Management of Stevens-Johnson Syndrome-Toxic Epidermal Necrolysis: Looking Beyond Guidelines!

Rajesh Kumar, Anupam Das¹, Sudip Das²

Abstract
Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe cutaneous adverse reactions, which are mainly caused by drugs; and these are usually associated with high degree of morbidity and mortality. Recently, two detailed guidelines were published on the management of SJS/TEN, Indian guidelines and UK guidelines. Still, there is no consensus on the management of SJS/TEN. In this article, our aim is to conceptualize the management aspect of SJS/TEN considering Indian setup. Early discontinuation of all medicines, supportive measures (hydration, electrolytes, and care of denuded skin), corticosteroids and cyclosporine has been found to be useful. Oral provocation test is reserved for patients, who undergo complete remission and this is to be done after hospitalization, under strict vigilance. As there is no consensus, the treatment should be individualized on case to case basis.

Key Words: Management, Stevens-Johnson syndrome, toxic epidermal necrolysis

Introduction
Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe cutaneous adverse reactions (SCAR), which are mainly caused by drugs; and these are usually associated with high morbidity and mortality.¹⁻³ The incidence of SJS varies from 1.2 to 6/million patient-years and that of TEN being 0.4–1.2/million patient-years, with the mortality rate in TEN being three times higher than that of SJS.⁴⁻⁷ High-risk drugs for the development of SJS-TEN include phenobarbital, phenytoin, carbamazepine, lamotrigine, nevirapine, nonsteroidal anti-inflammatory drugs, allopurinol, cotrimoxazole, homeopathic medicines, and fluconazole.⁸⁻²⁶

Diagnostic of Stevens-Johnson Syndrome-Toxic Epidermal Necrolysis
It is essentially a clinical diagnosis. Patients usually give a history of constitutional symptoms including fever, malaise, arthralgia, and sore throat. To start with, the lesions are erythematous to violaceous and purpuric macules which coalesce to form patches. Targetoid lesions may be present. Mostly, the lesions initially involve the trunk which spread distally to involve the limbs. One may also find flaccid bullae. These are usually followed by exfoliation of the skin. SJS is characterized by involvement of <10% body surface area; SJS-TEN overlap signifies 10%–30% involvement and the most severe form of the spectrum, TEN is characterized by involvement of >30% body surface area. Mucosal inflammation (oral, ocular, and genitourinary) is nearly universal. Pseudo-Nikolsky and Asboe Hansen signs can be elicited in most of the cases. Histopathology is usually not required for the diagnosis of SJS-TEN. However, the hallmark findings include full-thickness epidermal necrosis, subepidermal bulla, and scanty inflammatory infiltrate in the papillary dermis.²⁷ The
clinical differentials include morbilliform drug rash, erythema multiforme, drug-induced linear IgA disease, acute generalized exanthematous pustulosis, acute graft versus host disease, drug reaction with eosinophilia and systemic symptoms syndrome, staphylococcal scalded skin syndrome.

Recently, various serum markers have been studied, which can detect an early case of TEN and signal the progression of early morbilliform drug rash to a full-blown case of TEN. Some of them include soluble Fas ligand, granzyme B, soluble CD40 ligand, granulysin, serum high mobility group protein B1 (HMGB1), serum lactate dehydrogenase level, alpha-defensins 1–3 in the blister, Bcl-2 expression in the dermal infiltrate, thymus and activation-regulated chemokine, and glutathione-S transferase-pi expression.\(^ {28-33}\)

The prognosis of the disease is determined using the score of TEN (SCORTEN). It consists of 7 parameters: 

- Age ≥40 years, heart rate ≥120/min, presence of cancer/hematologic malignancy, >10% body surface area involvement, raised blood urea nitrogen (>28 mg/dL), serum bicarbonate <20 mmol/L, serum glucose level >14 mmol/L, calculated within the first 24 h of admission of the patient.\(^ {34}\) Recently, it has been proposed that serial analysis of SCORTEN may provide a better picture regarding the mortality in comparison to the SCORTEN calculation done only on day 1.\(^ {35}\)

Drug provocation tests have been reported to be an effective modality in the preparation of a list of drugs which can be provided to patients who have suffered a drug eruption previously. However, this has to be done under strict medical supervision, preferably in a daycare setting or prolonged admission in a hospital.\(^ {36}\)

