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Latin American guidelines for the diagnosis and treatment of Stevens-Johnson syndrome and toxic epidermal necrolysis

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ABSTRACT

Background: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe cutaneous reactions induced by delayed drug hypersensitivity, characterized by their complexity and multisystemic nature. Their diagnosis and management are challenging and require a multidisciplinary approach. Identifying the culprit drug is crucial to ensure that the patient has access to safe therapeutic options in the future. To date, there are no specific Latin American guideline or consensus documents on SJS/TEN.

Objective: To develop a Latin American guideline on the clinical diagnosis, management, and treatment of SJS/TEN, based on available scientific evidence and the experience of experts from various medical specialties.

Methods: This guideline was developed by a group of Latin American allergists and dermatologists involved in the management of SJS/TEN. A search of scientific publications was conducted, and the expert group evaluated the available evidence in the literature, providing grades of recommendation. In cases where there was insufficient evidence, consensus was reached among the experts.

Results: The Latin American guidelines on SJS/TEN were developed, addressing relevant practical aspects of clinical diagnosis, and the identification of culprit drugs using the ALDEN (Algorithm of Drug Causality for Epidermal Necrolysis). It also offers recommendations on management, treatment, and prevention of complications, along with a specific algorithm for disease management. This guideline includes a therapeutic strategy, developed and agreed upon by expert specialists involved in the treatment of SJS/TEN.

Keywords: Stevens-Johnson syndrome, Toxic epidermal necrolysis, Severe drug-induced cutaneous reaction, Corticosteroids, Biologics

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SCOPE

This guideline is intended for all medical staff, general practitioners, specialists, subspecialists, and other healthcare professionals involved in the care of patients with suspected severe cutaneous adverse reactions (SCARS) due to drugs. The recommendations generated here represent the outcome of an updated literature search; however, there is no universally accepted consensus or guideline for SCARS. These recommendations can be applied in emergency, inpatient, and outpatient care settings, depending on the availability of the resources suggested in this document.

OBJECTIVES

The primary objective is to offer recommendations for the diagnosis and general management of SCARS based on the best available evidence. In cases where the evidence is uncertain, expert recommendations will be considered.

Additionally, this document aims to discuss the state of the art in the epidemiology, pathophysiology, and clinical manifestations of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).

METHODOLOGY

The systematic literature review began with an exhaustive search for high-quality international medical guidelines on SJS/TEN in specialized electronic databases, aimed at answering PICO questions (Patients, Intervention, Comparison, Outcomes).

A bibliographic search was conducted in PubMed, EMBASE, and Cochrane using terms: *'patient care management' AND 'Stevens-Johnson syndrome' AND 'diagnosis' OR 'diagnosis'("Stevens-Johnson Syndrome"[Mesh]) AND ("Diagnosis"[Mesh] OR "diagnosis" [Subheading])*. The decision was made to adapt existing guidelines for TEN/SJS. The quality evaluation of the selected guideline(s) was performed using the AGREE II (Appraisal of Guidelines, Research and Evaluation for Europe II) instrument, internationally designed to facilitate the evaluation of clinical practice guidelines. This evaluation was independently conducted by 8 trained experts who rated each item contained in the various domains of the tool, and, subsequently, a total weighted score for each domain was calculated from the individual ratings. Then, each evaluator rated the overall quality of the guideline. For each guideline, the level of discrepancy in each domain was assessed to identify which ones needed to be reviewed.

Finally, the group established clinical recommendations by level of relevance and agreement. Recommendations that did not reach a certain level of consensus were removed from the final document.

INTRODUCTION

Severe cutaneous adverse reactions (SCARS) due to drugs are manifestations of non-IgE mediated hypersensitivity phenotypes, characterized by potential severity and multisystem involvement.[1,2] The etiology is complex and is clearly related to exposure to certain types of medications (eg, allopurinol, aromatic anticonvulsants, non-steroidal anti-inflammatory drugs [NSAIDs], beta-lactams, etc.). In some cases, the dosage plays a crucial role (with higher risk at doses $\geq$200 mg/day of allopurinol), as well as the individual host susceptibility.[2,3] This group of conditions includes SJS, TEN, drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP).

Although it has been considered a low-frequency disease, some reports have estimated that 2% of patients hospitalized in a referral center may present with SCARS.[2] Prevalence and mortality vary among populations, geographic distribution, and type of SCARS.[1,2] Most studies show that anticonvulsants are the medications most likely to cause SCARS. In the European Registry of Serious Adverse Skin Reactions (RegiSCAR), carbamazepine was the most implicated agent in DRESS and the second most implicated in SJS and TEN.[2]

In Latin America, the RACGRAD study by Rojas et al,[4] which included patients from several centers in 5 countries (Argentina, Brazil, Paraguay, Peru, and Colombia), described a total of 70 cases of SCARS, of which 60% corresponded to DRESS/drug-induced hypersensitivity syndrome (DiHS), 17.1% to TEN, 7.1% to SJS, and 8.5% to AGEP. Additionally, 5.7% were considered unclassified

severe cutaneous reactions, and 1.4% were interpreted as overlap syndrome SJS/TEN. The drugs involved were anticonvulsants in 44.3% of the cases, followed by beta-lactams in 15.7%, and non-beta-lactam antibiotics in 8.6%.

STEVENS-JOHNSON SYNDROME (SJS)/ TOXIC EPIDERMAL NECROLYSIS (TEN)

TEN, also known as Lyell's syndrome, and SJS are variants of a spectrum of epidermal necrolysis caused by a severe hypersensitivity reaction characterized by epidermolysis or diffuse skin detachment, accompanied by necrosis and mucosal involvement.[1,5] Both reactions constitute a spectrum of the same disease and are differentiated by the percentage of body surface area affected. In SJS, there is <10% involvement; in the overlap syndrome, there is 10-<30% involvement, and in TEN, there is ≥ 30% involvement.[5,6]

The extent of cutaneous and mucosal involvement can pose a life-threatening risk, and in some series, mortality rates as high as 40% have been reported.[5,7] Once the acute phase is resolved, the frequency of sequelae can be up to 90% during the first year,[5,7,8] with the main sequelae being xeroderma, residual hyperpigmentation, nail abnormalities, hair and sweat gland dysfunction, and xerostomia. Additionally, ocular complications frequently include dry eye syndrome, cicatricial conjunctivitis, symblepharon, and impaired visual acuity. Other described sequelae may affect genital organs and, more rarely, the digestive tract and bronchi, as well as dental abnormalities and post-traumatic stress.[5,6,9]

Epidemiology

These reactions are rare, with a reported incidence of 2 cases per million people per year and an estimated mortality rate of 20–25% during the acute phase, reaching values of 30–35% a year after the reaction.[10] It more frequently affects women with a ratio of 3:2, HIV patients, and the elderly.[11] In 85% of cases, the cause is medication, and symptoms appear between 5 and 28 days after initiation.[5,7]

