VANDERBILT UNIVERSITY MEDICAL CENTER

Guideline: Management of patients with suspected Stevens-Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN)

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Table of Contents

Introduction

Stevens-Johnson syndrome (SJS) and Toxic epidermal necrolysis (TEN) are rare (1-10 per million people per year) severe, life-threatening mucocutaneous reactions characterized by painful erythematous rash, bullae, and erosions secondary to T-cell mediated hypersensitivity. They typically follow medication changes but may also be secondary to infection or idiopathic. Characteristic features include a prodrome of fever and lethargy followed within weeks to days of inciting event, presence of coalescent erythematous macules with purpuric centers, painful/tender blistering and epidermal detachment which is worse with light pressure (Nikolsky's sign), and ocular and mucosal involvement. SJS is defined as < 10% TBSA, TEN is >30% TBSA, and between 10%-30% is the ill-defined SJS-TEN overlap. TBSA includes blistered/detached skin and Nikolsky's sign positive (detachable) skin, but not all areas of erythema.

Acute complications include infection, fluid losses, sepsis, and shock, as well as pneumonia, dysphagia, renal dysfunction, hepatitis, and death (20-30%). Ocular complications, mucosal stenosis (tracheal, esophageal, anal, vaginal, etc.), scarring, hypo- and hyper-pigmentation, as well as other skin and nail changes may occur in the chronic setting among survivors. [iii]

Objectives

Provide guidance on the initial workup of patients with suspected SJS/TEN. Providesuggested management of patients with confirmed SJS/TEN.

Scope

Standardizing the workup and management of patients with confirmed or suspectedSJS/TEN.

Audience

All providers caring for burn patients

Guidance

I. Management of referrals from outside hospitals via Access Center
   A. *If referral is from an ED*:
      - Standard access center call will take place with the addition of photographs of the affected areas emailed to the access center and forwarded to the burn surgeon and dermatology resident and attendingon call.
      - Burn surgeon and dermatology resident/attending on-call will review and if they believe the diagnosis is possible, burn surgery will accept transfer to VUMC ED or directly to Burn ICU for evaluation and management.
      - If Burn surgeon and dermatology resident/attending on-call do not believe that the diagnosis is SJS/TEN, dermatology will provide furtherinput on appropriate management.
      - If there is any discrepancy, the patient may be transferred to the ED for evaluation and appropriate disposition. Burn surgery and dermatology will be consulted to make a determination.
   B. *If referral is from an inpatient unit WITH biopsy-confirmed SJS/TEN:*
      - Patient will be accepted as a direct admit to the BICU using standard operating procedures.

C. *<u>If referral is from an inpatient unit WITHOUT biopsy-confirmed SJS/TEN:</u>*

- Standard access center call will take place with the addition of photographs of the affected areas emailed to the access centerand forwarded to the burn surgeon and dermatology resident and attending on-call.
- Burn surgeon and dermatology resident/attending will review and if they believe the diagnosis is possible, the burn surgeon will accept as a direct admit to the BICU. Definitive diagnosis will be pursued in Burn ICU and patients with proven alternative diagnoses will transfer to medicine/medical ICU with dermatology consult following
- If Burn surgeon and dermatology resident/attending on-call do not believe that the diagnosis is SJS/TEN, dermatology will provide furtherinput on appropriate management.

II. Initial Evaluation of the patient with possible SJS/TEN

A. Primary Survey (ABCs)

B. Complete history and physical exam paying particular attention to current medications, recent medication or dosing changes, recent illnesses, timing and progression of rash, history of independent risk factors for SJS and TEN (including immunosuppression/HIV, active cancer, common causative agents). Exam should include evaluation of the type of rash, presence and coalescence of blisters, presence of a Nikolsky's sign, and percent %TBSA that has sloughed, or would with slight pressure. Ocular and mucosal involvement must also be evaluated.

C. Recommend that all patients with suspected SJS/TEN should have a consultby the burn surgery team. The burn surgery resident should staff the case with the burn fellow and burn surgeon in a prompt manner.

D. The hallmark of appropriate care is *immediate* cessation of offending agent and initiation of supportive care. When the offending agent is not obvious, the Algorithm for assessment of drug causality in epidermal necrolysis (ALDEN) mechanism may be employed (Appendix A)[iii].

