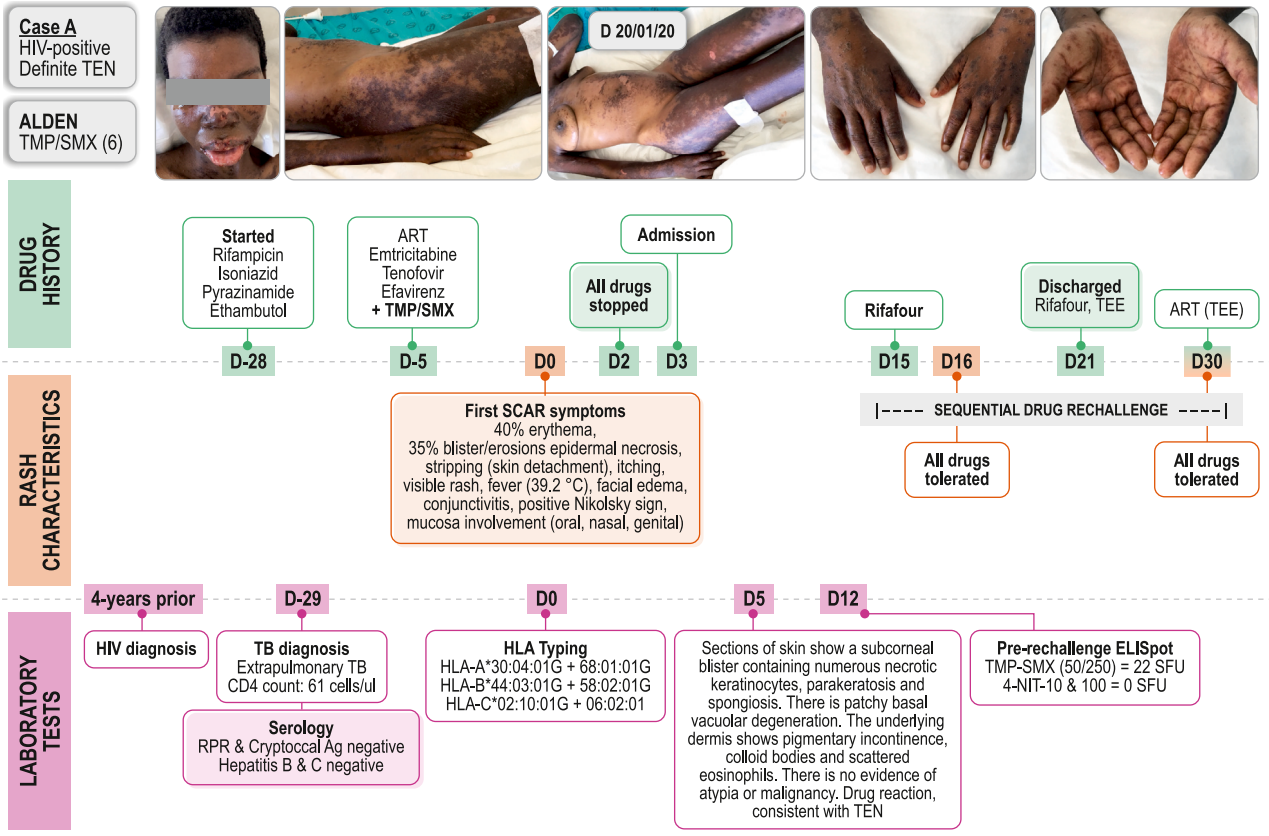

FIGURE 1. Case A: Timeline of drug introduction, skin evolution, and other diagnostic markers. *ART*, antiretroviral therapy; *RIFAFOUR*, fixed-dose combination of four active TB drugs: rifampicin 150 mg, isoniazid 75 mg, pyrazinamide 400 mg, and ethambutol HCl 275 mg; *SCAR*, severe cutaneous adverse reaction; *SFU*, spore forming units; *TEE*, tenofovir, emtricitabine, and efavirenz; *TEN*, toxic epidermal necrolysis; *TMP/SMX*, trimethoprim/sulfamethoxazole.

