

Toxic Epidermal Necrolysis Clinical Guidelines

Frederick W. Endorf, MD,* Leopoldo C. Cancio, MD,*† Nicole S. Gibran, MD*

Recommendations: Standards: 1) Cessation of causative medications is mandatory to halt progression of toxic epidermal necrolysis (TEN). 2) Early transfer to a burn unit or similarly qualified specialized center is the standard of care for TEN.

Guidelines: 1) Tissue diagnosis by full-thickness punch biopsy is recommended for the diagnosis of TEN 2) Systemic corticosteroids are not recommended in the treatment of TEN 3) The use of empiric prophylactic antibiotics is not recommended in patients with TEN 4) Coverage of areas of desquamated skin may be attained with a number of dressings, including biological, biosynthetic, and silver or antibiotic-impregnated dressings. Frequent dressing changes with topical antimicrobial ointments or solutions are not recommended 5) Enteral nutrition is recommended for patients with TEN 6) The clinical scoring system SCORTEN may be useful in predicting mortality of patients with TEN, particularly when repeated daily 7) Long-term outpatient follow-up is important in TEN survivors to manage late complications and identify at-risk patients for post-discharge mortality 8) Ophthalmologic consultation is highly recommended for patients with conjunctival involvement. Dermatology/dermatopathology consultation may be considered to rule out non-TENS diseases.

Options: 1) The efficacies of intravenous immunoglobulin (IVIG) and plasmapheresis are not well-defined. The dose of IVIG may be important. IVIG should be free of sucrose 2) No standard exists for the management of ocular manifestations of TEN, but amniotic membrane may be a useful adjunct to topical therapies such as topical steroids, antibiotics, and lubricants. Daily examination and separation of the

lids is necessary to prevent adhesions of the raw mucosal surfaces 3) Vulvovaginal and preputial complications are common, and may be ameliorated by early use of topical lubricants and daily manual separation of the mucosal surfaces.

OVERVIEW

Purpose

The purpose of this guideline is to review existing data regarding the diagnosis and treatment of toxic epidermal necrolysis (TEN), and to present an evidence-based and practical approach to the care of patients with TEN.

Users

This guideline is directed at physicians involved in the initial diagnosis and management of TEN, as well as those specialists involved in the definitive management of patients with TEN.

Clinical Problem

TEN is the most severe form of the exfoliating disorders that include the milder variants, Stevens-Johnson syndrome (SJS) and erythema multiforme. TEN is a rare but potentially lethal condition characterized by sloughing of the epidermis at the dermal–epidermal junction.¹ Medication reactions cause approximately 80% of TEN cases.² Patients afflicted with TEN are often cared for in burn centers,³ but no standard guidelines exist for the management of TEN.

Process

A *PubMed* literature search was performed for topics relating to TEN including diagnosis, management, treatment, outcomes, steroids, IVIG, ocular therapy, burn centers, SCORTEN, pathology, wound coverage, and nutrition. References were classified as class 1 evidence (prospective, randomized, controlled trials); class 2 evidence (prospective or retrospective studies based on clearly reliable data); class 3 evidence (clinical series, comparative studies, case reviews, or reports); or as Technology Assessment (a study which examined the utility/reliability of a particular technology).

*From the *Harborview Medical Center and †U.S. Army Institute of Surgical Research, University of Washington, Seattle.*

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Address correspondence to Frederick W. Endorf, MD, 325 Ninth Avenue, Harborview Medical Center and U.S. Army Institute of Surgical Research, University of Washington, Seattle 98104. Copyright © 2008 by the American Burn Association. 1559-047X/2008

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Scientific Foundation

TEN is the most severe manifestation of cutaneous drug reactions, on a spectrum that also includes erythema multiforme and SJS. A recently described syndrome known as drug reaction with eosinophilia and systemic symptoms has also been described as part of this spectrum of diseases,⁴ but definitions pertaining to this clinical entity are still evolving.⁵ The differential diagnosis of TEN includes SJS, *Staphylococcal* scalded skin syndrome, drug reaction with eosinophilia and systemic symptoms, acute generalized exanthematous pustulosis, and autoimmune immunobullous disorders such as pemphigus vulgaris and paraneoplastic pemphigus. The most commonly used classification system differentiates TEN from SJS by the amount of body surface area involved; TEN involves epidermal loss exceeding 30% of the total body surface area.⁶ In addition, some mucosal involvement (eg, alimentary tract, conjunctiva, airway, and/or genitourinary tract) is almost universally seen in TEN but less frequently in SJS; absence thereof indicates a different diagnosis.

