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**Case Series**

# Combination therapy in the treatment of Stevens-Johnson syndrome/ toxic epidermal necrolysis: a case series and review of literature

**Soumi Biswas, Arun Achar*, Chinmay Bera, Adityendu Chakraborty, Mahasweta Ghosh, Monika Kumari**

Department of Dermatology, Nil Ratan Sircar Medical College, Kolkata, West Bengal, India

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***Correspondence:**
Dr. Arun Achar,
E-mail: arunachar1967@gmail.com



## ABSTRACT

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are life-threatening disease of skin and mucous membrane that are mostly caused by drugs. Many studies have focussed on treatment that modify immunologic responses like corticosteroid, IVIG, cyclosporine, biologics like TNF-α inhibitors etanercept, infliximab etc. But there are few studies available on using two immunomodifier drugs simultaneously. However, no standardized treatment protocol has been established for SJS/TEN patients. We present a case-series of 10 SJS-TEN patients treated with both systemic corticosteroid and cyclosporine. We provide a review of literature on individual systemic corticosteroid, cyclosporine and also simultaneous use of both agents for SJS/TEN, including various outcome measures-stabilization, mortality rate, hospital length of stay and comparison to other systemic agents.

**Keywords:** SJS, TEN, Cyclosporine, Corticosteroid, SCORTEN

## INTRODUCTION

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe cutaneous adverse reactions mostly caused by medications. These two conditions are the different spectrum of severity of same diseases. It is classified into SJS (<10% body surface area involved), SJS-TEN overlaps (10-30% body surface area), TEN (>30% body surface area).[1] They have low incidence but high mortality rate. According to a global population-based study, the incidence of SJS and TEN is 1.0 to 6.0 per million and 0.4 to1.2 per million respectively.[2] Extensive skin detachment in SJS/TEN may lead to acute skin failure leading to significant morbidity and mortality. The prognosis parameters are assessed and scored within first 3 days of hospitalization through scoring system called as score of toxic epidermal necrolysis (SCORTEN) score which has following parameters-age >40 years, malignancy, body surface area involved >10%, heart rate >120 bpm, serum urea >10 mmol/l, serum bicarbonate <20 mmol/l, serum glucose >14 mmol/l. Every parameter scores 1 or 0. Higher score signifies poor prognosis and high mortality like score 0-1 denotes predicted mortality rate 3.2%, for score 2 it is 12.1%, score >5 it is 90% respectively.

SJS/TEN is characterised by painful blisters, purpuric macules, atypical target lesions with both skin and mucosal involvement. The skin rash is often preceded by malaise, fever and upper respiratory tract (flu-like) symptoms. Almost all patients with SJS/TEN have mucosal involvement like conjunctiva, genitals and oral cavity. Also cardiovascular, pulmonary, gastrointestinal, renal system can be affected. The major causes of mortality are skin infection, pneumonia, hepatitis and

sepsis. Psychological problems including anxiety, depression, and post-traumatic stress disorder have also been reported in these patients. According to a study, which included 121 patients of SJS/TEN, showed 43.3% patients developed depression, 19.5% developed post-traumatic stress disorder.[3]

Discontinuation of causative agent along with supportive care is the mainstay of treatment. The use of systemic agents is debatable as there is only retrospective data regarding their efficacy with the exception of one randomized control trial demonstrating the ineffectiveness of thalidomide in SJS/TEN.[4] It is our aim that this series of 10 cases and review of current literature will shed additional light on better treating this dermatological emergency.

## CASE SERIES

### *Case 1*

A 12 years old boy presented to us with a complaint of >30% body surface area peeling, purpuric rashes, haemorrhagic crust over lips, sore throat after taking 7 days of 200 mg Thrice daily carbamazepine which was prescribed for his seizure. He has cerebral palsy also. At the time of admission his SCORTEN score was 3. He was started injection dexamethasone at 0.1 mg/kg/day and cyclosporine 5 mg/kg/day. After 4 days of starting treatment, no fresh lesions appeared and the blackish discoloration of detached skin occurred which denotes inactivity of disease. We stopped dexamethasone after three days and continued cyclosporine for another ten days.

### *Case 2*

A 15 years old female with bipolar disorder came to us with a chief complaint of fever, sore throat, haemorrhagic crust over lips and haemorrhagic fluid filled blister almost all over body after taking carbamazepine 200 mg Thrice daily for 8 days which has been prescribed for her mood disorder. At the time of presentation, her SCORTEN score was 3. She was given injection dexamethasone 4 mg and cyclosporine 200 mg in divided dosages. After 3 days, fever subsided along with no fresh lesions occurred. She was discharged after 14 days from hospital.