Hamilton, New Zealand; free access) and DermIS.net (University of Heildelberg and University of Erlangen, Germany; free access) also offer helpful, vetted clinical images and information.

Clinical skin examination

Skin examination is critical to diagnosis, but identifying a blistering eruption is not always obvious. Blistering eruptions can present to a clinician before blistering or sloughing ensues, often leading to delays in diagnosis that can be deadly. Critical symptoms to assess include skin burning, tenderness, or pain, all of which are red flags. Pruritus, comparatively, is reassuring. Examination may reveal duskiness—a deep red or purple discoloration—that can signal incipient blistering. Significantly, as noted in case A, duskiness can vary across skin tones and may be difficult to detect by an untrained eye, potentially leading to delayed diagnosis and/or undertreatment in patients with skin of color.[16] Noting whether the rash or lesions are diffuse or localized, where they began (central vs acral), and if there is a pattern to their progression can be helpful. For example, lesions of erythema multiforme often begin acrally and progress centripetally, whereas lesions of SJS/TEN often begin on the trunk and subsequently spread to the extremities.[17]

Characterizing blister morphology further aids diagnosis. Tense bullae imply a deeper split below the epidermis, seen for example in bullous pemphigoid (BP), whereas flaccid bullae suggest a more superficial, intraepidermal split, as seen in pemphigus vulgaris (PV).[18] Lesions can be discrete, coalescing, or even sheets of desquamation, the last a feature of TEN and staphylococcal scalded skin syndrome (SSSS). Eroded skin in SSSS reveals residual partial epidermis (SSSS), whereas TEN shows full epidermal loss. Other characteristic morphologies include the annular blistering crown of jewels pattern in linear IgA bullous dermatosis[19] or target (bull's-eye) lesions. Target lesions are well-demarcated with three distinct zones: the central zone may be dusky or violaceous, blistered, or necrotic, followed by a paler zone, and then a red outer zone. Target lesions are classically observed in erythema multiforme. Targetoid (or atypical target) lesions, with two-color zones and typically less distinct borders, are sometimes observed in SJS/TEN and other conditions.[14]

Bedside maneuvers may be helpful. Nikolsky sign refers to dislodgement of the epidermis with gentle lateral pressure on the skin. It can help confirm non-obvious blistering while pointing toward particular diagnoses (SJS/TEN, PV, and SSSS, for example).

The Asboe-Hansen sign refers to the lateral extension of apparently unblistered skin when gentle pressure is applied to the top of a blister. This sign can be positive in SJS/TEN, PV, and BP, for example. Caution is advised with these maneuvers because they can be painful and worsen blistering or open skin.

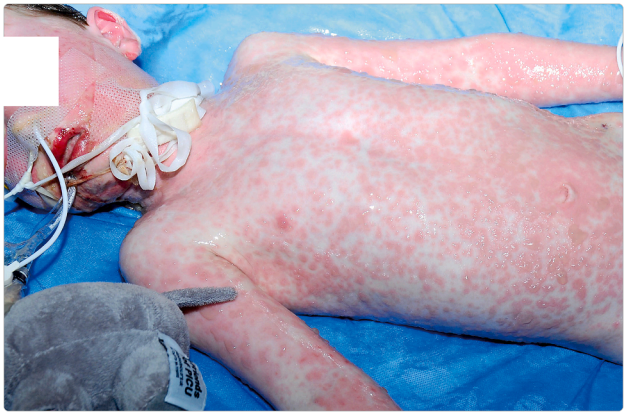

FIGURE 2. Case B: Clinical photo of the eruption: widespread erythematous rash that became bullous within 24 hours. Subsequently, the patient developed 26% skin detachment with marked oral mucosal ulceration and conjunctival injection. *ALDEN*, algorithm of drug causality for epidermal necrolysis; *ART*, antiretroviral therapy; *RPR*, rapid plasma regain; *SMX*, sulfamethoxazole; *TB*, tuberculosis; *TEE*, tenofovir, emtricitabine, and efavirenz; *TEN*, toxic epidermal necrolysis; *TMP*, trimethoprim.

