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High risk and low prevalence diseases: Stevens Johnson syndrome and toxic epidermal necrolysis

Christiaan van Nispen, MD [a,*], Brit Long, MD [a], Alex Koyfman, MD [b]

[a] Department of Emergency Medicine, Brooke Army Medical Center, Fort Sam Houston, TX, United States of America
[b] Department of Emergency Medicine, University of Texas Southwestern Medical Center, Dallas, TX, United States of America

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ABSTRACT

Introduction: Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are serious conditions that carry a high rate of morbidity and mortality.
Objective: This review highlights the pearls and pitfalls of SJS/TEN, including presentation, diagnosis, and management in the emergency department (ED) based on current evidence.
Discussion: SJS/TEN is a rare, delayed hypersensitivity reaction resulting in de-epithelialization of the skin and mucous membranes. The majority of cases are associated with medication or infection. Clinicians should consider SJS/TEN in any patient presenting with a blistering mucocutaneous eruption. Evaluation of the skin, mucosal, pulmonary, renal, genital, and ocular systems are essential in the diagnosis of SJS/TEN, as well as in the identification of complications (e.g., sepsis). Laboratory and radiological testing cannot confirm the diagnosis in the ED setting, but they may assist in the identification of complications. ED management includes stabilization of airway and breathing, fluid resuscitation, and treatment of any superimposed infections with broad-spectrum antibiotic therapy. All patients with suspected SJS/TEN should be transferred and admitted to a center with burn surgery, critical care, dermatology, and broad specialist availability.
Conclusions: An understanding of SJS/TEN can assist emergency clinicians in diagnosing and managing this potentially deadly disease.

1. Introduction

This article series addresses high risk and low prevalence diseases that are encountered in the emergency department (ED). Much of the primary literature evaluating these conditions is not emergency medicine focused. By their very nature, many of these disease states and clinical presentations have little useful evidence available to guide the emergency physician in diagnosis and management. The format of each article defines the disease or clinical presentation to be reviewed, provides an overview of the extent of what we currently understand, and finally discusses pearls and pitfalls using a question-and-answer format. This article will discuss Steven Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). These conditions' low prevalence but high morbidity and mortality, as well as the variable atypical patient presentations and challenging diagnosis, make them a high risk and low prevalence disease.

1.1. Definition

Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN) comprise a continuum of a delayed hypersensitivity reaction affecting the skin and mucous membranes and is associated with a high risk of morbidity and mortality [1-3]. After an exposure to a causative agent, such as medications or pathogens, a viral-like prodrome progresses into the development of an erythematous, then blistering, and ultimately desquamating rash which can involve the skin; eyes; and mucosa of the mouth, pharynx, gastrointestinal (GI) tract, respiratory tract, and genitals [2,3]. SJS and TEN are distinguished by the total body surface area (TBSA) of skin involved. The former is defined by a TBSA of <10% while the latter is defined by a TBSA of >30%. TBSA involvement between 10 and 30% is designated as SJS/TEN overlap [2,3].

1.2. Epidemiology

SJS/TEN is rare. A study of inpatient records from 2009 to 2012 in the United States demonstrated an incidence of 9.2 per million adults per year for SJS, 1.6 per million adults per year for SJS/TEN overlap, and

* Corresponding author at: 3551 Roger Brooke Dr, c/o, Department of Emergency Medicine, Fort Sam Houston, TX 78234, United States of America.
E-mail address: cvannispenmd@gmail.com (C. van Nispen).

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1.9 per million adults per year for TEN; in children, the incidences are 5.3, 0.8, and 0.4 per million, respectively [4,5].

Risk factors for the development of SJS/TEN include certain human leukocyte antigen (HLA) haplotypes; variations in cytochrome *p*450 metabolism; a history of allergies to medications; and past medical history of human immunodeficiency virus (HIV) infection regardless of treatment status, systemic lupus erythematosus (SLE), connective tissue disorders, psoriasis, epilepsy, malignancy, cerebrovascular accident, and diabetes mellitus [6-8].

SJS/TEN carries a high risk of morbidity and mortality. The mortality rate of SJS is estimated to be 1–5% while the mortality rate of TEN is estimated to be 15–50% [6,9-12]. Another study estimated the mortality of the SJS/TEN continuum at 23% at 6 weeks and 34% at one year [10]. Data suggest the mortality rate for pediatric patients with SJS, SJS/TEN overlap, and TEN is 0%, 4%, and 16%, respectively [5].