### *Case 3*

A 42 years old homemaker, with a history of systemic Lupus erythematosus, came to us with bullae, sheet like separation of skin, haemorrhagic crusts over lips, on and off fever, watering of eyes and congested conjunctiva after taking over the counter NSAIDS due to joint pain (Figure 1 A). A diagnosis of TEN was made on the basis of clinical features. Her SCORTEN score was 4 at the time of presentation. She was started injection dexamethasone 8 mg and cyclosporine 400 mg in divided dose along with other general measures like chlorhexidine mouth wash and moxifloxacin eye drops. After six days of treatment, fever subsided, conjunctiva became clear, no new lesion appeared and existing lesion became blackish and the dry (Figure 1 B) which is a sign of recovery. We stopped dexamethasone after the three days abruptly and continued cyclosporine for fifteen days. She was discharged after twenty-one days.


**Figure 1 (A and B): Case no. 3 patient at the time of admission and 4 days after starting oral cyclosporine and intravenous dexamethasone treatment.**

### *Case 4*

A 14 years old boy presented with haemorrhagic crust over lips, purpuric spot all over body with peeling of skin (Figure 2 A) after taking some over the counter NSAIDS due to fever. His SCORTEN score was 2. He was started dexamethasone injection 8mg and oral cyclosporine 5 mg/kg/day. After 4 days he showed sign of remission like blackish discoloration of lesions with no new lesion (Figure 2 B) and he was discharged after 10 days.

