

# Treatment Strategies in Toxic Epidermal Necrolysis Syndrome: Where Are We At?

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Toxic epidermal necrolysis syndrome (TENS) is a rare, life-threatening medical emergency typically associated with recent drug exposure. Although several theories exist, recent insight has implicated the innate immune system as a significant contributor to the initiation and propagation of this devastating reaction. Standard therapies including transfer to specialized burn units, nutritional support, and protection from infection, remain the mainstay in the treatment of TENS. While alternative treatment strategies have been pursued and reported, there remains no published data that convincingly supports these further interventions. Given the rare nature of this syndrome, multi-institutional studies will be necessary and essential in improving the understanding and treatment of TENS. (*J Burn Care Res* 2008;29:269–276)

Toxic epidermal necrolysis syndrome (TENS) is a rare, potentially life-threatening medical emergency characterized by wide-spread epidermal sloughing of skin accompanied by mucus membrane involvement. Ruskin first described a condition similar to TENS in 1948,<sup>1</sup> and in 1956 Lyell reported four more patients who had an acute rash followed by skin detachment and mucus membrane involvement.<sup>2</sup> Of the four cases originally described by Lyell, two were eventually attributed to staphylococcal scalded skin syndrome (SSSS). It was at this time that Lyell suggested that the reaction was a toxin-associated reaction. Although clinically similar in presentation, ie, sloughing of epidermal sheets, SSSS and TENS can be differentiated from a histologic perspective, which underlies the importance of the skin biopsy at the time of presentation. In SSSS, there is superficial detachment involving the upper epidermal layers, whereas in TENS there is pan-epidermal necrosis. Recognition of SSSS is important as treatment considerations are distinct, including the use of antibiotics, rather than viewing

antibiotics as causing the disease, as is often the case for TENS. On the other hand, the histologic difference between Steven-Johnson syndrome (SJS) and TENS is less pronounced. Although SJS and TENS are believed to be the same disorder of different severities, with SJS representing an attenuated form of TENS,<sup>3</sup> a significant proportion of SJS cases are not associated with drug ingestion. Despite a similar clinical presentation and course to TENS, the mortality associated with SJS ranges between 1% and 3%.<sup>4</sup>

The estimated annual incidence of TENS is reported between 0.4 and 1.3 cases per million per year, and can occur in all age groups, including newborns and the elderly.<sup>5–7</sup> Reported mortality varies from 30 to 50%, with the primary cause of death being infection and multi-system organ failure.<sup>8</sup> In the majority of the cases, there is a history of recent drug ingestion. Further supporting the notion of a drug-provoked reaction is provided by the fact that readministration of the suspect drug can cause a recurrence of TENS.<sup>9–11</sup> Antibiotics, NSAIDs, analgesics, and anticonvulsant medications are the most common drugs identified in cases of TENS.<sup>12–15</sup> Although many theories exist, several authors have suggested that there is an imbalance in the inherent activation and detoxification mechanisms, as well as an altered innate immune response, in individuals susceptible to TENS.<sup>15–18</sup> Further discussion of these points is covered in a subsequent section. The risk of developing TENS is a 1000 times higher in patients with HIV and AIDS than in the normal population.<sup>19</sup>

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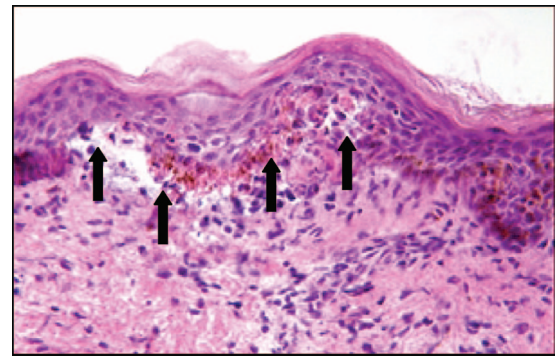
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## CLINICAL FEATURES AND DIAGNOSIS