Causal drugs

In the multinational case-control study RegiSCAR, which included 379 cases of SJS/TEN and 1505 controls, the most commonly implicated drugs were described, as cited in Table 1.[12]

Additionally, according to data from the EuroSCAR study the drugs responsible for more than

Strongly associated	Associated	Suspected association/low risk
Allopurinol	Diclofenac	Pantoprazole
Lamotrigine	Doxycycline	Glucocorticoids
Sulfamethoxazole	Amoxicillin/ampicillin	Omeprazole
Carbamazepine	Ciprofloxacin	Tetrazepam
Phenytoin	Levofloxacin	Dipyrone
Nevirapine	Amifostin	Terbinafine
Sulfasalazine	Oxcarbazepine	Levetirazetam
Oxicam NSAIDs	Rifampicin	
Phenobarbital		
Etoricoxib		

Table 1. Drugs associated with SSJ/NET in RegiSCAR. *The most implicated drugs in severe cutaneous adverse reactions, described in the multinational case-control study RegiSCAR. The agents are presented in decreasing order. Source: Up to Date*

half of the cases, and therefore considered high-risk, are:

- Allopurinol
- Sulfonamides including sulfadiazine
- Nevirapine
- Amines antiepileptics: Carbamazepine, oxcarbazepine, phenobarbital, phenytoin
- Lamotrigine
- Oxicam NSAIDs

In the RACGRAD study for Latin America, the drugs implicated were primarily anticonvulsants in 27.7% (carbamazepine, phenytoin, lamotrigine), beta-lactams in 16.7% (amoxicillin, meropenem, and piperacillin/tazobactam), non-beta-lactam antibiotics in 8.6% (azithromycin, clindamycin, erythromycin), allopurinol in 16.7%, NSAIDs in 11.1% (ibuprofen, ASA), and other medications in 11.1% (albendazole and meglumine antimoniate).[4]

Herbal medications and biologic agents targeting CTLA-4 (nivolumab), cetuximab, and vemurafenib have been reported in more recent publications.[1,6] Other drugs, such as thiazides, furosemide, sulfonylureas, beta-blockers, angiotensin-converting enzyme inhibitors, calcium channel blockers, proton pump inhibitors (except pantoprazole), statins, metformin, and oral contraceptives, are considered low-risk. The association with serotonin reuptake inhibitors, such as sertraline, has not been consistent in studies.[1,6]

Risk factors and pharmacogenetic associations

Poor prognosis factors include comorbidities such as hematological malignancies, HIV infection, fungal infections, liver disease, and kidney disease. Additionally, higher risk has been described in children between 1 and 10 years old and in those over 70 years old.

Certain human leukocyte antigen (HLA) genotypes have been observed to be associated with a higher risk of developing SJS/TEN, especially in East Asian populations. For example, the presence of HLA-B*15:02 in the Han Chinese population has been associated with a greater susceptibility to develop SJS/TEN with multiple drugs. Table 2 describes other HLAs considered to be at risk for developing these types of reactions.[2,13–15]

Drug	At-Risk Population	Genetic Predictor
Allopurinol	Han Chinese, Caucasian, Japanese, Thai	HLA-B* 58:01
Carbamazepine	Han Chinese, Taiwanese, Thai, Hong Kong, Malaysian, Indian, Western populations	HLA-B* 15:02 HLA-B* 15:11 HLA-A* 31:01
Phenytoin	Han Chinese, Thai	HLA-B* 15:02
Lamotrigine	Han Chinese	HLA-B* 38:01, HLA-B* 58:01, HLA-B* 68:01, HLA-A* 24:02, HLA-B* 15:02
Sulfamethoxazole	European	HLA-B* 38:02
Trimethoprim/ Sulfamethoxazole	Thai	HLA-B* 15:02 – V*0801
Metazolamide	Korean, Japanese	HLA-B* 59:01 HLA-CW* 1:02

Table 2. HLA genotypes and drugs associated with SJS/TEN. *Certain HLA genotypes have been observed to be associated with a higher risk of developing SJS/TEN, like the HLA-B*15:02, but there is other HLAs to be considered.* Modified from *Cheng L. Current Pharmacogenetic Perspective on Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis*[15]

PATHOPHYSIOLOGY

Although the pathophysiology is not fully understood, it is known with certainty that drugs are the most common triggers.[1,2,5–7] Mycoplasma pneumoniae infection has also been described as a possible cause, but its diagnosis is more common in children. Other atypical bacteria have also been identified, but their frequency is lower.[6,16,17]

The mechanisms that induce cutaneous damage and corneocyte detachment are poorly understood. Immunophenotyping studies of lymphocytes present in the lesions have suggested a type IVc hypersensitivity reaction mechanism mediated by cytotoxic T lymphocytes ($CD8^+$), generating massive corneocyte apoptosis. It has been demonstrated that these lymphocytes are specific to the culprit drug and are directed at the native form of the drug rather than the active metabolite.[1,2,6,16]

Granulysin has been identified as an important mediator in corneocyte apoptosis. Elevated levels of IL-15 have also been found to be related to severity and mortality. Other factors such as Fas ligand, perforin, TNF-alpha, TRAIL, and granzyme B are involved in non-apoptotic pathways and, although elevated in peripheral mononuclear cells and patient lesions, are not specific.[6,13,16]

DIAGNOSIS AND INITIAL EVALUATION

The diagnosis is clinical. Manifestations appear between 5 and 28 days after drug exposure. There may be prodromal symptoms such as general malaise, fever, ocular symptoms, flu-like symptoms, and skin pain that precedes the cutaneous lesions.[1,2,5–7]

Cutaneous symptoms

The initial lesions are irregular, purpuric erythematous macules that affect the face, upper trunk, and proximal areas of the upper limbs while sparing the distal areas and lower limbs. Subsequently, extensive erythema and large, flaccid blisters with a positive Nikolsky sign (epidermal detachment upon slight rubbing of the skin) develop. In 80% of cases, involvement of 2 or more mucous membranes (nasopharynx, oropharynx, eyes, genitals, and anus) occurs before the appearance of cutaneous lesions.[5,7] Mucositis and ulceration of the oral mucosa are observed in 100% of cases. Genital mucosa involvement occurs in 77% of women.[5,6]

Systemic symptoms

Ocular involvement is frequent and can range from mild (stage 1: conjunctival injection and/or chemosis) to moderate (stage 2: pseudomembranous conjunctivitis, reversible conjunctival adhesion, superficial keratitis, conjunctival fornix with slight distortion) to severe (stage 3: corneal ulcer, persistent symblepharon, persistent keratitis, visual acuity loss, persistent conjunctival fornix distortion).[18]

The disease progresses over 7–10 days. Multisystemic involvement can occur with transient elevation of liver enzymes, increased renal function, bronchial epithelial necrosis, and digestive tract involvement.[7] Re-epithelialization takes between 1 and 3 weeks, depending on the extent and severity of the disease. Hyperpigmentation and hypopigmentation occur in most patients. Nails frequently fall off (onychomadesis) and deformities may develop.[6,18,19]

For diagnosis, the presence of at least 3 criteria is required [5]:

- Purpuric macules or atypical targets disseminated and not predominant on the extremities; vesicles, bullae.
- Epidermal detachment (appearance of "wet clothing").
- Nikolsky sign.
- Multifocal mucosal erosions (enanthema, bullae, erosions in the oral cavity, nasopharynx, oropharynx, nose, eyes, or genital/anal area).