1.3. Pathophysiology

SJS/TEN is a delayed hypersensitivity reaction evoked by exposure to certain medications and, less commonly, to pathogens. There are a significant number of medications including allopurinol, anticonvulsants, antimicrobials, phenobarbital, and certain nonsteroidal anti-inflammatory drugs, as well as pathogens such as *Mycoplasma pneumoniae* and Herpes simplex virus (HSV), that are associated with SJS/TEN [2,8]. Although the microbiological intricacies of the disease process are yet to be fully elucidated, it is suspected that cytotoxic $CD8^+$ T lymphocytes and natural killer cells specific to the causative medication or infection release cytokines and chemokines which recruit other immune cells including neutrophils, monocytes, and eosinophils into the skin and mucosa, resulting in cellular necrosis [3,13-15]. With cessation of exposure to the instigating agent and meticulous supportive care, the affected areas will re-epithelialize [16].

2. Discussion

2.1. Presentation

The presentation of SJS/TEN includes an acute and chronic phase. Signs and symptoms develop at a median of 3 to 4 weeks after exposure to the causative agent, although presentations as early as 4 days and as late as 8 weeks post-exposure have been reported [3,14]. The acute, progressive phase lasts 7–9 days from the first symptoms, and during this phase, patients are at risk of electrolyte derangements, dehydration, organ injury (e.g., renal, hepatic, pulmonary), sepsis, hypothermia, and death [17,18]. The chronic phase with convalescent and recovery stages follows arrest of disease progression [19].

The disease starts with a viral-like prodrome lasting approximately 3 days leading to the development of rash, which may include fever, headache, sore throat, myalgias, and malaise [3,20]. Lesions most commonly start on the face and thorax and then spread with symmetrical distribution. Over a 5–7 day period, the rash may progress from ill-defined erythema into dusky, purpuric, and atypical targetoid macules. Ultimately, sheet-like desquamation occurs in affected areas [3,16]. Severe skin pain prior to the onset of rash may occur [18,21].

In addition to the cutaneous eruption, erosions of multiple mucous membranes are common, including the oral cavity, conjunctivae, genitals/urethra, nasal cavity, larynx, gastrointestinal tract, and bronchi [22-28]. Of note, up to 80% of patients have involvement of two or more mucosal surfaces, and mucous membrane involvement can precede cutaneous lesions [18,29,30]. The absence of mucosal involvement should prompt consideration of alternative diagnoses [3,31].

2.2. ED evaluation

Diagnosis of SJS/TEN is based on patient history and signs and symptoms. A careful review of any recent medication changes and infectious symptoms is paramount. The clinician must evaluate the skin, eyes, oral and nasal cavities, and genitourinary system to assess for the characteristic rash and mucosal erosions. Application of a gentle, lateral shearing force to erythematous, purpuric, or blistering areas should cause sloughing of the epidermis [3]. TBSA of the cutaneous lesions is calculated by including both detached and undetached areas of erythematous skin [14]. The skin examination should include assessment for superimposed cellulitis [3]. The eyes should be assessed with ultraviolet light and fluorescein staining [32]. An assessment of the airway and breathing is necessary due to the risk of mucosal lesions or superimposed pneumonia complicating the respiratory effort [1]. An assessment of volume status is also necessary due to the risk of volume depletion [3].

There is minimal role for laboratory and radiographic studies in the diagnosis of SJS/TEN in the ED. However, laboratory and radiologic studies are crucial in the assessment for superimposed infections and injury to the lungs, liver, and kidneys [1,3,33,34]. Therefore, it is reasonable for the emergency clinician to obtain a complete blood count (CBC), electrolytes and renal function, hepatic function panel, coagulation studies, lactic acid level, inflammatory markers, urinalysis with urine culture, blood cultures, and chest radiograph. HIV and *Mycoplasma pneumoniae* screening can be considered [3,33]. The diagnosis is aided through biopsy and histopathologic testing of lesions by specialists in dermatology and pathology, though the results will not be available in the ED setting. Suggestive histopathologic findings include apoptotic keratinocytes, full thickness epidermal necrosis, and infiltration of inflammatory cells into the dermis [3,35]. Histopathologic testing of perilesional skin can assist in ruling out autoimmune blistering conditions [3]. As in-person dermatologist consultation and histopathologic testing is not available in many EDs, the emergency clinician must heavily weigh the appearance of the mucocutaneous lesions and history of recent exposures to determine if SJS/TEN is likely.