The clinical features typically associated with TENS include a prodrome of 2 to 3 days characterized by fever, cough, sore throat, and general malaise before the cutaneous manifestations of TENS become apparent.<sup>20</sup> The acute phase, which is typically associated with the first 8 to 12 days, is characterized by an acute macular exanthema, with rapidly spreading necrosis of the mucous membranes at first, followed by similar events in the epidermis, eg, the skin. (Figure 1)<sup>21</sup> At the time of skin involvement, Nikolsky sign is universally present—epidermal separation induced by gentle lateral pressure on the skin surface.<sup>22</sup> Mucous membranes, including conjunctival, pharyngeal, tracheal, and esophageal, are involved in nearly all reported cases. Typically, the dermis remains undamaged, and dermatologic recovery takes 1 to 3 weeks, depending on the extent of skin detachment. However, mucosal lesions, including the ocular manifestations of TENS, generally require a longer time to heal.<sup>23</sup>

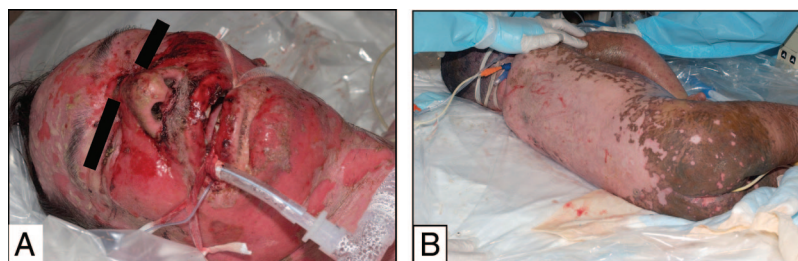
## PATHOPHYSIOLOGY OF TENS

Pathologic examination of perilesional skin can be used to support or exclude a clinical diagnosis of TENS. Characteristic histologic features include extensive keratinocyte death with separation of the epidermis from the dermis at the dermoepidermal junction (Figure 2). A paucicellular infiltrate, in which macrophages and dendrocytes predominate, has been commonly described. TENS has been characterized immunopathologically by an increased ratio of dermal dendrocytes to dermal lymphocytes, in contrast to the opposite pattern seen in erythema multiformis, where lymphocytes predominate.<sup>24</sup> The death of keratinocytes has been shown to be through apoptosis, the process of programmed cell death.<sup>25</sup> Laboratory investigation has revealed that the keratinocyte apoptosis is potentially mediated by Fas-FasL interac-



**Figure 2.** Histological appearance of lesional skin demonstrating typical features of TENS. Arrows signify extensive apoptosis in epidermal keratinocytes accompanied by focal dermal-epidermal separation and a mononuclear inflammatory infiltrate.

tions,<sup>26</sup> perforin,<sup>27</sup> and/or TNF- $\alpha$ ,<sup>28</sup> all of which are present in the epidermis of the patients with TENS. There are several theories regarding the pathogenesis of TENS. On the one hand, one theory suggests a direct “toxic” effect by which an ingested medication (and/or a metabolite) triggers cell death in epidermal keratinocytes. Alternatively, the drug triggers an immune reaction and the activated immunocytes mediate the cytopathic effects in much the same way that epidermal killing is seen in patients with acute cutaneous graft vs host disease. Currently it is difficult to determine with certainty whether the inflammatory reaction is a cause or consequence of the epidermal cell death and abrogation of barrier function. If TENS was simply a toxic reaction without any immunologic component, then one would generally expect the mortality rate to be similar to thermal injuries. However, the increased mortality of TENS vs thermal burns suggests additional disease processes are operating. Thus, investigators are actively pursuing the role of aberrant immune reactions and the involvement of cytokines in the pathogenesis of TENS. Based on these observations, effective treatment strategies should be



**Figure 1.** Clinical manifestation of TENS demonstrating (A) mucus membrane involvement and (B) significant epidermal involvement compromising the external barrier function of the affected surfaces.

focused on halting keratinocyte apoptosis, either by acting on the keratinocytes directly, or the effectors mediating the process.