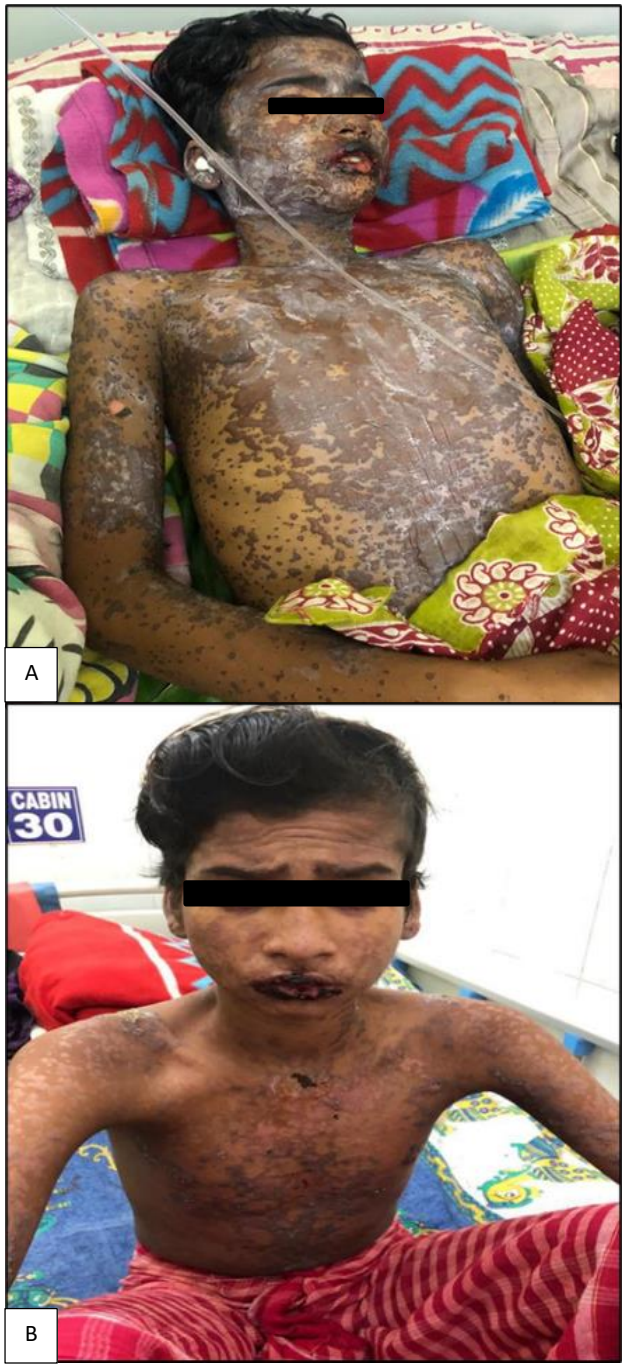


**Figure 2 (A and B): Case no. 4 at 1 day after admission and 14 days after starting of treatment.**


**Figure 3 (A and B): Case no. 5 at the 2 days after treatment and after 6 days after treatment.**

***Case 5***

A 40 years old female with conversion disorder presented with wide spread purpuric rashes, blister, haemorrhagic crust over lips (Figure 3 A) since 3 days after taking carbamazepine. SCORTEN score was 3. She was started dexamethasone 0.1 mg/kg/day and oral cyclosporine 5 mg/kg/day. After 4 days of treatment, no new lesion appeared and existing lesion became dried (Figure 3 B). Dexamethasone has been stopped after 3 days and cyclosporine continued for 10 days. She was discharged after 14 days.

***Case 6***

A 42 years old male, transferred from medicine ward with a diagnosis of toxic epidermal necrolysis with a SCORTEN score 4. Culprit drug was cefuroxime which was prescribed for sore throat. He was started dexamethasone injection 6 mg and cyclosporine 300 mg. After 3 days of starting treatment his TLC falls to 2000/microliter which was 3000 initially and he developed severe respiratory distress. Dexamethasone and cyclosporine had been stopped immediately and

supportive treatment was given in ICU but unfortunately, patient passed away after day 3 in ICU.

***Case 7***

A 52 years old male patient came to us with widespread skin lesions, red conjunctiva, erosions, haemorrhages over lips and oral cavity after taking over the counter painkiller. He is known case of HTN and hyperglycaemia for which he was taking medications for long time. He was started dexamethasone injection 0.1 mg/kg/day and oral cyclosporine 5 mg/kg/day in divided dose along with other general measures. He has been stabilized after 4 days of starting treatment without any adverse effects.

***Case 8***

A 50 years old male presented with skin and mucosal lesion after taking NSAIDS for fever. A diagnosis of TEN was made basis of clinical presentation. His SCORTEN score was 4. He was started dexamethasone injection 0.1 mg/kg/day and oral cyclosporine 5 mg/kg/day. He started recovering after 3 days of treatment. After 3 days dexamethasone was stopped and cyclosporine continued for 12 days.

***Case 9***

A 46 years old male came with severe sheet like separation of skin along with difficulty in swallowing and erosions and haemorrhages over oral mucosa after taking cefixime for sore throat. His SCORTEN score was 3. He was given dexamethasone injection 0.1 mg/kg/day along with oral cyclosporine 5 mg/kg/day. After 5 days of treatment his lesions became dried and blackish without any new lesions. Dexamethasone stopped after 3 days and cyclosporine continued for 15 days. He was discharged after 16 days of admission.

***Case 10***

A 50 years old hypertensive male patient presented to us with extensive peeling of skin with oral and genital mucosal erosions after taking NSAIDS for fever and body ache. His SCORTEN score was 4. He was started with dexamethasone 0.1 mg/kg/day and oral cyclosporine 5 mg/kg/day. His condition improved after 4 days of treatment. Dexamethasone stopped after 3 days and cyclosporine continued for another 10 days. During the treatment period, his blood pressure was within normal range. He was discharged after 14 days of treatment.

**Table 1: Patients demographics and clinical features.**

| Case no. | Age (in years) | Sex | Comorbid conditions | SCORTEN score | Etiology | Stabilization time and outcome (days) |
|---|---|---|---|---|---|---|
| **1** | 12 | Male | Cerebral palsy and seizure | 3 | Carbamazepine | 4, recovered |
| **2** | 15 | Female | Bipolar disorder | 3 | Carbamazepine | 3, recovered |
| **3** | 42 | Female | Systemic lupus erythematosus | 4 | NSAIDS | 6, recovered |
| **4** | 14 | Male | None | 2 | NSAIDS | 4, recovered |
| **5** | 40 | Female | Conversion disorder | 3 | Carbamazepine | 4, recovered |
| **6** | 42 | Male | Myelodysplastic syndrome | 4 | Cefuroxime | Expired |
| **7** | 52 | Male | Hypotension and hyperglycaemia | 4 | NSAIDS | 4, recovered |
| **8** | 50 | Male | None | 4 | NSAIDS | 3, recovered |
| **9** | 46 | Male | None | 3 | Cefixime | 5, recovered |
| **10** | 50 | Male | Hypertension | 4 | NSAIDS | 4, recovered |

## DISCUSSION

Due to the high morbidity and mortality of SJS-TEN, multidisciplinary care in a specialized burn unit is recommended. Identification and withdrawal of the culprit drug is the important part of management. In some case identification of the culprit drugs is difficult, especially in patients taking multiple drugs concurrently. The ALDEN (Algorithm of drug casualty for epidermal necrolysis) algorithm is generally used for assessment of drug casualty retrospectively but not in acute phase.[5] Pharmacovigilance data play an important role in detecting the culprit drugs.