Mucosal involvement

Evaluation for mucosal involvement (ocular, nasal, oral, pharyngeal, esophageal, urogenital, and perianal sites) is essential in suspected blistering disorders.[20] Here again, early involvement may not be immediately apparent on initial examination, so patients should be questioned about mucosal symptoms.

Proper wording is critical, particularly for ocular and genital involvement. The authors ask, "Do you feel grittiness, sandiness, irritation, or discomfort in your eyes?" and "Do you have burning with urination, itch, irritation, or discomfort in your genital area?" Even in the absence of symptoms, examination should be performed. Whereas the involvement of multiple specialists, including urology, otolaryngology, gastroenterology, gynecology, and/or oral medicine, may be necessary, rapid ophthalmologic care can be vision-saving in some blistering diagnoses such as SJS/TEN.

Notably, although the degree of mucosal involvement may point to particular phenotypes and/or triggers (Figure 3), at this time it does not reliably do so. Mucosal findings should therefore be considered in the context of the entire clinical and histologic picture to render a diagnosis.

Histological findings

Although a detailed discussion of histologic findings is beyond the scope of this review, we include salient points.

First, the authors recommend that a skin biopsy or biopsies be obtained whenever possible. These should be collected by an experienced dermatologist and read by an experienced dermatopathologist for standard histology (hematoxylin-eosin), ideally with a separate skin sample for direct immunofluorescence. It is acknowledged, however, that this may be influenced by access and cost. Accordingly, standards varied considerably across the four countries represented by the authors. Standard histology distinguishes most entities in the differential diagnosis of diffuse mucocutaneous blistering disorders, provided classic presentations are present.[21] An exception to this is the pemphigus/pemphigoid/linear IgA family, which typically requires direct immunofluorescence (requiring specialized medium, a microscope, and training), along with potentially serum studies, to diagnose fully.[22] However, even for highly experienced specialists, atypical cases exist in which histopathology reveals a diagnosis less suspected clinically, and/or communication between dermatology and dermatopathology is necessary to interpret complex findings correctly.

Second, histologic findings are influenced by the site and timing of the biopsy. A biopsy taken from an early non-blistered area of skin in SJS/TEN may not show full-thickness epidermal necrolysis. That does not rule out SJS/TEN. Third, and most critically, care should *never* wait for a histopathology result. If SJS/TEN or another potentially life-threatening blistering diagnosis is suspected, the patient should be managed initially based on the clinical presentation. The patient can always be transferred out of the intensive care unit, specialists can sign off, and treatment can be discontinued if an alternative diagnosis is identified.

Finally, we advise against jelly rolls. Jelly rolls are a type of skin sampling in which the denuded epidermis is rolled onto a cotton swab and frozen for rapid pathologic review. They are most effective in rapidly diagnosing SJS/TEN versus SSSS. However, they can misrepresent the level of epidermal split, leading not only to misdiagnosis but also to critical mismanagement, because the treatment for SSSS is antibiotics. In contrast, the treatment for SJS/TEN commonly involves avoiding antibiotics.

Identifying causes

Because many diffuse mucocutaneous blistering conditions can be caused by drug and/or non-drug etiologies (Figure 3), obtaining a thorough medical history is essential. A comprehensive drug history should include all medications (prescription, over-the-counter, herbal supplements, vaccines, etc) taken over the past 3 months, any recent dose or brand adjustments, whether they were discontinued and when, and a history of drug reactions. Table I details the most common drugs reported for the most common diseases.