Laboratory tests are useful in assessing multisystemic involvement and the severity of the patient.[14,18]

Laboratory test

Initial tests

- Complete blood count, ESR, CRP
- Renal function
- Electrolytes
- Transaminases and coagulation tests
- Blood glucose
- Arterial blood gases and blood ph test
- Chest X-ray
- Biopsies of skin adjacent to a blister for routine histopathology and direct immunofluorescence (to exclude an immunobullous disorder).

Additional test

Consider infectious screening and infectious disease support, depending on the specifics of each case:

- IgG and IgM for Mycoplasma pneumoniae at onset and 3 weeks after symptom onset.
- PCR for *Mycoplasma pneumoniae* from pharyngeal lesions (subject to the availability of each center).
- Serological tests and PCR for other related atypical pathogens such as Chlamydia spp, HSV, EBV, CMV, HHV6, parvovirus B19, varicella zoster, respiratory viruses, adenovirus, and enterovirus.

Complementary tests

- HIV test
- Consider performing ANAs (for underlying lupus), ENAs, soluble nuclear antigens (SSA, SSB).
- Skin lesion studies with biopsy for pathology and direct immunofluorescence are important to support the diagnosis and exclude other pathologies that may have similar clinical presentations.[13,18] Evidence of widespread apoptosis of corneocytes with confluent and patchy cell necrosis in the epidermis, separation of the dermoepidermal junction with subepidermal blister formation, and eosinophil infiltration in the dermis are characteristic findings.[6,14,18]

- It is recommended to perform initial laboratory tests to support the diagnostic suspicion, assess severity due to multisystem involvement, and conduct complementary and additional tests as needed (Grade D recommendation).
- It is recommended to perform biopsies of lesions according to dermatology protocols to exclude other pathologies with similar clinical presentations (Grade D recommendation).

CAUSE EVALUATION

It is extremely important to construct a timeline from drug exposure that preceded the onset of symptoms and the appearance of symptoms and lesions.[13,18] The half-life of the implicated drugs must be considered. In cases where there is doubt about the causative drug, the use of the ALDEN (Algorithm of Drug Causality in Epidermal Necrolysis) system is suggested to facilitate the identification of the responsible drug; however, in up to 15% of cases, the causative drug cannot be identified.[6,18,20]

It is essential to note that lesions appear between day 5 and 28 after exposure to the responsible drug; thus, avoiding re-exposure to the responsible drug is crucial to improving prognosis.[6,18]

The ALDEN system considers 6 criteria to establish a score and determine the likelihood of causality for each drug: latency time, presence of the drug in the body on the day of reaction onset (index day), pre-exposure/re-exposure, type of drug (notoriety), and alternative cause.[20]

The final score can range from −12 to 10, with <0 being very unlikely, 0–1 unlikely, 2–3 possible, 4–5 probable, and >6 very probable (Supplemental Table 1). The final evaluation for each drug is categorized as unrelated if it includes very unlikely, unlikely, and possible, or related if it includes probable and very probable.[20]

Additionally, it is important to note that in the near future, advancements in Artificial Intelligence (AI), as demonstrated in the study by Chongpison et al,[21] are likely to play a pivotal role in SCARs diagnosis by predicting non-immediate drug-induced hypersensitivity through machine learning. The incorporation of AI technology holds out a promise for revolutionizing diagnostic processes, leading to more accurate and timely

identification of SCAR, thereby improving patient outcomes.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis should be made with other diseases that may present with blistering, systemic symptoms and mucosal involvement should always be actively considered.[1,6] These include other SCARs (DRESS and AGEP), bacterial and viral infections (erythema multiforme, staphylococcal scalded skin syndrome). Other conditions that also should be considered are autoimmune diseases (pemphigus vulgaris, bullous pemphigoid, bullous systemic lupus erythematosus, linear IgA dermatosis), paraneoplastic pemphigus and fixed drug eruption.

CLASSIFICATION AND SEVERITY ASSESSMENT

Classification depends on the extent of the affected body surface area. SJS is present when <10% of the total body surface area (TBSA) is involved; TEN involves ≥30%, and overlap syndrome involves 10-<30%.[14,18] The calculation of the affected body surface area can be done according to Wallace's rule of nines or the modified Lund-Browder total body surface area method, the latter being more accurate for children and adults[22] (Fig. 1 and Supplemental Table 2). The palmar method can be used when the involvement is not extensive; it is calculated by assuming that the patient's palm from the wrist edge to the fingertips equals 1% of the TBSA. If considering the palm without the fingers, it equals 0.5% of the TBSA. This method can be used at any age.[22]

During the acute phase, mortality ranges from 10% to 40%, depending on the extent of the affected body surface area. The main cause of death is sepsis and post-infectious multiple organ failure or pulmonary involvement. The SCORTEN score is a mortality prognostic tool developed in 2000 by a group of researchers in France.[23] This study was conducted using an initial sample of