2.3. ED management

As in the management of any patient presenting to the ED with a serious illness, the emergency clinician must first identify and stabilize immediate life threats due to complications involving the airway, breathing, and circulation and resuscitate if necessary. In patients with SJS/TEN, the relevant considerations include tenuous airways due to oral, pharyngeal, and respiratory mucosal injury and hypotension due to hypovolemia, infection, or both [36,37]. Sepsis must be considered in any patient presenting in critical condition or with abnormal vital signs, as it is the leading cause of death in patients with SJS/TEN [15]. Therefore, initial ED care may include airway management, boluses of balanced crystalloids to achieve euvolemia followed by initiation of a maintenance crystalloid infusion with rate based upon the TBSA of desquamated cutaneous tissue and urine output, and initiation of vasopressors for persistent hypotension after fluid resuscitation. If infection is suspected, broad spectrum antibiotic therapy should be initiated [2,3,16,28,37]. After resuscitation and stabilization of immediate life threats, the emergency clinician must identify and discontinue the offending agent, which significantly improves survival in patients with SJS/TEN [39]. Supportive care in the ED includes the administration of analgesics and anti-emetics, correction of electrolyte abnormalities, and the provision of wound care [3,32]. Patients with suspected SJS/TEN require admission at a hospital with expertise in burn care and dermatology, as well as broad specialist availability, which is associated with improved outcomes [14,32]. As controversy exists regarding efficacies of such therapies, initiation of parenteral immunomodulating therapies, such as

cyclosporine, etanercept, infliximab, and/or IVIG should be deferred to the admitting physician [33].

3. Pearls and pitfalls

3.1. What are the key risk factors for SJS/TEN?

The most important risk factor for SJS/TEN is recent initiation of a medication with known associations to the development of the disease (Table 1). There is evidence that higher doses of these medications, or decreased medication clearance, such as due to decreased renal function, increases the risk for the development of SJS/TEN [40]. Additionally, recent exposure to certain infectious agents, such as *Mycoplasma pneumoniae* and HSV increases the risk for the development of SJS/TEN, particularly in children [41]. However, up to 30% of cases have no identifiable trigger [42].

Other risk factors associated with SJS/TEN include genetic predisposition because of HLA haplotype and cytochrome *p*450 metabolism, past medical history of HIV regardless of treatment status, SLE, connective tissue disorders, psoriasis, epilepsy, malignancy, cerebrovascular accident, diabetes mellitus, and allergies to other medications [8,15,40,43].

3.2. When should the emergency clinician consider SJS/TEN based on the history and examination, and what is the differential diagnosis?

In the ED, SJS/TEN must be suspected clinically when a patient presents with the characteristic, painful mucocutaneous eruption of erythematous or purpuric macules with progressive blistering and involvement of mucous membranes. Lack of mucous membrane involvement significantly decreases the likelihood of the diagnosis. Recent exposure to certain medications and infections supports the diagnosis of SJS/TEN; however, the absence of an identifiable trigger in the setting of a suggestive mucocutaneous eruption does not rule out the diagnosis. The Algorithm for Assessment of Drug Causality in Epidermal Necrolysis (ALDEN) is a useful tool to assist clinicians in the determination of causative medications (Table 2) [14]. However, due to the appearance of the skin findings and manifestations of SJS/TEN, there are a number of conditions that present in a similar manner (Table 3).

3.3. What is the Nikolsky sign?

The Nikolsky sign is a physical examination finding which describes the separation of epidermal cells from each other when a gentle, lateral shearing force is applied to an area of skin. The Nikolsky sign can be present over existing lesions, in the perilesional skin, and even in areas of normal-appearing skin distant from the active lesions. It is a manifestation of acantholysis, which is the loss of connection between epidermal cells at the desmosomes. When the Nikolsky sign is present, the differential diagnosis includes pemphigus vulgaris (PV) and staphylococcal scalded skin syndrome (SSSS). In these diseases, the desmoglein proteins which comprise the desmosomes are targeted by autoantibodies or infectious exfoliative toxins, resulting in sloughing when lateral shearing force is applied [59-63].