Because many adults are taking or have taken one or more medications preceding clinical presentation, it is easy to presume a rash is drug-induced.[23] Drugs are only one trigger for many of the included diagnoses. A history of infection exposure, a list of symptoms, and a history of stem cell transplant and cellular therapies[24-26] should be obtained, because these factors may predispose patients to atypical or severe mucocutaneous eruptions and influence both diagnostic considerations and therapeutic decisions. Indeed, as seen in case B, infection can trigger bullous eruptions identical to drug-induced SCAR. The medical history, a review of systems, and malignancy screening are also directly relevant and may point to a paraneoplastic or autoimmune etiology,[27] which can significantly alter management and prognosis.

In vivo and *ex vivo* drug allergy investigations

As illustrated in case A, drug identification in T cell–mediated reactions such as SJS/TEN may benefit from a combination of *in vivo* and *ex vivo*/*in vitro* diagnostic tools. Detailed discussion of these tools is beyond the scope of this review and has been covered in previous articles.[6,8,28-31]

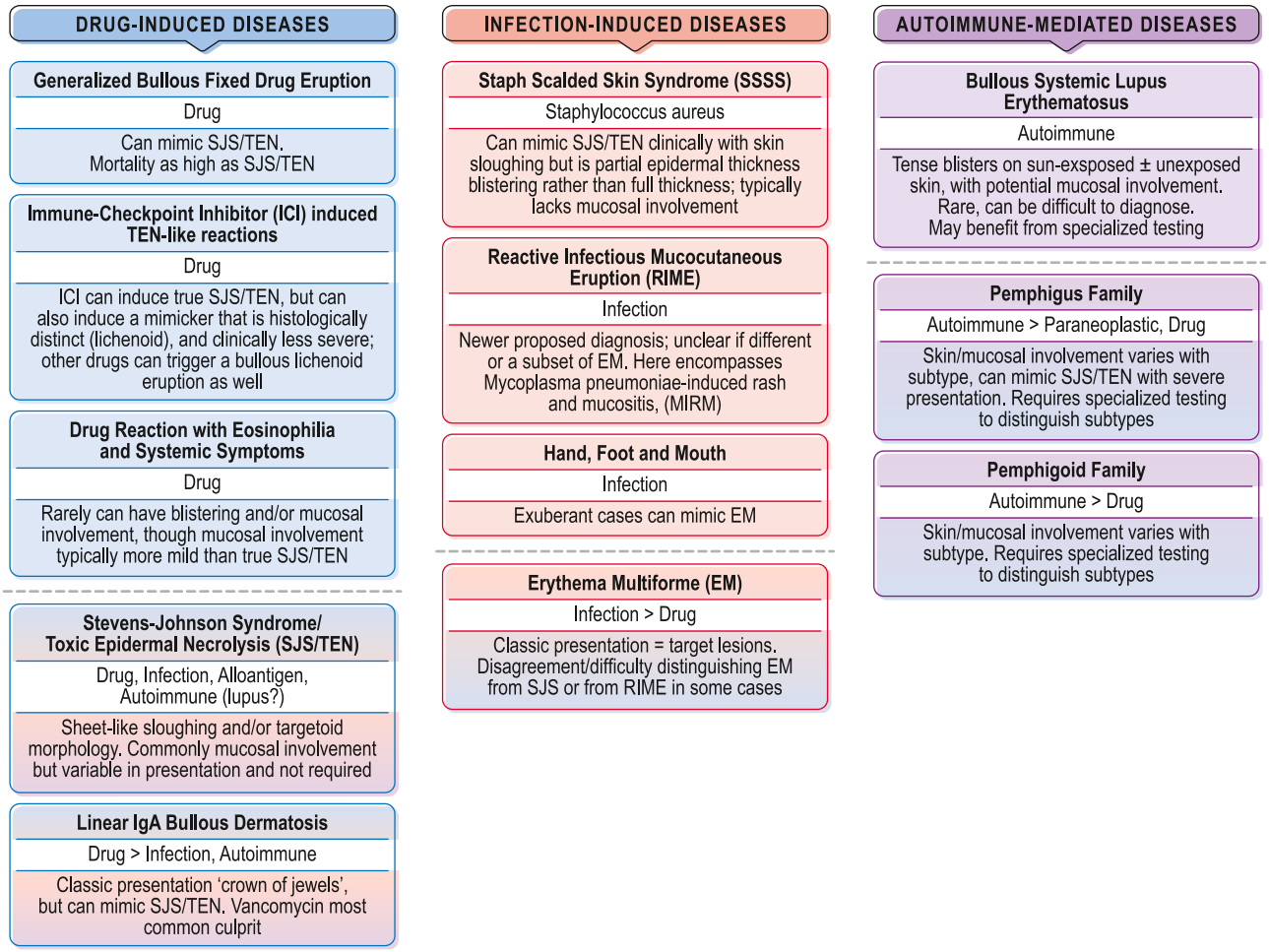

FIGURE 3. Diagram of bullous mucocutaneous eruptions (with focus on diagnoses with diffuse and widespread lesions and potential for significant morbidity and mortality). Diagnoses are bolded and organized in columns color-coded by predominant etiology (*blue* indicates drug; *orange,* infection; and *purple,* autoimmune), with multiple etiologies indicated in *blue/orange/purple*. Salient points are noted below each diagnosis.

TABLE I. Common drug triggers by disease

Disease	Common drug trigger
Erythema multiforme	Antibiotics (penicillins, cephalosporins), NSAIDs, anticonvulsants, allopurinol, antifungals
Stevens-Johnson syndrome/toxic epidermal necrolysis	Sulfonamides, β-lactam antibiotics, anticonvulsants, allopurinol, NSAIDs
Linear IgA bullous dermatosis	Vancomycin (most common), dapsone, other antibiotics, NSAIDs, diuretics
Generalized bullous fixed drug eruption	NSAIDs, sulfonamides, tetracyclines, penicillins, cephalosporins, fluoroquinolones, acetaminophen, contrast media
