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Clinical Considerations for Epidermal Necrolysis

Ryan P. Ellender, MD,[1] Cacey W. Peters, BA, BS,[1] Hannah L. Albritton, BS, MS,[1] Andrew J. Garcia, BS,[1,2] Alan David Kaye, MD, PhD[1,3]

[1]Department of Anesthesiology, Louisiana State University Health Sciences Center, New Orleans, LA
[2]School of Pharmacy, University of Arizona, Tucson, AZ
[3]Department of Pharmacology, Louisiana State University Health Sciences Center, New Orleans, LA

ABSTRACT

Background: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are considered a spectrum of acute life-threatening mucocutaneous reactions that differ only in severity. Both diseases are characterized by mucous membrane and skin involvement, are often caused by medications, and are collectively known as epidermal necrolysis (EN).

Methods: A severity of illness score has been devised to predict prognosis in patients with EN. The scoring system addresses 7 prognostic factors.

Results: Patients with EN require supportive care. Those with extensive skin involvement should be admitted to an intensive care unit or burn unit if possible. Suspected, as well as unnecessary, medications should be discontinued. Baseline laboratory tests, imaging, cultures, and biopsies should be obtained. Intravenous access should be established and hydration and nutritional support begun. Daily oral care, wound care, pain control, and early physician consultation are also important aspects of treatment.

Conclusion: EN requires early diagnosis, appropriate workup, and appropriate treatment to minimize potential morbidity and mortality. In many clinicians' experience, EN is rare; therefore, education and improved understanding of the potential causes and appropriate treatment regimens are vital when confronted with such a patient.

Address correspondence to
Alan David Kaye, MD, PhD
Professor and Chairman, Department of Anesthesiology
Professor, Department of Pharmacology
Louisiana State University Health Sciences Center
1542 Tulane Ave., Room 656
New Orleans, LA 70112
Tel: (504) 568-2319
Email: akaye@lsuhsc.edu

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INTRODUCTION

In 1922, a pair of US physicians, Stevens and Johnson, reported an acute mucocutaneous syndrome in 2 young boys.[1-3] In 1956, Lyell introduced the term toxic epidermal necrolysis (TEN) to describe 4 patients with eruptions that resulted in skin blistering.[1-3] Today, Stevens-Johnson syndrome (SJS) and TEN are considered a spectrum of acute life-threatening mucocutaneous reactions that differ only in severity. Both diseases are characterized by mucous membrane and skin involvement, are often caused by medications, and are collectively known as epidermal necrolysis (EN). Characteristically, patients initially present with fever, influenza-like symptoms, and painful skin, often preceding cutaneous manifestations by a few days.

PATHOGENESIS

SJS is classified as an epidermal loss $<$10% of the body surface area (BSA), and TEN is indicated by $>$30% BSA erosion. The range of epidermal loss between 10% and 30% is called SJS-TEN overlap.[4-8] Fortunately, epidermal necrolysis (EN) is a rare occurrence. SJS has an incidence of 1-6 cases per million person-years, and TEN has an incidence of 0.4-1.2 cases per million person-years.[1] EN occurs more frequently in women, and the incidence increases with age.[3-6] Patients with certain types of cancer, collagen vascular diseases, and especially human immunodeficiency virus are at increased risk for EN.[2,7-10] The average mortality is 1%-5% for SJS and 25%-35% for TEN.[3]

Medications are the causative agents in the majority of cases of EN, and more than 100 drugs have been implicated.[1] However about a dozen high-risk medications account for approximately half the cases of EN in Europe, including antibacterial sulfonamides, aromatic anticonvulsants, allopurinol, oxicam nonsteroidal antiinflammatory drugs, lamotrigine, and nevirapine.[2] Reports also indicate that allopurinol is the most common cause of EN in Israel and Europe.[4] The risk of developing EN as a result of medications seems confined to the first 8 weeks of treatment.[2] Many of these high-risk agents carry black