**Management**

**General measures**

- Immediate withdrawal of all the suspected drugs is the key to the management of SJS-TEN. Garcia-Doval et al. have shown that earlier withdrawal of the drug is associated with better prognosis. Moreover, it has also been demonstrated, and that patient who develops TEN due to drugs with long half-lives have an increased risk of death.\(^ {37}\)

- Maintenance of an ambient body temperature (31°C–32°C), proper fluid-electrolyte balance, and maintenance of a strict aseptic environment are crucial. Changing of dressing and wound debridement may be considered.\(^ {37}\) The aim should be maintenance of urine output of 50–80 mL/h with 0.5% NaCl supplemented with 20 mEq of KC\(^ {38}\)

- Banana leaf is used in many centers in India during the care of patients with SJS and TEN. It leads to pain reduction, increases the comfort, and leads to early wound healing.\(^ {39}\) However, leaves may be a source of infection and aggravate the chances of developing sepsis. Thus, autoclaved and aseptically handled banana leaves may be used to reduce chance of infection in the treatment of TEN.\(^ {40}\)

- Coverage of denuded skin should be done using paraffin gauze. Latest developments include utilization of porcine xenografts, human allografts, Biobrane (skin substitute made of a synthetic bilaminar membrane and Aquacel Ag, a moisture-retentive hydrofiber dressing known to release silver within the dressing).\(^ {41,42}\)

Patients with severe denudation may require umbilical cord mesenchymal stem cell transplantation.\(^ {43}\) The use of biological membranes reduces wound infections and prevents scarring during the healing phase. The use of biomembranes on exposed dermis and the sensitive dermal nerve endings avoids frequent dressing change and minimizes pain and discomfort, thus increasing the patient compliance.\(^ {44}\)

- It is debatable regarding the utility of transfer of the patient to a separate burn unit. Since there is not much literature available on the improved outcome of patients after transfer to a separate ward, it is difficult to comment on the same. However, there are studies published which have discussed the management of patients of TEN in the burn ward, with definitely improved outcome.\(^ {45-48}\) This emphasizes the role of early referral of cases of TEN to well-equipped centers

- Persistent inflammation and ulceration of the eyes with cicatrical complications of the lids lead to chronic sequelae including ocular surface damage and scarring. Good eye care with early referral to an ophthalmologist prevents complications such as scarring and synechiae formation.\(^ {49-51}\)

**Medical management**

- Steroids: From Indian perspective of the disease, systemic steroids have been used for decades in the management. Majority of cases are attributed to antibody-dependent cell-mediated cytotoxicity type of hypersensitivity phenomenon which is sensitive to corticosteroids. Early treatment with steroids was associated with improved outcome. Oral steroids, instituted within 24–48 h of onset of disease and tapering over the next 7–10 days gives best results.\(^ {52}\) Dexamethasone 8–16 mg/day is recommended, but the dose can be higher if considered necessary. In case, the recovery is not adequate, the dose of corticosteroids may be increased by 4 mg dexamethasone on the next day and the evaluation repeated on the next day.\(^ {52-55}\) However, there are no randomized controlled trials which have established the efficacy of steroids.\(^ {56}\) Methylprednisolone pulse therapy (MPT) has been found to reduce the levels of pro-inflammatory cytokines such as interferon-gamma, tumor necrosis factor (TNF)-alpha and interleukin-6 (IL-6), and
improves the survival rate in patients of TEN. However, blinded trials should be carried out to understand the role of MPT in TEN. On the other hand, multiple data have shown that use of steroids was associated with an increase in the duration of hospitalization. Moreover, it led to an increase in the rate of infective complications associated with SJS-TEN. Thus, the role of systemic corticosteroids in the management of TEN is controversial.