The Nikolsky sign is distinguished from the pseudo-Nikolsky sign, which is present in SJS/TEN, thermal burns, and bullous ichthyosiform erythroderma. The pseudo-Nikolsky sign is present when a gentle, lateral shearing force is applied to an erythematous or purpuric area and results in epidermal sloughing. Skin with normal appearance should not slough. The pathophysiology of the pseudo-Nikolsky sign is cellular necrosis, rather than acantholysis [60,61,64].

Table 1
Medications associated with SJS/TEN [2,6,8,41,44-47].

Acetic acid-type NSAIDs (e.g., diclofenac, indomethacin)	Nivolumab
Allopurinol	Oxcarbazepine
Abacavir	Oxicam-type NSAIDs* (e.g., meloxicam, piroxicam)
Atezolizumab	Pantoprazole
Carbamazepine*	Pembrolizumab
Cephalosporin-type antibiotics	Penicillin-type antibiotics
Durvalumab	Phenobarbital*
Fluoroquinolone-type antibiotics	Phenytoin*
Ipilimumab	Sertraline
Lamotrigine*	Sulfa-containing antimicrobials*
Macrolide-type antibiotics	Sulfasalazine*
Nevirapine*	Tetracycline-type antibiotics

* Highest risk medications for SJS/TEN per RegisSCAR/EuroSCAR data [10].

3.4. Other than the skin, which organ systems may be involved in SJS/TEN?

SJS/TEN frequently affects multiple organ systems. The eyes are involved in 60–100% of cases, with manifestations including conjunctivitis, conjunctival and corneal erosions, conjunctival ulcers, pseudomembrane formation, and anterior uveitis. Consultation with an ophthalmologic specialist is recommended within 1 to 2 days of diagnosis [3,23,25,65,66]. The gastrointestinal tract is commonly affected through mucosal erosions, hemorrhagic crusting, and pseudomembrane formation of the oral cavity (up to 90% of cases). Additionally, mucosal erosions can affect the nasopharynx (50% of cases) and laryngopharynx (30% of cases) [3,22]. Erosions of the epithelial lining of the esophagus and intestines can also occur [1,67]. In one retrospective review of patients admitted with SJS/TEN who underwent endoscopy during their hospitalization, 11 of 20 (55%) were diagnosed with esophageal lesions [67]. Esophageal stricture is a known complication of SJS/TEN [1]. Epithelial erosions can affect the urethra and genitals in 60–70% of cases, which can lead to urethral stricture, vaginal adenosis, and adhesions [1,26,27]. The lungs can be affected through bronchial and alveolar erosions, which occur in approximately 10% of cases [28,34]. Patients may develop bronchiolitis obliterans as a complication [1]. SJS/TEN is associated with renal injury due to pre-renal azotemia and/or acute tubular necrosis [1]. Finally, SJS/TEN is associated with liver injury, suspected to also be due to mucosal injury, though there are reports of hepatocellular necrosis and ischemic hepatitis [1].

3.5. What are the clues on laboratory testing for SJS/TEN?

There is minimal role for laboratory testing to confirm the diagnosis of SJS/TEN in the ED. Anemia, leukopenia, neutropenia, and elevated creatinine may occur in acute SJS/TEN, although are nonspecific for the diagnosis [3,18,68]. Additionally, serum lactate dehydrogenase level can be elevated, although this is also nonspecific [69].

Several biomarkers have been identified as being elevated in the serum of patients with SJS/TEN, including Fas ligand, granzyme B, soluble CD40 ligand, granulysin, high mobility group protein B1, RIPK3, galectin 7, CCR-27, and IL-15; however, these tests are not available in the ED setting and will not assist the emergency clinician [15,69].

Despite this, laboratory studies can assist the emergency clinician in risk stratification. The SCORTEN score is based on seven clinical and laboratory criteria and has been validated in determining prognosis, including mortality, in both adults and children (Table 3) [3,14,70-74].

Table 4 SCORTEN [70].

3.6. What are pearls and potential pitfalls in the management of SJS/TEN in the ED?

The most important step in the management of SJS/TEN early identification of the causative agent. Immediate cessation of the causative agent significantly improves survival [39]. As discussed, the ALDEN

Table 2
Algorithm of drug causality for epidermal necrolysis (ALDEN) [42].