TEN is a T-cell mediated immune reaction not unlike graft-vs-host disease in transplant patients. The keratinocyte apoptosis receptor fas (CD95)⁷ or cytotoxic T-cell release of perforin and granzyme B⁸ have been implicated as potential pathophysiological causes of TEN. The most common drugs implicated are antibiotics and anticonvulsants, but more than 100 medications have reported associations with TEN.² Less commonly, viral conditions have also been associated with TEN.⁹

TEN may have a prodromal phase characterized by fever and lethargy shortly after medication exposure. Oropharyngeal involvement may be presaged by dysphagia before the development of overt mucosal or cutaneous lesions. Clinical manifestations may include sloughing of the stratified epithelium of the upper tracheobronchial tree, upper gastrointestinal tract, vaginal mucosa, anal canal and the eyes and mouth. TEN does not affect columnar or cuboidal epithelium. Sloughing of the epidermal-dermal junction, which can be demonstrated with manual pressure on apparently intact skin adjacent to blisters (Nikolsky's sign) is pathognomonic for TEN.¹⁰ Diagnosis is made by performing two full-thickness punch biopsies, one for frozen section and one for routine formalin-fixed examination. Biopsies must be taken from a border of intact epidermis surrounding bullous lesions, because necrosis of the epidermis is crucial to making the definitive diagnosis.¹¹ Dermal mononuclear infiltrates are sparse in TEN when compared with the extensive inflammation seen in other

Table 1. SCORTEN variables

Prognostic Factors	Values	Weight
Age	≥40 yr	1
Malignancy	Yes	1
Body surface area detached	≥10%	1
Tachycardia	≥120/min	1
Serum urea	>10 mmol/L	1
Serum glucose	>14 mmol/L	1
Serum bicarbonate	<20 mmol/L	1

desquamating skin disorders. The degree of inflammation may be a tool to help predict patient survival.¹²

The clinical scoring system known as SCORTEN was developed to stratify severity of illness and predict mortality¹³ (Table 1). The initial report detailing this scoring system showed excellent correlation between predicted and actual mortality, but subsequent studies have had contradictory findings regarding the accuracy of SCORTEN.^{14–16} The original authors have validated their original findings and noted improved accuracy with repeating computation of the SCORTEN, with day 3 scoring showing the best correlation with patient survival.¹⁷ Recent data from another institution has confirmed that SCORTEN is an accurate predictor of mortality in TEN patients treated at a burn center.¹⁸

Prompt cessation of any suspicious medications is the foundation for the treatment of TEN. The timeliness of stopping the drug may impact the overall prognosis; although, medications with long half-lives may have persistent effects despite stopping administration.¹⁹ Treatment is primarily supportive; the goal is to protect the skin while it heals with special emphasis on care of the eyes, oral mucosa, and gastrointestinal and respiratory epithelia. Staples of critical care such as fluid and electrolyte management, nutrition, and pain relief are important in TEN patients, as in all critically ill patients. Fluid management differs from patients with burn injuries because the epidermal cytokine response and degree of microvascular injury are less, and the subsequent inflammatory response does not drive a systemic capillary leak. Nevertheless, insensible losses approach 2 to 3 L per day in adults with 50% TBSA involvement. Thus, an adult with TEN may require 5 to 7 L/24 hr of resuscitative fluid, with more needed if there have been delays in treatment.²⁰ As with other patients, the resuscitation fluids must be titrated to physiologic endpoints, such as a urine output of 0.5 to 1.0 ml/kg/hr, while avoiding overresuscitation. Patients who receive enteral nutrition seem to fare better than those who receive parenteral nutrition.⁷ Nutritional requirements may

be proportional to total body surface area involved,²¹ and immune modulating nutrition with glutamine may benefit patients.²²

Infectious complications are common in patients with TEN, particularly with Gram-positive skin organisms such as *Staphylococcus aureus* and later in the hospital course Gram-negatives such as *Pseudomonas aeruginosa*.²³ Increased vigilance is warranted, including frequent cultures of skin, blood, urine, and intravascular catheters. However, empiric use of antibiotics in the absence of culture-proven infection may select for resistant organisms and may contribute to increased mortality.²⁴