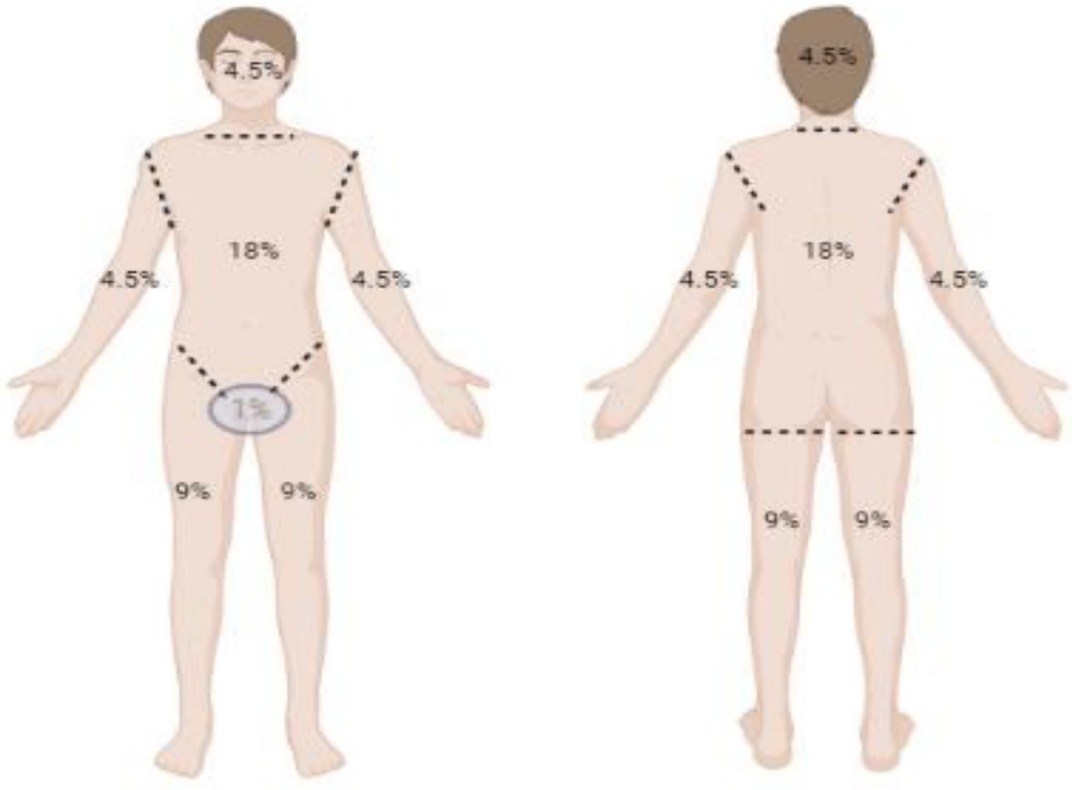

Fig. 1 Wallace's rule of 9 for calculating body surface area burned. Calculation of the affected body surface area for SJS/TEN according to Wallace's rule of nines, where head and neck represents 9%, trunk and back 18% each, upper extremities 9% each, lower extremities represent 18% each, and genitals represents 1% of the total body surface area.

165 patients to identify significant variables through a logistic regression model, followed by internal validation with an additional 75 patients.[23,24] The researchers identified seven parameters considered risk factors, assigning one point to each and summing only those present in the patient, as detailed in Table 3. This score is calculated at the time of admission and is recommended to be reevaluated on days 1 and 3 of hospitalization, predicting a mortality risk ranging from 3.2% to 90.0%.[18,25,26] It has been demonstrated that SCORTEN can overestimate expected mortality, resulting in a positively biased estimation of the efficacy of any intervention.[27]

MANAGEMENT AND TREATMENT RECOMMENDATIONS

Supportive care (UK 2022-Delphi consensus, JAAD 2020, and French protocol 2018–2021 PED)

There is no consensus on best practices and specific modalities for supportive care. The 2 most recent supportive care consensuses, UK 2022 and JAAD 2020,[5,6,28–31] emphasize the importance of timely referral of these patients to a specialized center where they should be managed in an intensive care unit experienced in burn patient management. Additionally, healthcare personnel should be trained in managing patients with skin loss and exposed body surfaces. Fig. 2 shows the proposed management algorithm for this guideline.

- To date, supportive care is the cornerstone of management in adult and pediatric patients, as studies have shown that adequate supportive care reduces mortality and improves prognosis (Grade C recommendation).

It is essential to involve various specialties in the patient's management to ensure a multidisciplinary approach and increase awareness in identifying the patients.[6,28–30] Although there is no complete agreement regarding the specialties that should be involved, it has been described that the participation especially of allergists, as it is not only a cutaneous

Criterion		Score
Age	≥40 years	1
Cancer	Yes	1
TBSA involved	≥10%	1
Tachycardia	≥120 bpm	1
Urea nitrogen	>28 mg/dL (10 mmol/L)	1
Glycemia	>252 mg/dL (14 mmol/L)	1
Serum bicarbonate	<20mEq/L (20 mmol/L)	1
Total		**7**
Mortality risk		
0–1		3%
2		12%
3		35%
4		58%
≥5		90%

Table 3. SCORTEN score. *The SCORTEN score is a critical tool for assessing mortality risk in patients with SJS/TEN. Is recommended to be reevaluated on days 1 and 3 of hospitalization. Modified from Ingen- Housz-Oro. et al.*[5]

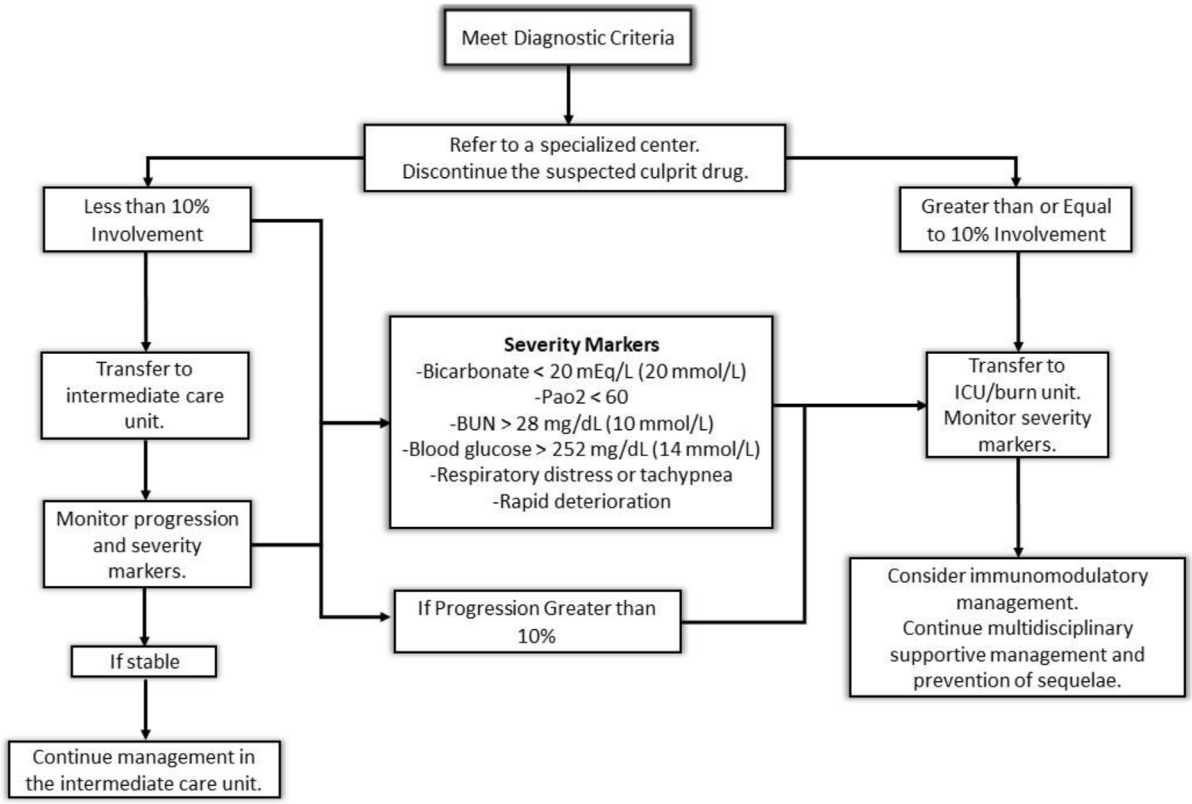

Fig. 2 Treatment recommendations SJS/TEN flowchart. Shows the proposed management algorithm for SJS/TEN, based on the best available evidence.

disease, but also dermatologists, internists, intensivists, ophthalmologists, and other specialties according to the particular needs of each case is very important.[6,28–31]

Immediate discontinuation of the responsible drug improves the disease prognosis (Level of evidence B).