Criterion	Result	Value
Delay from initial drug component intake to onset of reaction	From 5 to 28 days (If previous reaction to drug, from 1 to 4 days)	+3
	From 29 to 56 days	+2
	From 1 to 4 days (If previous reaction to drug, from 5 to 56 days	+1
	>56 days	−1
	Drug started on or after index day of reaction	−3
Drug present in the body on index day	Drug continued up to index day or stopped at a time point <5 times the elimination half-life before index day	0
	Drug stopped at a time point prior to the index day by more than five times the elimination half-life but liver or kidney function alterations or suspected drug interactions are present	−1
	Drug stopped at a time point prior to the index day by more than five times the elimination half-life, without liver or kidney function alterations or suspected drug interactions	−3
Pre-challenge/re-challenge	SJS/TEN resulted after use of same drug	+4
	SJS/TEN resulted after use of similar drug, or patient sustained a different reaction to the same drug	+2
	Non-SJS/TEN reaction after use of similar drug	+1
	No known previous exposure to drug	0
	Patient exposed to drug without any reaction	−2
De-challenge	Drug stopped	0
	Drug continued without harm	−2
Type of drug / notoriety of drug to cause SJS/TEN	Drug considered high risk according to EuroSCAR study	+3
	Drug with known association but not high risk according to EuroSCAR study	+2
	Several previous case reports, but ambiguous epidemiology results	+1
	Any drug not fitting the other categories	0
	No evidence of association from previous epidemiology studies with sufficient number of exposed controls	−1
Other cause	Rank all drugs from highest to lowest intermediate score. If at least one has an intermediate score >3, subtract 1 point from the score of each of the other drugs taken by the patient	−1

Score Interpretation:
<0: Very unlikely.
0 and 1: Unlikely.
2 and 3: Possible.
4 and 5: Probable.
>5: Very probable.

can be useful in determining the causative agent, but up to 30% of cases will not be associated with a specific trigger such as a medication or recent infection. In the setting of a mucocutaneous eruption suggestive of SJS/TEN, the diagnosis should not be excluded due to the failure to identify a trigger.

In SJS/TEN, superimposed infection is common, with sepsis the leading cause of death. Sepsis should be considered in any patient presenting in critical condition or with abnormal vital signs in conjunction with a suggestive mucocutaneous eruption [15,37]. Antibiotic therapy should include coverage for methicillin-resistant and sensitive *Staphylococcus aureus* (MRSA), *Enterobacteriaceae* subspecies, and *Pseudomonas aeruginosa*, though *Staphylococcus aureus* strains are more common in acute SJS/TEN while the latter are more common during hospitalization [2,3,6,16,37,38]. Accordingly, appropriate regimens include vancomycin or linezolid with cefepime, piperacillin-tazobactam, meropenem, amikacin, or aztreonam. If there is no evidence of superimposed infection, prophylactic antimicrobials are not recommended as their administration could increase the risk of the future development of a multidrug resistant infection [16,37,38].

Additionally, patients with SJS/TEN are at high risk of hypovolemia due to mucocutaneous breakdown. Boluses of crystalloid may be necessary to achieve euvolemia. Following resuscitation to euvolemia, a maintenance infusion of crystalloid should be started. The quantity of fluid replacement required in the first 24 h in patients with SJS/TEN was estimated in one retrospective study to be 2.2 mL per kg per percent TBSA detached, though it is recommended to adjust the hourly infusion rate as needed to maintain a urine output of 0.5–1 mL/kg/h

Table 3
SJS/TEN Differential Diagnosis.