Drug reaction with eosinophilia and systemic symptoms	Vancomycin, sulfonamides, minocycline, dapsone, allopurinol, anticonvulsants
Pemphigus vulgaris	Penicillamine, bucillamine, ACE inhibitors, β-lactam antibiotics
Bullous pemphigoid	Furosemide, gliptins, PD-1 inhibitors, NSAIDs

NSAIDs, nonsteroidal anti-inflammatory drugs.

However, we will underline some key elements. Among *in vivo* tools, patch testing is safe, but initial concentrations need to be reduced for SJS/TEN. However, its utility is limited by its inapplicability in the acute setting and its low sensitivity.[6,32] Currently, other *in vivo* approaches to identify the culprit drug after a SCAR event, such as intradermal testing, are not recommended owing to the risk of disease reactivation.[33]

Where access is available, *ex vivo*/*in vitro* assays such as the enzyme-linked immunospot and lymphocyte transformation test may be used to detect drug-specific T-cell responses.[29] These assays, primarily used in the research domain, measure cytokine release or lymphocyte proliferation on exposure to suspected drugs, providing a safer option for diagnosis.[29] These *in vitro* tests have been reported to be helpful in the acute stage in both

children and adults.[10] Importantly, blister fluid from affected skin sites (eg, blisters) has emerged as a valuable source of immune cells, particularly cytotoxic T cells, which can be analyzed to identify the culprit drug and characterize the immune response.[34] This approach enhances diagnostic accuracy by directly sampling the site of inflammation and necrosis.[34] Further, HLA genotyping can have a role in both the prevention and post-event management of SCAR.[35-37] Preemptively, in specific settings, it can identify individuals at increased risk of specific drug-induced SCARs, enabling safer prescribing practices.[37-39] After a SCAR event, HLA genotyping can help confirm genetic susceptibility, guide future drug avoidance, and inform counseling for both the patient and potentially at-risk family members.[35,37]

The integration of these tools into clinical practice is advancing the precision of drug hypersensitivity diagnosis and guiding safer therapeutic decisions.