The diagnosis of TENS can often times be made clinically, but differentiating TENS from SJS remains a point of contention. Although several proposed diagnostic criteria for SJS and TENS exist, authors do not agree on a universally accepted model. Presently, the most simplified model of differentiation involves total body surface area and type of associated skin lesion as a clinical guideline (Table 1).<sup>29</sup> Once the diagnosis of TENS is suspected, prompt withdrawal of potential causative drug(s) should be the priority, as this particular course of action is one therapeutic technique that has been shown to decrease mortality and improve prognosis.<sup>30</sup> In general, any medication initiated within 3 to 4 weeks before the onset of symptoms should be suspected, and should be strictly avoided, especially in the course of treatment. Principles guiding the care of treatment of TENS patients are similar to those in extensive thermal burns.<sup>31</sup> The treatment of patients with TENS is most appropriately provided in intensive care units, or, more specifically, burn centers, where staff is familiar with managing complex epidermal loss and associated complications, ie, mechanical ventilation, pressor support, and wound care.<sup>32,33</sup> Given the current confusion regarding the pathophysiologic mechanisms responsible for TENS, it should not be surprising that therapeutic approaches are diverse and relatively ineffective. Presently, there is a lack of consensus on

specific treatments for TENS. As such, patients are treated symptomatically and supportively. Supportive therapies include attention and protection of eroded mucosal surfaces, prevention, early detection and treatment of infection, nutritional support and monitoring of fluid and electrolyte balances.

## GENERAL TREATMENT STRATEGIES

Several approaches have been suggested for skin care. The care of the burn patient generally mandates debridement of nonviable epidermis and subsequent coverage. As such, several authors have recommended similar care in TENS, with extensive debridement of involved epidermis followed by coverage with biologic dressings, including cryopreserved cutaneous allografts, porcine cutaneous xenografts, amnion-based, or collagen-based skin substitutes.<sup>34–39</sup> Other authors advocate leaving the involved epidermis in place, with the use of biologic dressings only on exposed dermis.<sup>40</sup> Recent case reports have described successful coverage with Acticoat, a nanocrystalline silver dressing reported to reduce infection and exhibit antimicrobial activity in wounds.<sup>41,42</sup> Nonetheless, there is a lack of evidence in the literature which demonstrates improved outcomes with early/late debridement vs no debridement.

Treatment of ocular involvement deserves particular attention, because almost all cases of TENS are associated with ocular manifestations. Treatment includes topical lubricants, steroid drops, and regular release of symblepharon.<sup>43</sup> Conjunctivitis, corneal ulcers, lid margin keratinization, and infections are potential complications which underlies the importance of a thorough ophthalmologic review on admission to help minimize the long-term sequelae.<sup>44,45</sup> Ocular complications and mucosal scarring remain a significant risk for survivors.<sup>23</sup>

**Table 1.** Skin lesion-based diagnosis of necrotizing skin disease

Category	Type of Skin Lesion	Extent of Detachment (% TBSA)
EM major	Acral distribution; typical targets or raised atypical targets; mucosal erosions	<10
SJS	Widespread; macules with blisters or flat atypical targets; mucosal erosions	<10
SJS or TENS	Widespread; macules with blisters or flat atypical targets; mucosal erosions	10–30
TENS with “spots”	Widespread; macules with blisters or flat atypical targets; mucosal erosions	>30
TENS without “spots”	Blisters on confluent erythema; mucosal erosions	>10

TBSA, Total Body Surface Area; EM, Erythema Multiforme; SJS, Stevens—Johnson Syndrome; TENS, Toxic Epidermal Necrolysis.