Diagnosis	Classic Appearance
Pemphigus vulgaris (PV) [48]	Painful blisters on normal or erythematous skin with frequent mucosal involvement
Pemphigus foliaceus [49]	Superficial cutaneous lesions similar to PV, but no mucosal involvement.
SJS/TEN-like lupus erythematosus [50]	Akin to SJS/TEN, but cutaneous lesions occur in a photo distribution
Linear IgA bullous dermatosis [51]	Tense vesicles and/or bullae appear upon normal or erythematous skin, associated with mucosal erosions; can be drug-induced
Staphylococcal Scalded Skin Syndrome (SSSS) [52]	Painful, erythematous cutaneous patches with blister formation, sparing mucous membranes, progressing over the course of hours; young children most commonly affected
Acute Graft versus Host Disease (GvHD) [53]	Pruritic or tender maculopapular eruption within 100 days of allogeneic hematopoietic cell transplant; can be associated with oral lesions, abnormalities of the gastrointestinal tract and liver
Erythema multiforme [54]	Centripetally spreading erythematous papules which develop target-like appearance and can be associated with mucosal erythema, erosions, or ulcers
Drug reaction with eosinophilia and systemic symptoms (DRESS) [55]	Maculopapular eruption and/or coalescing erythema often involving >50% TBSA, mild mucosal involvement, no desquamation; often associated with fever, lymphadenopathy, visceral and hematologic abnormalities; occurs 2–8 weeks after exposure to a medication
Acute generalized exanthematous pustulosis (AGEP) [56]	Numerous non-infectious pustules on erythematous and/or edematous skin within hours to days of administration of a medication; 25% have mucosal involvement, but >1 mucous membrane is uncommon
Exanthematous drug reaction [57]	Maculopapular reaction within 1–2 weeks of new medication exposure, without mucosal involvement
Fixed drug reaction [58]	Round, hyperpigmented macule(s) with or without blistering and can involve mucous membranes within 2 weeks of medication exposure; rarely, can present as generalized reaction

Table 4
The SCORTEN score.

Prognostic Factors	
-Age > 40 -Heart rate > 120 per minute -Known malignancy -Initial TBSA >10% -Serum BUN >28 mg/dL -Serum bicarbonate <20 mEq/L -Serum glucose >252 mg/dL	
Prognostic Factors Present	Predicted Mortality During Acute SJS/TEN
0 or 1	3%
2	12%
3	35%
4	58%
5 or more	90%

[75,76]. If patients remain hypotensive after fluid resuscitation, vasopressors such as norepinephrine should be initiated.

SJS/TEN can cause acute respiratory compromise requiring airway management. Indications for intubation in the ED include inability to protect the airway and respiratory failure, which can occur secondary to mucosal injury, pneumonia, and other pulmonary sequelae [34]. In the setting of hypoxemia, bronchial mucosal injury should be suspected even if the chest radiograph is unremarkable [14]. An early intubation strategy can be considered in patients with signs of respiratory involvement, such as hypoxemia, hemoptysis, expectoration of bronchial casts, and respiratory hypersecretion. Intubation can also be pursued for refractory severe pain, although clinicians must balance this indication against the risks of the procedure, such as the development of ventilator associated pneumonia, barotrauma, and further injury to the pharyngeal and respiratory mucosa [34]. During the intubation procedure, a smaller diameter endotracheal tube may be required due to laryngeal edema. The ventilation strategy should mirror that of acute respiratory distress syndrome, which includes a tidal volume of 6 mL/kg of ideal body weight, a positive end-expiratory pressure sufficient to avoid atelectasis, maintaining plateau pressures <30 cm H_2O, and permissive hypercapnia [34].

Cutaneous wounds can be gently cleansed with sterile water or dilute chlorhexidine and covered with sterile non-adherent gauze. If available, silver-impregnated dressings may also be used [32,33]. Blistering and bullous areas should not be aggressively debrided or ruptured [32]. The emergency clinician may apply preservative-free artificial tears or sterile saline rinses to ocular wounds [32]. Other aspects of supportive care in patients with SJS/TEN include the administration of analgesics, antiemetics, and correction of any electrolyte abnormalities [2,3,15,38].

Several systemic therapies have been postulated to reduce mortality from SJS/TEN, including cyclosporine, etanercept, infliximab, intravenous immunoglobulin (IVIG), plasmapheresis, and parenteral corticosteroids [14]. While some of these medications, including cyclosporine, tumor necrosis factor (TNF)-alpha inhibitors, and IVIG have shown some promise in small trials, the body of evidence is mixed, and there is a paucity of large, randomized, placebo-controlled studies on the topic [14,15,20,33,77-87]. Therefore, it is not recommended that these treatments be empirically initiated by the emergency clinician without consultation with the admitting physician.

Patients with suspected SJS/TEN require admission at a hospital with a burn unit [14,32]. The treatment of SJS/TEN requires a multidisciplinary approach, with consultations with specialists in critical care, dermatology, burn surgery, ophthalmology, otolaryngology, pulmonology, gastroenterology, nephrology, urology, gynecology, psychiatry, wound care, and nutrition often necessary [2,14,32,88]. Therefore, it is crucial for the emergency clinician to arrange for the patient to be admitted to a facility with these capabilities in an expeditious fashion, as delay is associated with increased mortality [89].