The principal of skin care in TENS is to prevent infection while protecting the viable subepidermal tissue, from which the wound will heal spontaneously in about 6 to 10 days. Debridement of sloughed epidermis must be followed by either temporary wound closure of, or application of antimicrobial agents to, all exfoliated areas. Temporary wound closure offers the advantage of protecting the healing tissue. A number of case reports and small case series have touted the benefits of the biosynthetic dressing Bio-brane (Bertek Pharmaceuticals, Research Triangle Park, NC).²⁵⁻²⁷ Biologic dressings, including porcine xenograft^{15,28} and cryopreserved human allograft,^{29,30} have been reported by several centers to be associated with improved outcomes. Amniotic membrane has also been used for skin coverage in TEN.³¹ If temporary wound closure is not performed, the most frequently utilized treatments are those which provide ionic silver, such as 0.5% silver nitrate solution.³² Silver-impregnated dressings, such as the nanocrystalline silver dressing Acticoat (Smith & Nephew, Largo, FL),³³ offer the advantage of not requiring daily dressing changes, which may damage the healing epidermis. One reported alternative to debridement of the sloughed epidermis is to leave it in place and to dress the wounds with silver-nitrate soaked nonadherent dressings (Soft-Sorb, De Royal Industries Inc., Powell, TN), which are changed every 3 days.³⁴ Whereas, this would seem to contradict the report from the multi-center review that silver nitrate treatment is associated with worse outcomes.⁷ The authors of this report state that the epidermis, when not infected, acts as a biological dressing to prevent damage to the underlying tissue.

Amniotic membrane has been suggested to ameliorate long-term ocular complications^{35,36} that may affect up to 75% of patients with TEN.³⁷ Other frequent ocular therapies include topical steroids, topical antibiotics, and lubricants with daily mechanical separation of the mucosal membranes to prevent synchia.³⁸ Vulvovaginal complications are also com-

mon. A thorough pelvic examination should be done in all TEN patients, and preventative therapies such as emollients, lubricant gels, and topical steroids should all be considered. Late scar and contracture complications are difficult to repair surgically.³⁹

Systemic therapies for TEN continue to be sources of controversy. The use of corticosteroids has been associated with increased infections, hospital length of stay, and mortality;^{40,41} although, data in one retrospective multi-center study of combined TEN and SJS patients showed possible benefits with pulse corticosteroids.⁴² Cyclosporine has been investigated by some centers.⁴³ Intravenous immunoglobulin (IVIG) has stimulated extensive investigation as an adjunctive therapy for TEN. IVIG blocks in vitro interaction of the fas receptor with fas ligand and prevents keratinocyte death, and was reported to reduce mortality in patients with TEN.⁴⁴ Initial reports of the use of IVIG were favorable, with higher survival rates than reported in the existing literature^{14,45,46} or predicted by SCORTEN. However, replication of those results has been difficult, and several studies have shown no benefit or worse outcomes.⁴⁷⁻⁵⁰ IVIG does not seem to be protective against ocular complications of TEN.⁵¹ IVIG in concert with plasmapheresis has also been advocated,⁵² but plasmapheresis alone has only been reported in small case series with mixed results.⁵³⁻⁵⁵ Therefore, neither of these adjuvant therapies can be recommended as guidelines.

When using IVIG, several factors should be considered. First, some formulations of IVIG contain sucrose, which may cause acute renal failure in the doses commonly recommended for TEN; these formulations should be avoided. Second, IVIG represents a significant colloid dose, and the fluid balance of patients receiving it should be monitored to avoid volume overload. Third, IVIG may be associated with thromboembolic events and caution should be used in patients with a history of deep vein thrombosis or pulmonary embolism. Fourth, the dose of IVIG should be carefully considered. A meta-analysis (nine studies, 107 patients) found that mortality decreased with increasing IVIG total dose. One approach to dosing IVIG is to give 1 g/kg/day, continuous infusion, for days 1 to 4 after admission for TENS.⁵⁶

TEN patients may develop neutropenia, and a white blood count (WBC) nadir has been reported to be an independent predictor of mortality in one study.³² Some authors recommend the use of recombinant human granulocyte colony-stimulating factor (filgrastim, Neupogen®, Amgen Inc., Thousand Oaks, CA) for TEN patients with neutropenia (eg, absolute neutrophil count <1000).⁵⁷