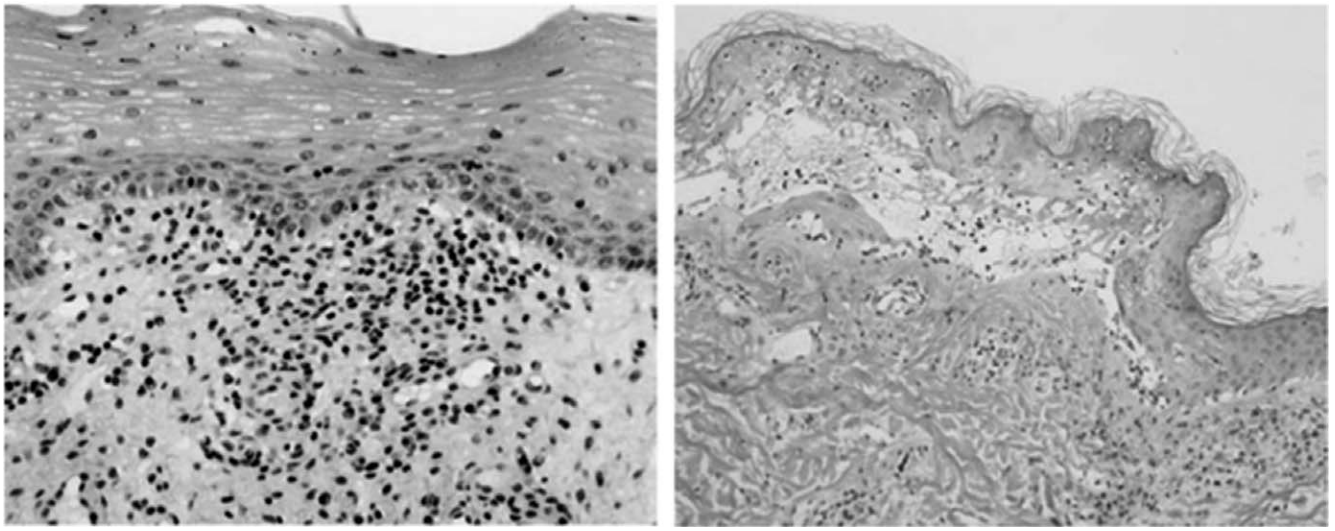

Figure 1. Histopathology of Stevens-Johnson syndrome. (Left) Focal basal cell vacuolar change with dense superficial dermal lymphocytic inflammation and occasional eosinophils in a patient with Stevens-Johnson syndrome secondary to lamotrigine therapy (hematoxylin and eosin stain, original magnification ×40). (Right) Full-thickness necrosis, basal vacuolar change, and subepidermal bullae in a patient with Stevens-Johnson syndrome secondary to *Mycoplasma pneumoniae* infection (hematoxylin and eosin stain, original magnification ×20). (Reprinted from *Mayo Clinic Proceedings,* 85(2), Wetter DA, Camilleri MJ, Clinical, Etiologic, and Histopathologic Features of Stevens-Johnson Syndrome During an 8-Year Period at Mayo Clinic, 131-138, 2010, with permission from Elsevier.)

box warnings to heighten clinician awareness and limit inappropriate dosing regimens and potential drug-drug interactions that can predispose patients to EN. For example, the coadministration of lamotrigine with valproic acid requires a significant reduction in the dose of lamotrigine to minimize the risk of EN. The coadministration of allopurinol with an angiotensin-converting enzyme inhibitor requires patients to be monitored closely for possible complications.[11-13] Other causes of EN include infection and bone marrow transplantation; approximately 20% of cases are idiopathic.[4]

The exact pathogenesis of EN is not completely understood; however, immunologic mechanisms, reactive drug metabolites, and genetic susceptibility—especially among individuals of Asian ancestry—are all thought to play roles in the development of the disease. Evidence shows that widespread keratinocyte cell death via apoptosis results in the tissue damage known as EN.[10] Skin biopsies are often obtained to confirm diagnosis; EN histology reveals full-thickness necrosis of the epidermis associated with a lymphocytic infiltrate (Figure 1).[3]

CLINICAL FEATURES

Patients suffering from EN often initially present with fever, influenza-like symptoms, and painful skin that typically precedes cutaneous manifestations by a few days. Many of the initial presenting symptoms, such as fever and early dermatological features, could have differing diagnoses, so a high index of suspicion and a good medical and drug history are paramount to identify EN in its early stages. Macular eruptions tend to appear first on the face and trunk and can spread quickly to the rest of the body. The arms and legs are relatively spared, but the lesions can involve the palms and soles.[4] Lesions of EN are characterized by flat atypical targets or red purpuritic macules. The lesions then evolve into flaccid blisters resulting in extensive sloughing of necrotic skin (Figure 2).[7-9]

Mucous membrane involvement can precede or follow skin lesions and is present in almost all patients.[6] Mucosal lesions begin with erythema followed by superficial erosions in ocular, oral, and anogenital mucosa. EN is often associated with high fever, pain, and weakenss.[2] Pulmonary, gastrointestinal, and renal epithelium also can be involved.