- It is recommended to initially identify the suspected drug through a directed interrogation using the ALDEN algorithm if there are doubts or multiple drugs involved.

Chronic medications that are not suspected should not be discontinued during the acute phase management to prevent complications of underlying diseases.[6,28–31]

Infection prevention[5,6,28–31]

- Adherence to hand hygiene and the WHO 5 Moments for Hand Hygiene (before touching a patient, before a clean/aseptic task, after body fluid exposure risk, after touching a patient, after touching patient surroundings) is crucial for infection prevention. Additionally, follow other measures such as the use of single-use non-sterile gloves, facial masks, and antiseptics (Grade D recommendation).
- Prophylactic antibiotic treatment is not recommended, and antimicrobials should only be administered if there are signs of infection (Grade D recommendation).
- Due to the high risk of infection, if symptoms suggest it, a bacteriological study with skin culture may be required until epithelialization is achieved. Additionally, follow-up with urinalysis monitoring for nitrites, leukocyte esterase, urine culture, and blood cultures, especially if there are signs of sepsis (Grade D recommendation).
- Routine use of topical antibiotics is not recommended unless necessary based on microbiological cultures of affected areas (Grade D recommendation).
- Routine use of silver sulfadiazine is not recommended (Grade D recommendation).

- Daily antiseptic topical management is recommended (as an option with chlorhexidine for bathing) (Grade D recommendation).
- Severe TEN has a significant association with pulmonary infection (Grado D recommendation).
- Fibrobronchoscopy evaluation is suggested in cases of dysphonia, dyspnea, and progression of pulmonary involvement (Grade D recommendation).
- If the patient presents with diarrhea, it should be managed to prevent wound contamination (Grade D recommendation).

Hydro-electrolytic management[5,6,28–31]

- Fluid replacement should be adjusted to the patient's needs. Patients with TBSA involvement greater than 30% will require larger quantities for replacement (Grade D recommendation).
- Peripheral catheters are the preferred vascular access, preferably placed in unaffected skin and should be secured with non-adhesive materials (Grade D recommendation).
- Strict daily monitoring of electrolytes and fluid balance is recommended, increasing the frequency of monitoring according to the patient's clinical severity (Grade D recommendation).
- Consider placing a urinary catheter to quantify diuresis (Grade D recommendation).
- Fluid administration should be titrated to achieve a urine output of 0.5–1 mL/kg/hour (Grade D recommendation).
- The amount of fluids needed is calculated using various formulas. The French management protocol by Ingen-Housz-Oro et al[5] proposes using the modified Brooke formula, considering that these patients have less fluid loss than adult burn patients (Grade D recommendation). Modified Brooke formula: Volume for the first 24 h: 1.5 mL x % of affected body surface area x weight in kg.
- In case of shock and/or renal failure, hemodynamic monitoring is suggested. Non-invasive monitoring is recommended to limit the risk of catheter-related infections (Grade D recommendation).
- Manage hypovolemic shock if required before calculating maintenance fluids. (Grade D recommendation).
- In pediatric patients, it is recommended to quantify fluid balance, fluid replacement according to balance and urine output, and monitor sodium levels. In severe cases, it is important to assess hypoperfusion by monitoring lactate, base excess, BUN, and electrolytes. Additionally, increase oral fluid administration as much as possible (Grade D recommendation).

Airway management[5,6,28–31]

- During the acute phase, there is a high risk of respiratory failure due to upper and lower respiratory tract involvement (Grade D recommendation).
- Nasal evaluation should be part of the routine physical examination during the initial assessment and daily follow-up in the acute phase (Grade D recommendation).
- Arterial blood gas analysis and chest X-ray should be performed upon patient admission (Grade D recommendation).
- Tracheobronchial involvement should be suspected in the presence of productive mucopurulent cough, hemoptysis, dyspnea, hypoxemia, or radiological abnormalities (Grade D recommendation).
- Non-invasive mechanical ventilation is contraindicated (Grade D recommendation).
- About 25% of patients require orotracheal intubation and mechanical ventilation. Difficult orotracheal intubation due to laryngeal involvement should be anticipated. Orotracheal intubation should be performed by personnel trained in managing difficult airways whenever possible (Grade D recommendation).

Temperature control and hypothermia prevention[5,6,28–31]

- The room temperature should be maintained between 28 and 32 °C to avoid heat loss and hypothermia (Grade D recommendation).

Nutritional support[5,6,28–31]

- Early enteral nutrition is recommended via the oral route, unless esophageal involvement is documented. Enteral nutrition reduces the occurrence of stress gastric ulcers, bacterial translocation, and intestinal-origin infections (Grade D recommendation).
- Avoid placing a nasogastric tube if there is nasopharyngeal mucosal involvement (Grade D recommendation).
- Patients on enteral nutrition do not require medications for stress gastric ulcer prevention. If required, due to a high risk of bleeding (coagulopathy, respiratory failure, renal replacement therapy, liver disease, 3 or more comorbidities), proton pump inhibitors are preferred over H2 blockers (Grade D recommendation).
- A caloric intake of 20–25 kcal per kg of dry weight per day is suggested for the first week (acute phase), increasing to 25–35 kcal per kg of weight after the first week (Grade D recommendation).
- Monitor glucose levels frequently, adjusted to the specifics of each case. It is suggested to monitor every 4–6 h in case of metabolic stability (Grade D recommendation).
- Intravenous insulin should be initiated if two consecutive glucose measurements exceed 180 mg/dL, aiming for a glucose level of $\leq$180 mg/dL. Glucose monitoring should be done every 2 h until stable values are obtained (Grade D recommendation).
- In pediatric patients, early enteral nutrition with a nasogastric or nasojejunal tube is also recommended, if necessary, with nutritional lab evaluations every 24 h or according to established protocols. It is necessary to monitor weight weekly at a minimum and involve pediatric nutritional support personnel (Grade D recommendation).

Ocular management[6,18,28–31] (French consensus on ocular management)

- An ophthalmological evaluation should be performed within the first 24 h of the acute phase to determine initial treatment, maintenance, and follow-up frequency (Grade D recommendation).
- Protection and lubrication of the cornea and ocular surface are recommended to avoid complications such as symblepharon. The use of artificial tears without preservatives and/or vitamin A ophthalmic ointment should be administered every 2 h (Grade D recommendation).
- As there is no consensus among management groups on the use of topical steroids, this guideline recommends that only an ophthalmologist should indicate their use (Grade C recommendation).
- Ophthalmic antibiotic therapy, symblepharon management, pseudomembrane debridement, and ocular amniotic membrane transplantation may be necessary and should be performed according to ophthalmology consultation during the acute phase (Grade C recommendation).