Apoptotic keratinocyte and dermo-epidermal separation are the hallmark of the disease. This is the mainly CD8 T lymphocyte mediated through an interaction between Human leucocytic antigen (HLA) and drug antigens. Fas-Fas ligand (FasL) interaction, perforin/granzyme B, granulysin are mainly responsible for keratinocyte apoptosis.

Due to paucity of randomized control studies because of its high mortality, there is lack of standard treatment guidelines. Different studies concentrate on different immunomodulator drugs.

Corticosteroids are extensively used for SJS/TEN treatment. But a European multi-centre retrospective study found no added benefit of corticosteroid.[6] Meta-analyses by Zimmermann et al and Houschyar et al suggested that steroid may improve survival.[7,8]

IVIG (Intravenous immunoglobulin) is another treatment option for SJS/TEN. A retrospective multi-centre study of 12 patients with SJS/TEN, IVIG at 0.6 g/kg dose for an average of 4 days prevented the progression of epidermal necrolysis and reduced time of mucocutaneous healing.[9] Other studies also showed beneficial effect of IVIG.

Cyclosporine A, a calcineurin inhibitor, has been wide spread used in recent years. Many studies have shown beneficial effect of cyclosporine.

Another treatment option for SJS/ TEN is TNF-α inhibitors. It acts through upregulation of FasL in keratinocytes. Some case reports and case series stated beneficial effects of biologic TNF-α inhibitors such as etanercept and infliximab.[10]

Plasmapheresis is another option in the treatment of SJS/TEN. It acts through removal of drugs, drug metabolites, and cytokines from the patient. In 2017, Giudice et al reported the safety and efficacy of the combination of plasmapheresis and cyclosporine A in the management of TEN.[11]

We summarize the different studies on the different treatment options of SJS/TEN in (Table 2).

**Table 2: Summary of different studies/ meta-analysis on different treatment modalities of SJS/TEN**

| Authors | Included studies /treatment | Outcome |
|---|---|---|
| **Arevalo et al[12]** | Oral cyclosporine vs cyclophosphamide | Complete re-epithelialization within 12 days vs 17.6 days with cyclophosphamide |
| **Valeyrie-Allanore et al[13]** | Oral cyclosporine | 62% stabilised at day 3 vs 35% with IVIG. |
| **Singh et al[14]** | Cyclosporine vs corticosteroid | Stabilized within 3.18 days vs 4.75 days with corticosteroid. |
| **Kirchhof et al[15]** | IVIG vs cyclosporine vs IVIG and cyclosporine | Mortality rate 1 of 13 vs 11 of 37 with IVIG. |
| **Lee et al[16]** | Cyclosporine vs supportive care | Mortality rate 3 of 24 vs 6 of 20 with supportive care only. |
| **Sachdeva et al[17]** | 38 studies/ biologics | TNF-α inhibitors monotherapy improved outcomes. |
| **Zhang et al[18]** | 27 studies/ TNF-α inhibitors | TNF-α inhibitors (Infliximab and etanercept) are safe and effective treatment. |
| **Ye et al[19]** | 26 studies/ IVIG +corticosteroid | Markedly reduced recovery time but not mortality. |
| **Our study** | 10 patients with SJS/TEN treated with inj. dexamethasone and oral cyclosporine | All patients survived except one. Stabilization time was average 4 days. |

## CONCLUSION

SJS/TEN is life-threatening disease. Paucity of randomized control studies on therapeutic agents in the management of SJS/TEN is due to its high mortality. Therefore, an evidence -based approach is needed. In our case-series, the simultaneous use of corticosteroid and oral cyclosporine showed low mortality and starting of rapid re-epithelialization without any significant adverse effects even in hypertensive and diabetic patients which is consistent with previous studies. However, limitation of this is small sample size and lack of control.

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