A severity of illness score (SCORTEN [Score of TEN]) has been devised to predict prognosis in patients with EN (Table). This scoring system addresses 7 prognostic factors: age, malignancy, heart rate, BSA involved, serum urea, serum glucose, and serum bicarbonate levels.[7] However, a potential limitation is that SCORTEN may underestimate mortality in patients with respiratory involvement.[4] Other parameters affecting outcome include neutropenia and thrombocytopenia, as well as late withdrawal and long half-life of a causative medication.[3]

Patients with EN do not require surgical interventions as frequently as patients with burn injuries;

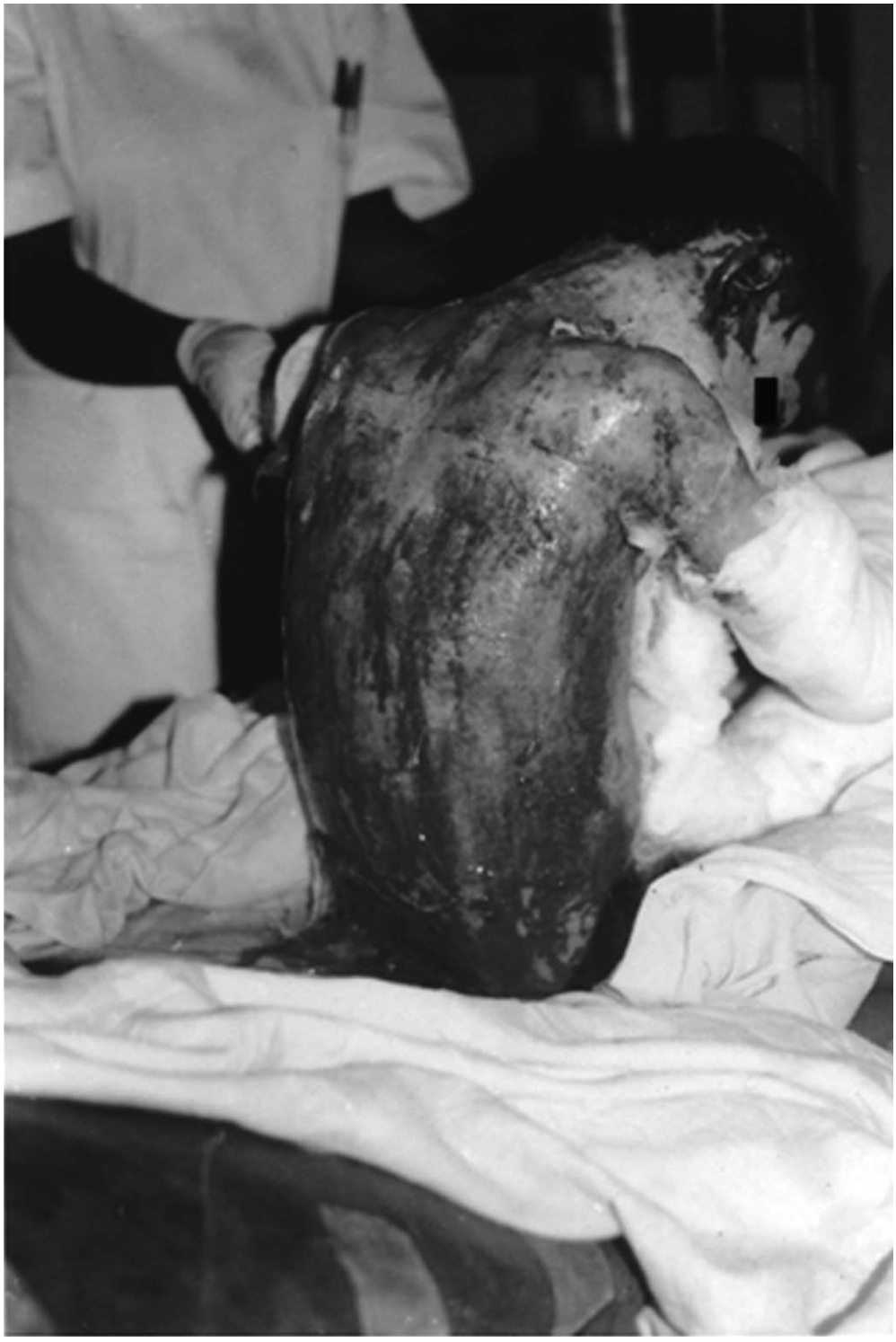

Figure 2. Patient with toxic epidermal necrolysis showing bleeding during dressing change. (Reprinted from *Burns*, 34(5), Ugburo AO, Temiye EO, Ilombu CA, A 12-year retrospective study of non-burn skin loss (burn-like syndromes) at a tertiary burns unit in a developing country, 637-643, 2008, with permission from Elsevier.)

Table. SCORTEN System for Predicting Outcome in Toxic Epidermal Necrolysis

Clinical-Biologic Parameter	Individual Score	SCORTEN (Sum of Individual Scores)	Predicted Mortality, %
Age >40 years	Yes=1, No=0	0-1	3.2
Malignancy	Yes=1, No=0	2	12.1
Tachycardia >120/min	Yes=1, No=0	3	35.8
Initial surface of epidermal detachment >10%	Yes=1, No=0	4	58.3
Serum urea >10 mmol/L	Yes=1, No=0	≥5	90
Serum glucose >14 mmol/L	Yes=1, No=0		
Serum bicarbonate <20 mmol/L	Yes=1, No=0		

SCORTEN, toxic epidermal necrolysis (TEN)–specific severity-of-illness score.
(Reprinted from *Int Immunopharmacol,* 6(4), French LE, Trent JT, Kerdel FA, Use of intravenous immunoglobulin in toxic epidermal necrolysis and Stevens-Johnson syndrome: our current understanding, 543-549, 2006, with permission from Elsevier.)

however, patients with EN also undergo wound debridement in the operating room. Preoperative preparations should focus on the airway, as it can be acutely compromised and difficult to secure if oral lesions are severe. General anesthesia via endotracheal intubation is the preferred anesthetic modality.[8] Respiratory epithelium is involved in about 25% of patients with TEN, and acute respiratory distress syndrome can develop.[9] Fluid maintenance, temperature regulation, and pain control are the mainstays of intraoperative care.

COMPLICATIONS