Table 5 provides pearls and pitfalls concerning the evaluation and management of SJS/TEN.

4. Conclusions

SJS/TEN is a continuum of a rare, delayed hypersensitivity reaction causing de-epithelialization of the skin and mucous membranes and is associated with a high risk of morbidity and mortality. Most cases are triggered by recent exposure to medications, although some cases are associated with a recent infection or have no apparent trigger. SJS/TEN should be considered in any patient presenting with a blistering mucocutaneous eruption. Laboratory and radiographic studies commonly available in the ED are nonspecific for confirming the diagnosis, though they can assist in identifying complications such as infection, which is the most common cause of death in patients with SJS/TEN. ED management should include identification and stabilization of any threats to the airway and breathing, provision of fluid resuscitation, and treatment of any superimposed infections with broad spectrum antibiotic therapy. Although there are several immunomodulating medications which have shown promise in decreasing mortality from SJS/TEN, controversy exists regarding their efficacies. All patients with suspected SJS/TEN should be admitted to

Table 5
Summary of pearls and pitfals in the management of SJS/TEN.

Cutaneous findings suspicious for SJS/TEN include ill-defined painful erythema which progresses into dusky, purpuric, and atypical targetoid macules. Involvement of at least one mucous membrane is typical and up to 80% of cases involve multiple mucous membranes.
Any patient presenting with a suspicious mucocutaneous eruption should be treated as a case of SJS/TEN until proven otherwise through histopathologic testing. Such patients should be admitted to a hospital with specific expertise in the condition, and broad specialist availability to manage potential complications, including experts in burn/wound care, dermatology, critical care, ophthalmology, otolaryngology, pulmonology, gastroenterology, nephrology, urology, and gynecology. SCORTEN can assist in the prediction of mortality from the disease.
Sepsis is the leading cause of death in patients with SJS/TEN; the emergency clinician must have a low threshold to initiate broad-spectrum antibiotic therapy. However, prophylactic antibiotics in the absence of infection are not advised. Other organ systems commonly affected include the eyes, respiratory tract and lungs, gastrointestinal tract, and genitourinary system.
Patients with SJS/TEN are at risk for hypovolemia. Boluses of balanced crystalloids may be used to achieve euvolemia, with subsequent transition to a maintenance infusion to maintain a urine output of 0.5 to 1 mL/kg/h.
Consider intubation in patients with extensive oral, pharyngeal, and/or respiratory involvement.
Although most cases of SJS/TEN are associated with a specific exposure to a medication, such as aromatic anti-epileptics and sulfonamide antimicrobials, or infections, such as *Mycoplasma pneumonia* and the Herpes simplex virus in as many as 30% of cases there will be no identifiable trigger; the absence of an obvious exposure on history does not preclude SJS/TEN in a patient presenting with a characteristic mucocutaneous eruption. The ALDEN can assist in the identification of causative medications.
In the ED, cutaneous wounds can be cleansed with sterile water or dilute chlorhexidine and then covered with sterile, non-adherent gauze. Silver-impregnated dressings may also be used. Blistering areas should not be aggressively debrided or intentionally ruptured.
There are other dermatologic conditions associated with sloughing of skin, including PV and SSSS. However, in PV, normal appearing skin can slough with the Nikolsky test, which is not the case in SJS/TEN; SSSS can be clinically distinguished from SJS/TEN as the mucous membranes are typically spared.
Although there are immunomodulating therapies which may decrease mortality from SJS/TEN, controversy exists regarding their efficacies. The decision to initiate such therapies should be deferred to the admitting physician.

a burn center, where patients will receive care from a multidisciplinary team.

CRediT authorship contribution statement

Christiaan van Nispen: Writing – review & editing, Writing – original draft, Conceptualization. **Brit Long:** Writing – review & editing, Supervision, Conceptualization. **Alex Koyfman:** Conceptualization, Supervision, Writing – review & editing.

Declaration of competing interest

CvN, BL, and AK conceived the idea for this manuscript and contributed substantially to the writing and editing of the review. This manuscript did not utilize any grants, and it has not been presented in abstract form. This clinical review has not been published, it is not under consideration for publication elsewhere, its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder. During the preparation of the work the authors used neither generative artificial intelligence (AI) nor AI-assisted technologies.

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