Table 2. Evidentiary table

Reference	Description	Data Class	Comments
Roujeau et al 1995	Retrospective case-control study of 245 patients with TEN and SJS	II	Examination of risks of causative medications in TEN, including sulfonamides, anticonvulsants, NSAIDs, allopurinol, chlormezanone, corticosteroids, etc.
McGee et al 1998	Retrospective review of 36 patients	II	Referrals to burn center earlier than 7 days had 4% mortality, greater than 7 days had 83% mortality
Palmieri et al 2002	Retrospective multicenter review of 199 patients	II	Patients treated at burn centers had more appropriate use of enteral nutrition, less empiric antibiotics and steroid use, and decreased mortality
Bastuji-Garin et al 1993	Retrospective review of 28 cases	II	Validation of classification system for EM, SJS, and TEN based on TBSA involvement
Amon et al 1975	Pathologic examination of patients with staphylococcal skin disease and TEN	III	Establishes technique for biopsy diagnosis of TEN
Quinn et al 2005	Retrospective analysis of clinical records and pathologic slides of 37 patients	II	Correlates degree of histologic inflammation with SCORTEN and patient outcomes
Bastuji-Garin et al 2000	Retrospective review of 165 patients	II	Created and internally validated SCORTEN score for prognosis in TEN
Trent et al 2003	Retrospective analysis of 16 patients treated with IVIG	II	Found decreased mortality with IVIG compared to predicted outcome with SCORTEN
Imahara et al 2006	Retrospective review of 109 patients	II	Observed mortality less than predicted by SCORTEN with an established clinical protocol
Trent et al 2004	Retrospective review of 24 patients	II	Clinical mortality not statistically than predicted mortality by SCORTEN
Guegan et al 2006	Retrospective review of 144 patients	II	Improved performance of SCORTEN with repeat scoring
Garcia-Doval et al 2000	Retrospective review of 203 patients	II	Patients with early withdrawal of causative medications had decreased mortality, except in drugs with prolonged half-lives
Schulz et al 2000	Retrospective review of 39 patients	II	Worse outcomes with early empiric antibiotics
Arevalo et al 1999	Case series of eight patients	III	Use of Biobrane useful in wound coverage in TEN
Bradley et al 1995	Case series of three patients	III	Use of Biobrane useful in wound coverage in TEN
Bannasch et al 2004	Case report of one patient	III	Use of Biobrane successful in a pediatric patient
Asz et al 2006	Case report of one patient	III	Use of Acticoat safe and convenient in TEN
Lehrer-Bell et al 1998	Retrospective review of 11 patients	II/III	Soft-Sorb dressings with silver nitrate useful for wound coverage in TEN
Heimbach et al 1987	Retrospective review of 19 patients	II	Decreased mortality compared to prior reports with use of biologic dressings and intensive supporting care
Birchall et al 1987	Case report of one patient	III	Successful use of allograft for wound coverage in TEN
Pianigiani et al 2002	Case report of two patients	III	Successful use of allograft for wound coverage in TEN
Prasad et al 1986	Case report of one patient	III	Successful use of amniotic membrane for wound coverage in TEN
John et al 2002	Case report of two patients	III	Successful use of amniotic membrane for ocular involvement in TEN
Kobayashi et al 2006	Case report of one patient	III	Successful use of amniotic membrane for ocular involvement in TEN
Chang et al 2007	Retrospective review of 207 patients	II	Most common ocular therapies topical steroids, topical antibiotics, and lubricants
Meneux et al 1998	Retrospective review of 40 patients	II	Difficult to surgically repair vulvovaginal complications- attempt prevention with topical therapies
Engelhardt et al 1997	Retrospective review of 14 patients	II	No benefit of corticosteroids in TEN
Halebian et al 1986	Retrospective cohort study of 30 patients	II	Improved survival without corticosteroids in TEN
Schlingman et al 2004	Retrospective multi-center study of 281 patients	III	Abstract only- possible benefits with pulsed corticosteroids
Viard et al 1998	Pilot study of 10 patients treated with IVIG	II	Favorable outcomes with IVIG in TEN patients- no controls

(Continued)

Table 2. (Continued)