Skin management[6,28–32]

- Determine the percentage of affected body surface area, considering skin detachment or positive Nikolsky sign (Grade D recommendation).
- Management should be conservative, with daily care, but individualizing each case to minimize the risk of infection, insensible fluid losses, and pain (Grade D recommendation).
- Blisters and vesicles may be drained only for comfort. The detached epidermis should not be removed as it should serve as a biological cover (Grade D recommendation).
- Surgical debridement should only be performed if conservative treatment fails and should never be considered as the first management option (Grade D recommendation).
- Regular cleaning of lesions with sterile water, saline solution, or diluted chlorhexidine (1/5000) should be performed with dressing changes (Grade D recommendation).
- After washing and disinfecting with antiseptics, the affected areas should be fully covered with non-adherent or vaseline-impregnated gauze dressings (Grade D recommendation).
- Limit epidermal trauma by avoiding the use of sphygmomanometer cuffs, adhesive ECG leads

and electrodes, adhesive dressings, or wrist identification tags (Grade D recommendation).

- Avoid unnecessary skin manipulation (clothing changes), minimize friction as much as possible, and use devices such as a fluidized air bed if available (Grade D recommendation).

Oral mucosa management[6,28–31]

- The mouth should be examined as part of the initial evaluation during the acute phase and should be assessed daily (Grade D recommendation).
- Oral rinses containing antimicrobials should be applied twice daily, and topical anesthetic (such as 2% lidocaine jelly) every 3 h and before cleaning (Grade D recommendation).
- Consider the use of chlorhexidine in oral rinse presentation (Grade D recommendation).
- Gently clean the mouth daily with warm saline solution or a lip sponge to remove debris and prevent crust accumulation (Grade D recommendation).
- Apply vaseline to the lips every 2 h during the acute phase (Grade D recommendation).
- Consider the use of a hyaluronic acid-based mucoprotective agent as needed to reduce pain (Grade D recommendation).

Genital mucosa management[6,28–31]

- Perform a urogenital examination as part of the initial evaluation during the acute phase, preferably by a gynecology-urology specialist (Grade D recommendation).
- Prevent adhesions by daily retraction of the foreskin and applying vaseline twice daily to the glans, encouraging and educating the patient to perform this themselves if possible (Grade D recommendation).
- Apply vaseline to the labia minora, and if possible, to the intravaginal mucosa using gauze, a tampon, or a lubricated condom to prevent adhesions. If this is not possible, use a device for application twice daily. In virginal patients, use smaller vaseline-coated devices, encouraging and educating the patient to perform this themselves if possible (Grade D recommendation).
- A local anesthetic such as 2% lidocaine jelly can be used on the vaginal introitus and glans for pain management (Grade D recommendation).
- Consider the topical use of high-potency steroids in cases of significant genital mucosa inflammation, with gradual reduction based on clinical response (Grade D recommendation).
- Based on gynecology consultation, consider alternating the use of topical steroids and estrogens to promote vaginal mucosa healing and prevent synechiae (Grade D recommendation).

Pain management[6,28–31]

- Pain assessment is a priority and should be evaluated every 4 h, especially during wound care. It is suggested to use a visual analog scale for pain assessment (Grade D recommendation).
- For mild pain, acetaminophen should be used. If this is not sufficient, consider starting opioids such as tramadol. If pain persists, the use of potent opioids such as fentanyl or morphine, either enteral release, intravenous infusion, or patient-controlled analgesia (PCA), is suggested according to pain management protocols (Grade D recommendation).

Thromboprophylaxis[6,22,25,28,29]

- Thromboprophylaxis is suggested unless contraindicated (Grade D recommendation).

Prevention of emotional stress[6,28–31]

- Active prevention of post-traumatic stress should be considered necessary, requiring psychological and/or psychiatric evaluation in selected cases (Grade D recommendation).

Specific immunomodulatory treatment

Currently, there are no standardized recommendations or specific immunomodulatory treatment guidelines for SJS/TEN and overlap syndrome.[32] Based on the available evidence, specific immunomodulatory management cannot be recommended due to the differing results reported in the literature. Additionally, studies have been primarily limited by the few randomized clinical

trials (RCTs) available for analysis, with most being observational, retrospective studies with risk of bias, heterogeneity, and difficulties in analyzing patient comorbidities in relation to mortality outcomes. Moreover, it has been suggested that the inclusion of the SCORTEN score may overestimate mortality risk, potentially leading to biases. The "center effect" has also been described, where better outcomes are observed in reference centers.

Clinical evidence

The search revealed that the available international management guidelines considering immunomodulatory treatment do not make a specific recommendation due to the low quality of the evidence. A search was conducted according to the hierarchy of evidence, analyzing meta-analyses and systematic reviews, emphasizing those found from 2018 to May 2022. The search results are summarized in Table 4.

Biological treatment

Focus has been on TNF-alpha inhibitors, as it has been suggested that they may upregulate granulysin gene expression, which is the most notable mediator in corneocyte detachment and apoptosis. Additionally, an increase in regulatory T lymphocytes has been described following TNF-alpha inhibitors administration in patients with SJS/TEN. Some studies have suggested that etanercept could reduce mortality and re-epithelialization time in patients with TEN.

The efficacy of etanercept was evaluated in a 2018 randomized, nonblinded trial involving 91 patients. This study compared etanercept (25 or 50 mg twice weekly) with intravenous prednisolone (1–1.5 mg/kg/day). Mortality was lower with etanercept (8.3%) than with corticosteroids (16.3%), but without statistical significance.[33] The observed mortality in both groups was lower than predicted by SCORTEN. The time to reepithelialization was shorter with etanercept (14 days) compared to corticosteroids (19 days). Serious adverse events occurred in 13% of patients with etanercept and 27% with corticosteroids, though these were considered unrelated to treatment except for gastrointestinal bleeding. This study supports the use of etanercept for SJS/TEN, but further research is needed to confirm these findings and determine the optimal dosage and treatment duration.

Zhang et al[34] performed a systematic review focusing on etanercept and infliximab in SJS and TEN, analyzing 27 studies. They reported that TNFα inhibitors, used primarily as first-line monotherapy or second-line after systemic treatment failure, achieved a high response rate (86.8%) with few complications. However, they stressed the need for more RCTs to strengthen the evidence base. TNFα inhibitors appear to be safe and effective treatments for SJS/TEN, pending further high-quality research.

A Cochrane review from 2022, encompassing nine studies involving 308 patients, suggested that treatment with etanercept might reduce mortality compared to systemic corticosteroids, albeit with low-certainty evidence.[13] A search according to the hierarchy of evidence from 2018 to June 2021 found two systematic reviews. Table 5 describes the systematic reviews found.