E. In patients in whom SJS/TEN is the likely diagnosis, the patient should be admitted to the burn ICU.

1. Airway/Breathing: Sloughing of the oral mucosa or bronchial tree can present a significant problem for the maintenance of an airway and appropriate gas exchange. Patients with difficulty controlling their secretions and/or difficulty phonating or with a muffled voice shouldbe considered for intubation in addition to those patients that meet traditional criteria for intubation and mechanical ventilation.
2. Circulation: Patients with SJS/TEN DO NOT require aggressive fluid resuscitation unlike a patient with a large thermal burn. Fluid resuscitation should be based on the patient's physiologic status atthe time of admission and their response to fluid administration.[iv] For adults, a urine output of 0.5cc/kg/hr is adequate. In patients with >20%TBSA involved, a Foley catheter should be placed for monitoring urine output.
3. Severity: The Severity-of-illness score for TEN (SCORTEN) is a highly accurate predictive model for mortality and should be calculated on the day of admission. (Appendix B).[v] Factors contributing to this include the following:
    i. Age>40
    ii. Malignancy
    iii. Tachycardia
    iv. >10% TBSA
    v. Serum urea >10mmol/L
    vi. Serum glucose >14mmol/L
    vii. Serum bicarbonate <20mmol/L
4. Consultations:
    i. Dermatology: This is a *required* consult for all suspected casesof SJS/TEN
    ii. Ophthalmology: This is a *required* consult for all patients with SJS/TEN.[vi]
    iii. Gynecology: In female patients with concern for involvementof

their vaginal or labial mucosa, a gynecology consultation is recommended for evaluation and *possible* management with vaginal dilators and/or packing as well as steroid cream.

iv. Urology: A Foley catheter should be placed for patients with difficulty urinating (dysuria, hematuria, inability to void) as they may have sloughing of their GU tract. In this case, a urology consultation should be placed at time of Foley insertion to manage a potential urethral stricture.

5. Nutrition: If possible, oral feeding should be continued after admission. If a non-intubated patient is unable to swallow or unable to consume adequate calories (for example, in severe stomatitis), a feeding tube should be placed and tube feeds started. All intubated patients should have a feeding tube placed and tube feeds started onadmission.
6. Wound management: Based on % open TBSA
    i. For <20% TBSA: The blisters should be unroofed and the sloughed skin should be debrided gently. No intact skin should be debrided. The open areas should be covered in Bacitracin and Xeroform gauze, a silver-based dressing, allograft, or other appropriate dressing. The patient should be made NPO at midnight for possible need foroperative intervention should the sloughing extend to ≥20% TBSA.
    ii. For ≥20% TBSA, early consideration is encouraged for operative debridement of all of the blisters/sloughed skin and placement of appropriate epidermal substitute. Many reasonable agents are available at the burn surgeon's discretion.
    iii. Rapid worsening of cutaneous or systemic symptoms may drive operative debridement and skin substitute, even if the patient's TBSA is ≤20%. This is at the discretion of the burn surgeon.
7. Systemic Management: Administration of corticosteroids and immunoglobulins is not widely supported, and the data is controversial due to possible associations with worsening mortality and failure to re-epithelialize. Cyclosporine A and Etanercept are promising and, in the correct patients, may represent the future of routine care. Decisions on the use of these agents must be discussed between the burn surgeon and dermatology, as well as the intensivist.
8. Research: Multiple, concurrent clinical trials are occurring on this patient population and every patient suspected of having a diagnosis of SJS or TEN must be screened by the research teams. As soon as the patient is accepted or arrives, the research team must be paged at (615) 831-4277. If the patient is coming from outside the hospital, any information about them should be relayed to the research team by phone and by email (sjs@vumc.org), as appropriate (i.e., Images, MRN, etc.)

F. In patients in whom SJS/TEN is possible but not a clear diagnosis, a punch biopsy will be performed by the dermatology service. This biopsy should betaken at an edge of sloughed tissue to involve normal tissue as well.
    1. If the patient is admitted to another service, and the burn service should be consulted and will follow as needed and make recommendations. If the diagnosis is not SJS, the burn team will signoff. If the diagnosis is SJS/TENS, burn surgery will assume care and the patient will be transferred to an appropriate bed in the burn unit.
    2. If the patient is a consultation from the ED and SJS is suspected, burn surgery will admit the patient and manage until biopsy results are confirmed. ICU vs. floor admission will be at the discretion of the attending physician(s). If, after biopsy, the diagnosis is not SJS, the patient will be transferred to an appropriate medicine team with dermatology consultation.
G. In patients in whom the diagnosis is not SJS/TEN, the burn service may sign off at the discretion of the consulting surgeon with a recommendation for dermatology consultation.

[i] Lerch M, et al. Current perspectives on stevens-johnson syndrome and toxic epidermal necrolysis. Clinical Rev Allergy Immunol 2018; 54 :147-176

[ii] Charlton OA, et al. Toxic epidermal necrolysis and stevens-johnson syndrome: a comprehensive review. Adv Wound Care. 2019;9 (7):426-439

[iii] Fouchard N, et al. SCORTEN: A Severity-of-Illness Score for Toxic Epidermal Necrolysis. J Inv Derm 2000;115(2):149-153

[iv] Shiga S, Cartotto R. What are the fluid requirements in toxic epidermalnecrolysis? *Journal of burn care & research: official publication of theAmerican Burn Association.* 2010;31(1):100-104

[v] Sassolas B et al. ALDEN, an algorithm for assessment of drug causality in Stevens-Johnson Syndrome and toxic epidermal necrolysis: comparison with case-control analysis. Clinical pharmacology and therapeutics 2010; 88(1): 60–68