## MORTALITY AND PROGNOSIS

The mortality associated with TENS ranges from 30 to 50%, which is significantly higher than episodes of SJS (1–3%). The primary cause of death in TENS is infection and multi-system organ failure. As in burn patients, age and extent of skin detachment are still considered major prognostic factors. However, after controlling for extent of skin detachment, a diagnosis of TENS generally carries a worse prognosis. The SCORTEN (severity-of-illness score for TEN) is a validated model of disease severity which has been shown to accurately predict mortality from TENS based on a seven point checklist.<sup>46</sup> Tables 2 and 3 demonstrate the seven variables identified and pre-

**Table 2.** The SCORTEN scoring system

SCORTEN variables
1. Extent of epidermal detachment >10%
2. Age >40 yr
3. Heart rate >120/min
4. Bicarbonate <20 mmol/l
5. Serum urea nitrogen >28 mg/dl
6. Glucose >252 mg/dl
7. History of malignancy

**Table 3.** Predicting mortality in TENS based on SCORTEN

Scorten Value	Predicted Mortality Rate (%)
0-1	3.2
2	12.1
3	32.4
4	62.2
5	85.5
>6	95

dicted mortality, respectively. The SCORTEN value is calculated by giving one point to each of the variables present in the first 24 hours after admission. However, given the lack of consensus on what constitutes a standardized protocol of care, there still remains significant heterogeneity in the treatment of TENS patients.<sup>47</sup> A recent report suggested that mortality is overestimated by SCORTEN in the setting of a standardized protocol and that the implementation of a standardized clinical pathway in the treatment of TENS significantly reduces the mortality rate.<sup>48</sup> Despite improvement in the standardized care of the burned patient, standard therapy in TENS remains controversial. Despite best efforts, the mortality associated with TENS continues to be high. Further investigation into novel treatments, including

debridement strategies and therapeutic interventions, is warranted.

## NOVEL TREATMENT STRATEGIES

Given the low incidence of TENS, randomized controlled trials comparing potential therapeutics are rare. As such, the number of patients required to achieve statistical power in a prospective study would mandate a multi-institutional approach. Recent therapeutic interventions in TENS are based on the proposed molecular mechanisms involved in the clinical manifestations of TENS, ie, apoptosis of keratinocytes. As such, the majority of reports in the literature involve single case observations or small, uncontrolled studies. To date, only one prospective, randomized-controlled clinical trial has been reported in the literature.<sup>49</sup> Theoretically, effective treatment strategies should focus on halting keratinocyte apoptosis, either by acting on the keratinocytes directly, or the effectors mediating the process. Table 4 offers a mechanistic overview of reported therapeutic efforts investigated.

Plasmapheresis has been reported to be effective in several studies in the treatment of patients with TENS.<sup>50-57</sup> The theoretical mechanism of action involves the actual removal of the toxin or drug metabolite that was potentially responsible for the direct killing reaction of epidermal keratinocytes. There has also been some suggestion that the mechanism involves removal of the cytokines implicated in the propagation of keratinocyte destruction. Nonetheless, the exact mechanism remains speculative. In six series using plasmapheresis, there was a combined overall mortality rate of 11%. Furthermore, two studies (N = 12) reported the lack of ocular sequelae in the group treated with plasmapheresis.<sup>52,54</sup> One report, however, demonstrated no difference in mortality, length of stay, or time to re-epithelialization between treatment group and the group treated

**Table 4.** Proposed mechanism and medications attempted in the treatment of TENS

Proposed Mechanism	Medication/Intervention	Level of Support
Inhibition of circulating cytokines, mediators	Plasmapheresis	Case series
	Anti-TNF antibodies	Case reports
Direct Inhibition of keratinocyte apoptosis—Fas/FasL	IVIg	Case series, retrospective reviews
	High-dose glucocorticoids	Laboratory evidence
Inhibition of T-cell activation	Glucocorticoids	Case series, retrospective reviews
	Cyclophosphamide	Case series, retrospective reviews
	Cyclosporin A	Case series, retrospective reviews
Modulation of TNF- $\alpha$ activity	Thalidomide	Prospective, randomized trial
	Pentoxifylline	Case series, retrospective reviews

symptomatically.<sup>58</sup> Although the exact mechanism of action is unknown, this current modality would require further investigation to determine efficiency and effectiveness.