Clinical evidence

The systematic reviews evaluating the use of biologics as a primary intervention in these cases are scarce. In addition to the limitations described for studies evaluating specific immunomodulators, there is not enough bibliographic support to recommend them routinely in the management of SJS/TEN. However, there is a need for further controlled clinical trials to strengthen the evidence base and determine optimal management strategies, including dose optimization and combination with other immunomodulatory treatments in different clinical scenarios.

Recommendations for systemic treatment

Question: For the treatment of SJS/TEN, is combined therapy with IVIG (human Immunoglobulin G) and corticosteroids more effective compared to corticosteroids as monotherapy?

Meta-analysis and Systematic Reviews	
Jacobsen A. et al. 2022.[13]	A Cochrane systematic review evaluated systemic interventions in SJS, TEN, and overlap syndromes. The primary outcomes were mortality within the first month after diagnosis, excluding other causes or therapy-related adverse effects within the first month of treatment. Secondary outcomes included hospital stay, re-epithelialization time, and sequelae. The review included 9 studies: 3 randomized clinical controlled trials (RCTs) and 6 prospective observational comparative studies. Additionally, a quantitative meta-analysis included 2 studies. With a total of 308 patients from seven countries, the researchers found that most studies did not report the duration of the study or follow-up time. Only one of the 3 RCTs was considered to have a low risk of bias across all domains. All prospective observational comparative studies had a high risk of bias. The authors concluded that compared to corticosteroids, etanercept might reduce mortality. For comparisons between corticosteroids versus no corticosteroids, IVIG versus no IVIG, and cyclosporine versus IVIG, the certainty of the evidence for mortality was very low. They indicated that more multicenter studies focused on the most important clinical comparisons are needed to provide reliable answers.
Krajewski A. et al. 2022[35]	A meta-analysis with meta-regression of observational studies evaluated the impact of various treatments on mortality as the primary outcome and hospital stay and re-epithelialization time as secondary objectives. They included forty-two studies, of which only one was an RCT, with a total of 1942 patients. Patients received cyclosporine, steroids, etanercept, and plasmapheresis. Seventeen studies had at least 2 treatments. The risk of bias for the observational studies and the RCT was high. They performed a random-effects model due to the heterogeneity of the analyzed studies. The lowest mortality rate was found in the etanercept group, followed by those receiving cyclosporine. The highest was for plasmapheresis and IVIG. Re-epithelialization took an average of 12.3 days, being slower for cyclosporine and faster with steroids. The average hospital stay was 19.9 days, longer with the use of plasmapheresis or plasmapheresis plus IVIG, and shortest with the use of corticosteroids. Finally, the authors emphasize that there are no high-quality studies in the management of this pathology.
Patel et al., 2021[36]	A network meta-analysis was conducted for TEN and overlap syndrome NET-SJS to evaluate interventions that reduced mortality. They included randomized controlled and observational studies with $\geq$5 patients. They assessed a total of 24 studies: 18 retrospective, 3 prospective, 2 RCTs, and 2 prospective retrospective. Sixteen studies had a high risk of bias, as most did not describe details of ineligible or eligible patients who refused to participate. In direct and indirect comparisons, they obtained a higher SUCRA (surface under the cumulative ranking curve used to determine which treatment has the highest probability of being the best) for cyclosporine, followed by the combination of steroid + IVIG, etanercept, steroid alone, IVIG alone, supportive care, and thalidomide, with the latter associated with higher mortality compared to supportive care

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Meta-analysis and Systematic Reviews	
	alone. The rest of the comparisons were not statistically significant.
Torres-Navarro. et al. 2021[26]	A systematic review and network meta-analysis evaluated the effectiveness of immunomodulatory management for TEN and SJS using SCORTEN, with the primary outcome being a reduction in mortality. They included 38 studies and performed a random-effects model due to the heterogeneity of the analyzed studies. The risk of bias assessment revealed concerns for the IGIV group but not for the supportive care, cyclosporine, corticosteroids, and corticosteroid + IVIG groups. In the meta-regression analysis, they found that the combination of corticosteroid + IVIG and cyclosporine alone reduced mortality. For the network meta-analysis, they conducted 14 direct comparisons, and although the estimates did not achieve significant reductions in mortality, they did show that cyclosporine, corticosteroid + IVIG, and etanercept reduced mortality compared to corticosteroid or IVIG alone. The authors noted that these findings are consistent with the EuroSCAR cohort, where lower mortality was found in 40 patients treated with corticosteroid + IVIG compared to 35 patients receiving IVIG alone. No increased mortality was observed with corticosteroid use, like the RegiSCAR study. Regarding cyclosporine, they highlighted an open phase 2 study showing survival benefits using doses of 3 mg/kg/day for 10 days, along with other inconclusive studies reporting lower mortality compared to IVIG, plasmapheresis, and thalidomide. However, they caution that this treatment tends to be used in younger patients without comorbidities, especially those of renal origin. For etanercept, they mentioned that at the time of the systematic review, only 2 studies had used this drug with varying doses, insufficient for a recommendation. Finally, they emphasized the absence of prospective controlled studies, as the analyzed studies were of low- quality evidence, with differences in treatment administration and patient comorbidities affecting mortality.
Tsai Y. et al. 2020[37]	A network meta-analysis and systematic review also evaluated immunomodulatory management for reducing mortality in TEN and overlap syndrome. They included 77 studies with 2079 patients. Most of the included studies were case series or retrospective comparative studies, with only 3 RCTs and 6 comparative studies. In the SUCRA analysis, none of the treatments was superior to supportive care in reducing mortality, and thalidomide was associated with higher mortality. However, in a study-by-study review without using SUCRA, the authors suggested that cyclosporine and etanercept might be promising, with potential survival improvement with the corticosteroid + IVIG combination. This meta-analysis has limitations, as most analyzed studies were retrospective, but the bias assessment was not significant, and the analyses found no inconsistencies in the publication.
(Xian Q. et al., 2018[38]	A meta-analysis of cyclosporine for SJS and TEN evaluated mortality as the primary outcome. They included 9 studies with 358 patients: Seven retrospective case series, one open phase 2 study, and one prospective study. The bias assessment revealed indications of bias. They performed a fixed-effects

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Meta-analysis and Systematic Reviews	
	model due to the homogeneity of the analyzed studies. The 9 studies revealed a significant reduction in mortality risk, with good overall drug tolerance, even in critically ill patients. The authors highlight the need for double-blind randomized trials to confirm the intervention's efficacy.