- **Cyclosporine:** As per the survey, cyclosporine is the second most commonly used immunomodulator in the treatment of SJS-TEN. It specifically targets granulysin, an important mediator of apoptosis of keratinocytes; and thus, leads to arrest of disease progression. In a clinical trial on 29 patients, cyclosporine was administered at the dose of 3 mg/kg/day for a duration of 10 days and thereafter, it was tapered over a month; there was stabilization of epidermal detachment. Besides, the drug was not associated with any increased mortality. Excellent results were also noted by Arévalo et al. who administered cyclosporine 3 mg/kg daily to 11 patients, with rapid epithelialization and better prognosis. In addition, Reese et al. reported good results in four patients who were given cyclosporine. In a recent study patients, from India, where cyclosporine was given at a dose of 3 mg/kg in three divided doses for 7 days and then tapered over the next 7 days. The mean duration of re-epithelialization and duration of hospital stay was significantly lower in patients receiving cyclosporine in comparison to those patients who were managed using supportive treatment only. Besides, there was no mortality. A recent retrospective study of 71 patients compared cyclosporine and intravenous immunoglobulin (IVIg) in the management of TEN and the use of cyclosporine offered a greater mortality benefit, in terms of standardized mortality ratio. Patients receiving IVIg had a higher mortality than predicted by SCORTEN, but those receiving cyclosporine had a lower mortality. Suprapharmacologic doses of intravenous dexamethasone followed by cyclosporin leads to modification of the immune response. Besides, the side-effects of steroids are minimized with interruption of the disease progression.

- **Tacrolimus:** Recently, a patient of phenytoin-induced SJS was given oral tacrolimus 0.12 mg/kg/day in 2 divided doses. The patient showed dramatic improvement within 48 h. Tacrolimus was tapered after 3 days, at the rate of 0.5 mg/kg body weight/day. Thus, tacrolimus which shares the similar mechanism of action like cyclosporine can be used in the management of SJS although larger studies must be done.

- **IVIgs:** According to a recent survey, this is the most common immunomodulator worldwide, used in the treatment of SJS-TEN. IVIg interferes with death ligand-induced apoptosis. It is used at a dose of 2 g/kg. Low-dose IVIg appears to be a safe and effective treatment for TEN in children as well. Eight controlled and five small, nonrandomized, retrospective studies have been documented. The interesting point is most of the studies favor the use of IVIg in TEN; a large, randomized, placebo-controlled trial (with and without corticosteroids) should be done to make things more conclusive. Paquet et al. concluded that the infusion of IVIg provides significant protection to the keratinocytes, thus limiting the disease progression. There are case reports and studies showing the effectiveness of IVIg in combination with methylprednisolone, IVIg with steroids and infliximab. Combination therapy with low-dose IVIg and steroids is more effective because it reduces mortality and leads to rapid resolution of the condition when compared to steroids alone in TEN. However, there are conflicting reports as well. A study has recently shown that IVIg is not effective in SJS-TEN in both adults and pediatric population. In a paper published by Huang et al., univariate analysis showed that high dosage in adults (>2 g/kg) is associated with reduced mortality, but when the data were adjusted by a multivariate logistic regression model, the doses did not correlate with mortality. Similarly, an analysis of 289 patients from the EuroSCAR study did not find any benefit from corticosteroids or IVIg compared to supportive therapy only. Adding to these data, a recent study did not find any significant decrease in the mortality rate in patients receiving a combination therapy of IVIg and corticosteroids. This could be attributed to other comorbidities in association with the drug hypersensitivity. An important consideration regarding administration of IVIg is the presence of renal impairment. In such cases, IVIg may actually lead to deterioration of the condition. From Indian perspective, management of SJS-TEN using IVIg is not at all cost-effective.

- **Cyclophosphamide:** Since it inhibits CD8, it has been used with success in TEN, at doses of 300 mg/day, tapering to 100 mg/day for up to 6 days. Larger studies are needed to corroborate these results, keeping in mind the chances of potential side effects.

- **Plasmapheresis:** It is a promising alternative modality. Egan et al. reported a series of six patients who underwent plasmapheresis, with good outcome. Besides, not a single case of mortality was reported. This has also been used with success in a patient of TEN with AIDS. However, this procedure requires intensive training and the cost factors also limit the use of plasmapheresis in our setting.

- **Intravenous N-acetylcysteine (NAC):** When this compound is used at a dose of 300 mg/kg/day, it was
found to reduce the time for re-epithelialization.\(^{[95]}\) Saavedra et al. administered 600 mg of intravenous NAC 8 h to a patient, which led to significant improvement of the lesions.\(^{[96]}\)

- **Biologics:** Cytokines such as IL-6 and TNF-alpha are found in higher quantities in the skin of patients of TEN. With this background, anti-TNF-alpha agents such as infliximab and etanercept have been used successfully.\(^{[97-100]}\)
- **Others:** Miscellaneous agents such as GSF have been used in patients of TEN (with or without neutropenia). Recombinant granulocyte colony-stimulating factor (G-CSF), 5 µg/kg/day for 5 days leads to rapid re-epithelialization of skin.\(^{[101]}\)