The use of cyclosporin A (CSA) has been considered as a potential treatment strategy in TENS. As an immunosuppressant, CSA's activity is directed toward T-cell function and macrophage activation. It has been demonstrated in previous *in vitro* studies that CSA is capable of inhibiting the drug-induced expression of Fas-L and Fas-R mRNA, and TNF- $\alpha$  secretion by human keratinocytes.<sup>59</sup> Several case reports and two case series have reported generally beneficial results associated with cyclosporin.<sup>60-68</sup> All patients from the case reports involved received a varied dose of cyclosporin, ranging from 3 to 5 mg/kg daily, either intravenously or orally, with a broad range of treatment duration, ranging from 8 to 24 days. The case series reported a significantly shorter time to arrest of disease and re-epithelialization in the treatment group, compared with historical controls from the same institution.<sup>60</sup> However, conflicting evidence was demonstrated in another study, suggesting the CSA treatment did not improve re-epithelialization or the morbidity and mortality associated with TENS.<sup>64</sup> Although septic complications were observed in nearly 60% of all patients receiving cyclosporin, treatment with CSA did not appear to increase the risk of septic complications when compared with patients not receiving immunosuppression. The conflicting results suggest that further investigation is warranted.

Cyclophosphamide has been proposed as a treatment strategy in TENS.<sup>69,70</sup> Beneficial effects of cyclophosphamide would arise as a result of this agent's ability to induce apoptosis in immunocytes, which would inhibit the cell-mediated lysis of keratinocytes. With a dose of 300 mg/d, a beneficial clinical effect on pain, re-epidermization, and survival was documented. Early results suggest a potential benefit, but further investigation is warranted.

Corticosteroids have been used as a treatment modality for over 30 years. The main mechanism of intended action is the modification of almost all components of the inflammatory and immune response. Glucocorticoids have been shown to inhibit T-cell activation, as well as NF- $\kappa$ B activation, which is a transcription factor associated with the regulation of production of pro-inflammatory and immunoregulatory cytokines, including IL-6, IL-12, IFN $\gamma$ , and TNF $\alpha$ .<sup>71</sup> Furthermore, in a coculture system, high doses of glucocorticoids were able to inhibit T-cell induced apoptosis of cultured keratinocytes.<sup>72</sup> Historically, high-dose corticosteroid treatment was advocated, particularly during the initial phase of TENS,

specifically to inhibit inflammation.<sup>73-76</sup> Daily doses as high as 1 g of hydrocortisone were recommended to prevent the extension of epidermal loss.

Despite laboratory evidence of potential success, the use of corticosteroids in the treatment of TENS remains controversial. Several studies have concluded that corticosteroid treatment does not affect the mortality in TENS.<sup>77-79</sup> In fact, several authors contend that systemic corticosteroids have been shown to be detrimental in TENS, especially with prolonged use.<sup>80</sup> In a retrospective study, a multivariate analysis of prognostic factors showed glucocorticoid therapy was an independent risk factor for increased mortality.<sup>33</sup> This study suggested that administration of systemic glucocorticoids for more than 48 hours was associated with a higher rate of infection, a longer hospitalization, and an increased mortality rate. Adding more doubt on the usefulness of corticosteroids in TENS is the observation that between 5% and 7% of TENS cases have been reported in patients already on high-dose corticosteroids for preexisting diseases.<sup>81,82</sup> Based on these data, corticosteroid use is no longer recommended by most authors.<sup>79,83-88</sup>

Thalidomide has been proposed as a treatment of TENS because it inhibits the production of TNF $\alpha$  and IL-6 by monocytes and lymphocytes. Of all treatment strategies discussed in this review, thalidomide is the only treatment tested in a double-blind, randomized, placebo-controlled study.<sup>49</sup> The trial was stopped before completion due to increased mortality in the treatment group—83% vs 30%. It has been demonstrated that the negative effect was the result of a paradoxical enhancement of TNF $\alpha$  production in TENS patients treated with thalidomide.<sup>49</sup> Furthermore, thalidomide can also act as a costimulator of cytotoxic T-cells *in vitro*, which could potentially account for increased cell-mediated death.<sup>89</sup> Enough evidence has demonstrated that thalidomide is not recommended in the treatment of TENS.