Table 4. **Meta-analysis and systematic reviews of specific immunomodulatory treatments in SJS/TEN**. *Search results about immunomodulatory treatment in SJS/TEN, analyzing meta-analysis and systematic reviews, emphasizing in those found from 2018 to May 2022*

Systematic Reviews	
Ponzo MG. et al. 2021[39]	A systematic review evaluated the management of biologicals etanercept, infliximab, and adalimumab as monotherapy and in combination with other systemic therapies (eg, systemic corticosteroid, IVIG) in patients with SJS and TEN. They included 38 studies: 27 case reports, 6 case series, 3 retrospective reviews, and 2 RCTs. The average age of participants was 46.4 years, with an average body surface area involvement of 31%. The outcomes evaluated were actual mortality compared to that predicted by SCORTEN, time to re-epithelialization, and cessation of epidermal detachment. They also assessed reported adverse events. The risk of bias in the included RCTs was low.[33,39] The authors concluded that due to the heterogeneity of the studies, a meta-analysis could not be performed. However, they highlighted that management, whether as monotherapy or in combination with other immunomodulators, appears to be effective, with the standout being the Wang et al RCT, which had a low risk of bias,[33] this study compared the use of prednisone at doses of 1–1.5 mg/kg/day versus etanercept 25–50 mg (>65 Kg) twice a week for 1 week (dose interval 3–4 days). In the etanercept group, 48 patients had faster re-epithelialization (14 vs. 19 days) and fewer adverse events, specifically gastrointestinal bleeding, compared to the corticosteroid group. Eleven patients died from sepsis or respiratory failure: 4 in the etanercept group and 7 in the corticosteroid group. These results were like those described in most of the case series reviewed.
Zhang et al. 2019[34]	A systematic review evaluated the efficacy and safety of the biologicals etanercept and infliximab in patients with SJS and TEN. They analyzed 27 studies: 21 case reports, 4 case series, and 2 RCTs; a total of 91 patients were included, of which 24 received infliximab (300 mg single dose) and 67 etanercept (50 mg single dose or 2 doses in 1 week). The management protocol included TNFα inhibitors as first-line monotherapy and after the failure of response to a systemic treatment (e.g., corticosteroid, IVIG, and cyclosporine), or in combination with another systemic therapy (systemic corticosteroid, IVIG, or N-acetylcysteine) as second-line treatment. In the first-line management group, for infliximab, they analyzed 6 case reports and for etanercept, a case series of 10 patients and an RCT.[26] In the second-line management group, for infliximab, they reviewed a case series of 2 patients, another with 3 patients, an RCT with 5 patients[39]), and 9 case reports. In this group, only 2 patients died. Overall, seventy-nine patients (86.8%) responded well to the biologicals evaluated, and there were few side

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Systematic Reviews	
	effects or complications. They did not describe the evaluation of the included studies. Based on the described information, the authors concluded that TNFα inhibitors could be safe and effective for the treatment of SJS/TEN, but more RCTs are needed to provide accurate and higher quality evidence.

Table 5. Systematic reviews of Anti-TNFα management in SJS/TEN. *Systematic reviews found from 2018 to June 2021, about treatment with Anti-TNFα in SJS/TEN*

Conditional in favor	**Recommendation** En In patients with SJS/TEN, combined therapy of systemic corticosteroids and IVIG is suggested. **Certainty of the evidence**: Very low (expert consensus).

DISCUSSION

The Latin American guidelines for the diagnosis and treatment of SJS and TEN present a comprehensive approach tailored to the unique needs and contexts of Latin American populations. These guidelines fill a critical gap, as there were no prior region-specific guidelines addressing these severe cutaneous adverse reactions.

The guidelines cover various critical aspects, including the clinical diagnosis, identification of culprit drugs using the ALDEN system, and management and treatment strategies. Notably, provide detailed recommendations on supportive care, the use of corticosteroids, immunomodulatory treatments, and emerging biologics, reflecting the latest evidence and consensus among Latin American experts, including both allergists and dermatologist.

One significant difference between these guidelines and others, such as those from North America and Europe, is the emphasis on regional epidemiology and specific drug causality profiles. For instance, the higher prevalence of anticonvulsant-induced SJS/TEN in Latin America necessitates tailored recommendations for drug monitoring and patient management. Additionally, the guidelines incorporate the SCORTEN score, a critical tool for assessing mortality risk, with a recommendation to calculate it on days 1 and 3 of hospitalization to monitor disease progression and adjust treatment plans accordingly.

The guidelines also recognize the future role of artifical intelligence (AI) technology in improving diagnostic accuracy and patient outcomes. By incorporating AI technology, healthcare providers may be able to achieve more timely and accurate identification of SJS/TEN, improving patient safety and treatment efficacy.

A noteworthy aspect of these guidelines is the discussion on biologic therapies, such as TNF-alpha inhibitors, which show promise in reducing mortality and re-epithelialization time in SJS/TEN patients. The guidelines recommend further research and clinical trials to validate the efficacy and safety of these treatments. Provide a nuanced view of the current evidence, acknowledging the limitations of existing studies while highlighting the potential benefits of biologics in managing severe cutaneous adverse reactions.

In conclusion, these Latin American guidelines offer a vital resource for healthcare professionals managing SJS/TEN. By addressing region-specific needs and incorporating the latest advancements in diagnostics and treatment, they aim to improve patient outcomes and standardize care across Latin America. Future updates should continue to integrate emerging evidence and technological advancements, ensuring that the guidelines remain relevant and effective in guiding clinical practice.

Abbreviations

SJS, Stevens-Johnson syndrome; TEN, Toxic epidermal necrolysis; ALDEN, Algorithm of Drug Causality for Epidermal Necrolysis; SCARS, Severe cutaneous adverse reactions; PICO questions, Patients, Intervention, Comparison, Outcomes; AGREE II, Appraisal of Guidelines,

Research and Evaluation for Europe II; DRESS, Drug Reaction with Eosinophilia and Systemic Symptoms; AGEP, Acute Generalized Exanthematous Pustulosis; RegiSCAR, European Registry of Serious Adverse Skin Reactions; HIV, Human immunodeficiency virus; NSAIDs, Non-steroid anti-inflammatory drug; ASA, Acetylsalicylic acid; CTLA-4, Cytotoxic T-Lymphocyte Antigen 4; HLA, Human leukocyte antigens; TNF-alpha, Tumor necrosis factor-alpha; TRAIL, TNF-Related Apoptosis Inducing Ligand; ESR, Erythrocyte sedimentation rate; CRP, C-reactive protein; HSV, Herpes Simplex Virus; EBV, Epstein-Barr virus; CMV, Cytomegalovirus; HHV6, Human herpesvirus 6; ANAs, AntiNuclear Antibodies; ENAs, Anti-extractable nuclear antigens; AI, Artificial Intelligence; TBSA, Total body surface area; ECG, Electrocardiogram; SCORTEN, SCORe of Toxic Epidermal Necrolysis; JAAD, Journal of the American Academy of Dermatology; WHO, World Health Organization; BUN, Blood urea nitrogen; PCA, Patient-controlled analgesia; RCTs, Randomized clinical trials; IVIG, Human Immunoglobulin G.

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Author contributions
All authors participated in the design and the development of the present study.

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The study was approved by the ethics committee, and all the data contained in it is available with the authors.

Authors' consent for publication
All authors wrote, read, approved, and consented to the publication of this manuscript.

Declaration of competing interest
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Appendix A. Supplementary data
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