[vi] Saeed HN, Chodosh J. Ocular manifestations of Stevens-Johnson syndromeand their management. *Current opinion in ophthalmology.* 2016;27(6):522-529

Appendix A

Algorithm for assessment of drug causality in epidermal necrolysis (ALDEN)

Criterion	Values	Rules to apply	
Delay from initial drug component intake to onset of reaction (index day)	Suggestive +3	From 5 to 28 days	−3 to 3
	Compatible +2	From 29 to 56 days	
	Likely +1	From 1 to 4 days	
	Unlikely −1	> 56 days	
	Excluded −3	Drug started on or after the index day	
		In case of previous reaction to the same drug, only changes for: Suggestive: +3: from 1 to 4 days Likely: +1: from 5 to 56 days	
Drug present in the body on index day	Definite 0	Drug continued up to index day or stopped at a time point less than five times the elimination half-life[a] before the index day	−3 to 0
	Doubtful −1	Drug stopped at a time point prior to the index day by more than five times the elimination half-life[a] but liver or kidney function alterations or suspected drug interactions[b] are present	
	Excluded −3	Drug stopped at a time point prior to the index day by more than five times the elimination half-life[a], without liver or kidney function alterations or suspected drug interactions[b]	
Prechallenge/rechallenge	Positive specific for disease and drug: 4	SJS/TEN after use of same drug	−2 to 4
	Positive specific for disease or drug: 2	SJS/TEN after use of similiar[c] drug or other reaction with same drug	
	Positive unspecific: 1	Other reaction after use of similar[c] drug	
	Not done/unknown: 0	No known previous exposure to this drug	
	Negative - 2	Exposure to this drug without any reaction (before or after reaction)	
Dechallenge	Neutral 0	Drug stopped (or unknown)	−2 or 0
	Negative - 2	Drug continued without harm	
Type of drug (notoriety)	Strongly associated 3	Drug of the "high-risk" list according to previous case-control studies[d]	−1 to 3
	Associated 2	Drug with definite but lower risk according to previous case-control studies[d]	
	Suspected 1	Several previous reports, ambiguous epidemiology results (drug "under surveillance")	
	Unknown 0	All other drugs including newly released ones	
	Not suspected −1	No evidence of association from previous epidemiology study[d] with sufficient number of exposed controls[c]	
		Intermediate score = total of all previous criteria	−11 to 10
Other cause	Possible −1	Rank all drugs from highest to lowest intermediate score	−1
		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 (another cause is more likely)	
Final score − 12 to 10			

<0, Very unlikely; 0–1, unlikely; 2–3, possible; 4–5, probable; ≥6, very probable

ATC, anatomical therapeutic chemical; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis

[a] Drug (or active metabolite) elimination half-life from serum and/or tissues, taking into into account kidney function for drugs predominantly cleared by kidney and liver function for those with high hepatic clearance. [b] Suspected interaction was considered when more than five drugs were present in a patient's body at the same time. [c] Similar drug = same ATC code up to the fourth level (chemical subgroups). [d] Definitions for "high risk," "lower risk," and "no evidence of association" in Methods

Appendix B

Independent prognosis factors of TEN.

Variables	Odds ratio (95% CI[a])	p-value
Age (≥ 40 y old)	2.7 (1.0–7.5)	0.05
Heart rate (≥ 120 per min)	2.7 (1.0–7.3)	0.04
Cancer/hematologic malignancy	4.4 (1.1–18.0)	0.04
BSA[b] involved at day 1		
< 10%	1	0.04
10–30%	2.9 (0.9–8.8)	
> 30%	3.3 (1.2–9.6)	
Serum urea level (> 10 mmol per liter)	2.5 (0.9–7.3)	0.09
Serum bicarbonate level (< 20 mmol per liter)	4.3 (1.1–16.0)	0.03
Serum glucose level (> 14 mmol per liter)	5.3 (1.5–18.2)	< 0.01
SCORTEN	2.45 (2.26–5.25)	$< 10^{-4}$

[a]Confidence interval; [b]BSA, body surface area detached. SCORTEN represents the number of abnormal parameters among the seven independent prognosis factors (a weight of 1 was assigned to each independent parameter), odds ratio corresponds to one score points.

Mortality rates and relative risks according to the SCORTEN

SCORTEN	No. of patients	Mortality rate		Odds ratio (95% CI[a])
		Percent	95% CI	
0–1	31	3.2	(0.1–16.7)	1
2	66	12.1	(5.4–22.5)	4.1 (0.5–35.2)
3	34	35.3	(19.8–53.5)	14.6 (2.0–138.0)
4	24	58.3	(36.6–77.9)	42.0 (4.8–367.0)
≥ 5	10	90.0	(55.5–99.8)	270.0 (15.0–487.0)

[a]Confidence interval, SCORTEN represents the number of abnormal parameters among the seven independent prognosis factors (a weight of 1 was assigned to each independent parameter).