High dose pentoxifylline (PTX) has been demonstrated to be of potential benefit in the treatment of TENS. *In vitro*, PTX modulates TNF $\alpha$  production, possibly by the inhibition of the messenger RNA transcript.<sup>90,91</sup> PTX has also been shown to inhibit T-cell activation and proliferation, as well as NK cell activity.<sup>92</sup> Two separate case series have reported favorable outcomes with the use of high-dose PTX.<sup>93,94</sup> The efficacy of this treatment must be confirmed in a larger group of patients.

Selective blockade of TNF $\alpha$  provides another potential avenue of therapeutic intervention. Theoretically, by binding excess TNF $\alpha$ , the deleterious effects of TNF $\alpha$  could be regulated. Two recently published case reports describe the successful treatment of

TENS using infliximab, a monoclonal chimeric IgG antibody designed to bind and neutralize TNF $\alpha$ .<sup>95,96</sup> The authors reported that the progression of disease was halted after a single dose (5 mg/kg). Further studies are required to assess the safety and efficacy of infliximab in the treatment of TENS.

Three case reports document the use of recombinant granulocyte colony-stimulating factor for the treatment of TENS associated with leucopenia and neutropenia.<sup>62,97,98</sup> All three patients treated with G-CSF survived after treatment. It is possible to suggest there may be a role for G-CSF in the treatment of the neutropenic/leucopenia as adjunctive therapy. What is uncertain is whether G-CSF has a role as a primary agent. Further investigation is warranted to determine its efficacy as both primary therapy and adjunctive therapy.

The in-vitro studies of Viard et al<sup>26</sup> showed that up-regulation of keratinocyte FasL expression is the critical trigger for keratinocyte destruction during TENS. Furthermore, this induced apoptosis could be completely abrogated by the addition of pooled IVIg, which contained naturally occurring anti-FasL antibody. Others speculate that IVIg may also contain products involved in the inhibition of inflammatory cytokines. Following the in-vitro study, the group demonstrated the efficacy in 10 consecutive TENS patients with IVIg doses ranging from 0.2 to 0.75 g/kg/d with marked clinical improvement. Treatment of TENS with IVIg has been reported in several case studies with wide variation in patients and treatment protocols. As a consequence, results have been inconsistent and, at times, conflicting. Several case series support the use of IVIg, suggesting that mortality rates are improved in IVIg treated cohorts.<sup>99-102</sup> Other groups have demonstrated no improvement in outcome.<sup>103-105</sup> Given such conflicting results, it is difficult to draw a conclusion on the efficacy of IVIg in the treatment of TENS. Much of the conflicting results may be attributable to the inconsistency of pooled IVIg lots. Several questions remain unanswered, including what is the optimal neutralizing titer that is necessary to halt the progression, and, more importantly, what is the true target that is affected with pooled IVIg. Well-designed prospective studies are needed to address whether IVIg does improve outcome.

## CONCLUSION

TENS is a rare, but life-threatening medical emergency with significant morbidity and mortality. Despite continued research efforts and an enhanced understanding of the likely mechanisms involved, no

specific treatment has demonstrated significant enough improvement to truly affect the associated morbidity and mortality. Current accepted standard of care for all TENS patients should include stopping all possible drugs associated with the new onset of symptoms, prompt referral and treatment in a specialized burn center, fluid resuscitation, maintenance of nutritional needs, and local wound care. Further investigation into the basic pathophysiologic disease mechanisms, as well as multi-institutional collaborative efforts will be necessary to develop better treatment strategies, including early/late debridement of wounds vs no debridement, improved nutritional support, and medical therapeutics to halt the progression of widespread premature apoptosis of epidermal keratinocytes.

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