Reference	Description	Data Class	Comments
Prins et al 2003	Multicenter retrospective review of 48 patients	II	Success with early infusion of IVIG
Stella et al 2001	Retrospective review of five patients	II/III	Low mortality with IVIG compared with predicted SCORTEN mortality
Brown et al 2004	Retrospective cohort study of 45 patients	II	No improvement in mortality with IVIG, may actually be detrimental
Bachot 2003	Prospective noncomparative study of 34 patients	II	No benefit with use of IVIG
Shortt et al 2004	Retrospective cohort study of 32 patients	II	No improvement in outcome with IVIG
Morici et al 2000	Retrospective cohort study of 12 pediatric patients	II	No improvement in outcomes with IVIG in pediatric patients
Yip et al 2005	Retrospective cohort study of 18 patients	II	No reduction of ocular complications with use of IVIG
Lissia et al 2005	Case series of five patients	III	Low mortality with combined IVIG and plasmapheresis compared to predicted SCORTEN mortality
Chaidemenos et al 1997	Case series of seven patients	III	Successful use of plasmapheresis in TEN
Egan et al 1999	Retrospective cohort study 16 patients	II	Decreased mortality with use of plasmapheresis in TEN
Furubacke A et al 1999	Retrospective comparative case series	III	No differences in outcomes with plasmapheresis in TEN
Kelemen et al 1995	Retrospective review	II	Decreased morbidity with early transfer to burn center, higher mortality with corticosteroids
Haber et al 2005	Retrospective chart review and survey of 13 TEN survivors	II	High level of independent functioning but high rate of long-term complications
Oplatek et al 2006	Retrospective review of 64 patients	II	High postdischarge mortality, predicted by age, SCORTEN, TBSA, delayed admission to burn unit, multiple comorbidities
Arevalo et al 2000	Comparative case series of 11 patients	III	Low mortality with use of cyclosporine in TEN patients
Fischer et al 2002	Case report of one patient	III	Successful use of infliximab in the treatment of TEN
Goulden et al 1996	Case report of one patient	III	Successful use of granulocyte colony-stimulating factor in a patient with TEN and neutropenia

TEN, toxic epidermal necrolysis; SJS, Stevens-Johnson syndrome; IVIG, Intravenous immunoglobulin; EM, erythema multiforme.

Transfer of patients with TEN to a burn center has become a standard of care. The combination of critical-care expertise and experience with large wounds and extensive skin injury makes burn units ideally suited to deal with these complex patients. A large multicenter retrospective comparison of treatment of TEN at burn centers and nonburn centers found that burn centers had increased use of enteral nutrition, decreased steroid use, decreased use of empiric antibiotics, and more intensive wound management, all of which seemed to contribute to better outcomes.⁷ Delayed transfer to a burn unit is associated with increased mortality in patients with TEN.^{3,7,32}

Patients who survive TEN can usually return to functional lifestyles, but many have long-term complications including skin and nail changes, ocular sequelae, and vulvovaginal complications.⁵⁸ However, patients who survive TEN have also been reported to have increased mortality rates after discharge. High

SCORTEN scores and delayed admission to a burn unit after onset of symptoms may be predictors of mortality as long as 2 years postdischarge.⁵⁹ Whether this is due to TEN or increased co-morbidities is not clear. But, it seems imperative that these patients with TEN be followed long-term as outpatients to identify patients at risk.

Summary

TEN is a rare but severe exfoliating skin disease caused primarily by medication reactions. Ideal management should consist of stopping the offending drug, intensive supportive care, and rapid transfer to a burn unit. Diagnosis by punch biopsy may be useful, and the SCORTEN score may be helpful in prognosis. Wound management consists of debridement of sloughed epidermis and wound coverage with an appropriate biological or long-term dressing. Corticosteroids and empiric antibiotics are not recom-

mended. The use of IVIG or plasmapheresis cannot be strongly recommended based on available evidence. The importance of close long-term outpatient follow-up cannot be overstated.

Key Issues for Further Investigation

Refinement of evidence regarding the use of IVIG may help define its utility in patients with TEN. The low overall incidence of TEN requires that a multicenter collaboration be formed for prospective randomized trials. This might include a multidisciplinary prospective registry of patients with SJS and TEN. Potentially useful therapies that may be worthy of prospective randomized evaluation include cyclosporine,⁴³ infliximab,⁶⁰ and granulocyte colony-stimulating factor.⁵⁷

Evidentiary Table

Table 2 summarizes the current research pertinent to the management of patients with TEN.

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