Literature for management of SJS-TEN in children is lacking. However, a recent review\(^{[102]}\) found that IVIg, systemic corticosteroids (prednisolone, methylprednisolone, and dexamethasone),\(^{[103]}\) dressings,\(^{[104,105]}\) surgical debridement, and support treatment alone; were the major treatment modalities. Few children were given ulinastatin, plasmapheresis, G-CSF,\(^{[106]}\) IV pentoxifylline,\(^{[107]}\) skin substitutes,\(^{[108]}\) and cyclosporine. Steroids and IVIg were associated with improved outcome and those treated only with supportive therapy seemed to have higher morbidity and mortality.

**Management of sequelae**

Since the disease involves ocular, oral, genitourinary, gastrointestinal, and respiratory mucosa, complications can be plenty, depending on the extent of the disease and the point of therapeutic intervention. Early referral to an ophthalmologist is quintessential for estimation of involvement of ocular mucosa. Visual outcome is better in those receiving ophthalmological treatment (topical steroids and lubricants), preferably within 7 days of onset of disease.\(^{[109,110]}\) Serious ocular complications such as corneal scarring, corneal xerosis, trichiasis, and subconjunctival fibrosis need gas permeable scleral contact lens therapy and amniotic membrane transplantation (AMT).

AMT has been reported to be an adjunct to conventional membrane transplantation for the maintenance of best-corrected visual acuity. Besides, AMT also helps to prevent intermediate-term scarring complications of the ocular surface.\(^{[111]}\)

Cutaneous complications are managed by nonadherent dressings. Management of bronchitis, bronchiectasis, bronchiolitis obliterans, and bronchiolitis obliterans organizing pneumonia is done using aerosols, nebulized saline, bronchodilators, bronchial aspiration, physical therapy, intubation and mechanical ventilation. Hypopharyngeal stenosis and esophageal strictures are rare complications. Removal of oral crusting should be done whenever required. Early institution of enteral feeding is crucial for the prevention of such sequelae. Severe cases may require laryngectomy.\(^{[112]}\) Prevention of genitourinary complications such as dyspareunia, adhesions, stenosis, erosions, and strictures require a mandatory consultation with a urologist along with catheterization to maintain the patency of the urinary tract.

**Prevention: Is it possible?**

Keeping in mind, the significant morbidity and mortality associated with the disease; it would have been extremely beneficial if the disease per se could be prevented. Pharmacogenomic screening of HLA alleles before initiating a drug has already been shown useful in the prevention of cutaneous adverse drug reactions.\(^{[113]}\) In December 2007, US Food and Drug Administration (USFDA) recommended HLA-B*1502 testing before the use of carbamazepine in the Asian population. Since then, HLA testing has been made mandatory in Hong Kong, Taiwan, and Singapore. However, there are many debatable points regarding this strategy. It is not clear whether to avoid phenytoin, oxcarbazepine, and lamotrigine in patients who test positive for HLA-B*1502.\(^{[114]}\) Besides, the hypothesis of increased incidence of carbamazepine-induced SJS-TEN in HLA-B*1502 positivity does not hold true in a few parts of Korea and Japan.\(^{[115]}\)

Most importantly, in a country like ours; where financial constraints become the rate-limiting factor before executing any strategy; pharmacogenomic testing is not a practical option. In Hong Kong and Taiwan, the HLA-B*1502 tests are offered without any cost to patients. However, in Singapore, the tests are subsidized up to 25% in government hospitals the private patients pay for the test in full. Of note, there are reports of cases of carbamazepine-induced SJS-TEN in HLA-B*1502 negative patients.\(^{[116]}\) Adding to the already existing problems, in near future, it is possible that Asian countries will face the problem of testing for HLA-B*5801 before prescription of allopurinol.\(^{[117]}\) Since the patients with chronic kidney disease and those who test positive for HLA-B*5801 are at a significantly higher risk of allopurinol-induced SCAR; a question arises; whether the HLA testing should be made mandatory in Asia-Pacific regions in patients who can afford. Besides, USFDA recommends testing for HLA-B*5701 for patients receiving abacavir.\(^{[118]}\)

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

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**What is new?**

- A practical approach to deal with both the conditions.
- Management of sequelae.
- Thought to ponder, can it be prevented?
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