Complications arising in the acute phase of the disease are vast and resemble those of patients with burns. Extensive fluid loss can lead to electrolyte imbalances, hypovolemia, and renal insufficiency. Decreased alimentation and hypercatabolism can result in hypoalbuminemia and hyperglycemia. Loss of the protective skin layer can cause bacteremia and septicemia. For patients with EN, sepsis is the most common cause of death, and *Staphylococcus aureus* and *Pseudomonas* are among the most common pathogens.[8]

Patients with EN require supportive care, and physicians at the University of Florida have devised practical guidelines for the management of these patients.[13] Patients with extensive skin involvement should be admitted to an intensive care unit or a burn unit if possible. Suspected, as well as unnecessary, medications should be discontinued. Baseline laboratory tests, imaging, cultures, and biopsies should be obtained. Intravenous access should be established and hydration and nutritional support begun. Fluids should not be administered as aggressively as in patients with burns involving the same BSA because fluid overload could result.[10] Daily oral care, wound care, pain control, and early physician consultation are important aspects of treatment.

Clinicians treating patients with EN could also consider corticosteroids, intravenous immunoglobulin, cyclosporine A, antitumor necrosis factor agents, and plasmapheresis.[10] These treatment modalities are not proven to be effective but have been described in case reports.

EN has recurred in rare instances from inadvertent readministration of the inciting medication or a closely related medicine. For this reason, patients who have suffered from EN should carry an allergy card or wear an allergy bracelet. Furthermore, because of the genetic role of EN, the patient's relatives also should avoid the offending medication.[2]

CONCLUSION

SJS and TEN are diseases characterized by mucous membrane and skin involvement and are collectively known as EN. Medications are the causative agents in the majority of cases. EN requires early diagnosis, appropriate workup, and appropriate treatment to minimize potential morbidity and mortality. In many clinicians' experience, EN is rare; therefore, education and improved understanding of potential causes and appropriate treatment regimens are vital when confronted with such a patient.

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