TREATMENT AND MANAGEMENT

Any and all potential causative drugs should be discontinued immediately. In cases triggered by infection, appropriate antimicrobial therapy should be initiated without delay. Treatment remains controversial in SJS/TEN; a detailed discussion is beyond the scope of this article. In brief, care ranges from supportive, meticulous wound care to topical corticosteroids to high-dose systemic corticosteroids and/or cyclosporine, anti-TNFs, intravenous immunoglobulin, and/or Janus kinase inhibitors.[7,40] Treatment choice is influenced by patient comorbidities as well as by cost, availability, and regional differences in care. Prompt ophthalmological assessment is crucial because intervention, particularly with amniotic membrane transplantation in SJS/TEN, can be vision-saving.[41]

Complications in severe blistering mucocutaneous reactions are frequent and potentially severe, most notably infections resulting from compromised skin barrier function. Multidisciplinary care is essential for optimal outcomes.

TEACHING POINTS

- Stevens-Johnson syndrome and TEN are rare but life-threatening mucocutaneous reactions most often triggered by medications. However, infections can also act as precipitants. Presented case B underscores the importance of considering infectious etiologies in the differential diagnosis of severe skin eruptions.
- Early signs of SJS/TEN may include prodromal upper respiratory tract infection-like symptoms followed by the rapid onset of painful, erythematous, or targetoid skin lesions, mucosal involvement (oral, ocular, or genital), and systemic symptoms. Disease may be missed early in presentation. A low threshold for dermatologic and ophthalmologic evaluation should be maintained.
- Differentiating between bullous skin reactions such as SJS/TEN, generalized bullous fixed eruption, and linear IgA bullous dermatosis can be helpful. However, given the controversy and limited data, clinicians should avoid waiting for a final diagnosis before initiating appropriate treatment. Instead, management should be driven by the clinical picture and a broad consideration of potential etiologies, including drug reactions, infections, and other systemic causes. A thorough medical history, including recent infections and drug exposures, is essential. Diagnostic tools such as skin biopsy and serologic testing may help identify triggers. Regardless of classification, management typically involves multidisciplinary care, including dermatology, ophthalmology, and gynecology, as well as airway protection and wound care. Supportive care and withdrawal of suspected drugs remain central, and antimicrobial therapy may be indicated when infectious triggers are identified. Ultimately, a flexible, patient-centered approach is important to optimizing outcomes.

CONCLUSION

This review highlights two distinct cases of blistering eruptions: one consistent with drug-induced TEN (case A) and the other with infection-induced SJS/TEN (case B). These cases underline the diagnostic and management challenges posed by SCAR, particularly when clinical features overlap or evolve rapidly. Importantly, they demonstrate that visual assessment alone may be insufficient for accurate diagnosis. Early recognition and intervention are critical in minimizing morbidity and mortality. A multidisciplinary approach is essential for comprehensive evaluation and treatment. Histologic analysis is a valuable tool in confirming the overall diagnosis of blistering eruptions.

These cases reinforce the importance of a structured differential diagnosis, which enhances diagnostic precision and informs appropriate therapeutic decisions. Ultimately, blistering drug eruptions demand a high index of suspicion, timely drug withdrawal, and coordinated care to optimize outcomes and prevent long-term complications.

Looking ahead, future research should focus on refining diagnostic algorithms, such as integrating molecular and immunogenetic markers (eg, HLA associations), to enhance early and accurate identification of culprit drugs. Prospective studies are needed to evaluate the utility of emerging biomarkers and validate immunomodulatory therapies in SJS/TEN. Additionally, collaborative registries and multicenter studies could help elucidate risk factors, improve prognostication, and guide personalized treatment strategies.

Acknowledgments

The authors acknowledge the assistance of Dr Saleem Taibjee, Department of Dermatology, Dorset County Hospital, Dorchester, United Kingdom, in case 2.

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