

# Steven-Johnson Syndrome and toxic epidermal necrolysis at a tertiary care centre in South India: a 12 year retrospective analysis

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## Abstract

**Background** Stevens-Johnson syndrome and Toxic epidermal necrolysis are life threatening mucocutaneous reactions with high mortality. Drugs are the major implicated etiologic agents; others include infections, immunisation, malignancies, radiotherapy and idiopathic. The knowledge on the drugs causing SJS/TEN in a given population can be ascertained by knowing the type of prescription and associated conditions of the patients.

**Aims** 1-To study the demography, etiologic agents, associated conditions and mortality in patients with SJS/TEN. 2- To study the impact of HIV on SJS/TEN with respect to mortality.

**Materials and Methods** A retrospective study was performed by analysing the medical records of patients with SJS, TEN, SJS/TEN overlap admitted in a tertiary care hospital over a period of 12 years.

**Results** Out of 86 patients enrolled in the study, TEN constituted 69(80.23%), SJS 13(15.11%) and SJS/TEN overlap 4 (4.65%). Male to female ratio was 0.72. Maximum number of patients were in 4th decade (25.58%). Antimicrobials (50.00%), antiepileptics (22.91%) and NSAIDs (16.66%) were responsible in majority of patients. HIV (39.53%) and epilepsy (20.93%) were the most common associated conditions. Mortality was seen in 9 patients (10.0%) amongst which 4 patients had HIV infection. There was no statistically significant difference between mortality seen in HIV infected patients and those who did not have HIV ( $p$ -value=0.75).

**Conclusion** Drugs constituted major causative agents. HIV infection had no significant impact on SJS/TEN with respect to mortality. However further studies are needed to substantiate this finding.

## Key words

Steven-Johnson syndrome, toxic epidermal necrolysis, HIV, drugs.

## Introduction

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are acute life-threatening mucocutaneous reactions

characterized by extensive necrosis and detachment of epidermis.<sup>1</sup> The two conditions are considered to be spectrum of identical disease process which only differ in degree of body surface involvement; with epidermal

detachment less than 10% of body surface area classified as SJS, >30% as TEN and 10-30% as SJS/TEN overlap.<sup>2</sup> Clinically, SJS and TEN are characterized by erythematous macules, papules, plaques, vesicles and bullae. Target lesion with bull's eye appearance is characteristic of SJS and TEN.<sup>3</sup>

It is estimated that medications contribute up to 30-50% of cases of SJS and up to 80% of TEN cases in adults.<sup>4</sup> More than 100 drugs have been associated with SJS and TEN, most commonly implicated are anti-epileptics, sulphonamides, beta lactam antibiotics, non-steroidal anti-inflammatory drugs and allopurinol.<sup>5</sup> There is strong HLA association seen with few drugs like allopurinol and carbamazepine.<sup>6,7</sup> There are wide varieties of drugs which do not have proven susceptible genetic factors to cause SJS and TEN. In addition, there are reports where infections, immunisation, malignancies are implicated as etiologic agents and there are reports in which radiotherapy and lupus erythematosus increased the risk of SJS and TEN. Furthermore, there are cases of SJS and TEN which are idiopathic.<sup>1,2,8-11</sup> This implies that there is an interplay of plethora of factors which leads to SJS and TEN.

With this background, a retrospective study of SJS and TEN was undertaken in a tertiary care hospital in South India to know the demography, offending agents, associated conditions and mortality.

### **Aims and Objectives**

1. To study the demography, etiologic agents,

associated conditions and mortality in patients with SJS/TEN.

2. To study the impact of HIV on SJS/TEN with respect to mortality

### **Materials and Methods**

This retrospective study was performed by analyzing the medical records of patients with TEN, SJS and SJS/TEN overlap admitted to tertiary care hospital in South India over a period of 12 years from April 2004 to June 2016. Besides patients who presented to the Department of Skin and sexually transmitted diseases, it included the referred cases from other departments including emergency department. The charts were identified by using the International Classification of Diseases, 10th Revision (ICD-10) discharge code L51.1 for SJS and ICD-10 code L51.2 for TEN. In addition to the patients' demographic data, detailed information pertaining to duration of the rash, drug intake, the time period between the drug intake and the appearance of the rash, systemic symptoms, extent of epidermal necrosis or detachment, mucosal involvement, associated co-morbidities, lab investigations and survival status was noted. Drugs that were taken within eight weeks prior to the onset of symptoms were taken as culprit drugs. The criteria lay down by Bastuji et al. was used for the diagnosis of SJS, TEN, and the SJS-TEN overlap. A note on treatment aspects was also made.

### **Statistical Analysis**

Data was entered into Microsoft ® Excel, and doubly checked for errors. The statistical analyses were performed with the PASW version 19. Continuous data was summarised as Mean and SD. Categorical data was summarised as proportion. Chi square test was used to analyse categorical data. *p*-value <0.05 was considered significant in the analysis.

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## Results

We came across 86 patients with the diagnosis of SJS, TEN and SJS/TEN spectrum. TEN constituted 69 (80.23%), SJS 13 (15.11%) and SJS/TEN overlap 4 (4.65%) patients (**Table 1**). Females (58.1%) outnumbered males (49.1%) both in SJS (9 females and 4 males) and TEN (40 females and 29 females). The mean age was 29.93±(16.12) years. The youngest patient was 1 year old child and oldest was 70 years. Maximum number of patients were seen in 4<sup>th</sup> decade (25.58%) followed by 3<sup>rd</sup> decade (23.25%). 14 patients (16.27%) were under the age group of 12 years.

The duration between exposure to drugs and appearance of symptoms ranged from 1 to 60 days and the mean was 13.06±(12.17) days. The mean delay between symptoms and rash was 2 days for SJS and 6 days for TEN. The mean duration between onset of symptoms and admission was 9.91±(14.05) days. The duration of hospital stay varied from 1 day to 42 days. Majority had hospital stay of 2 weeks (38.40%).

96 drugs were implicated as causative agents in total (**Table 2**). Single drug was implicated in 46

cases, however, more than one drug was suspected in 23 cases. The type of drug taken was not known in 6 cases and 11 patients denied history of drug intake. The major category of drugs causing TEN and SJS were antimicrobials (50.00%) followed by antiepileptics (22.91%) and NSAIDS (16.66%). Nevirapine (25/86) was the major causative drug implicated. Among the single drug culprit cases, nevirapine (17/46), phenytoin (10/46) and diclofenac (4/46) were the most common implicated drugs.

The involvement of oral mucosa was seen in 59 (68.60%) patients, ocular mucosa in 47 patients (54.65%) and genital mucosa in 11 patients (12.79%). All three mucosae were involved in 6 patients (6.97%). Sixty seven (77.90%) patients had associated conditions some of which were the reasons for taking tablets (**Table 3**). Out of 34 patients (39.53%) infected with HIV, 29 patients were on antiretroviral therapy. Septicaemia and DIC were the major complications in the patients. Mortality was seen in 9 patients (10.0%) amongst which 4 patients had HIV infection. There was no statistically significant difference between mortality seen in HIV infected patients and those who did not have HIV (*p*-value=0.75) (**Table 4**).

**Table 1** Various clinical parameters of SJS, TEN and SJS/TEN Overlap

| Parameters   | SJS          | TEN          | SJS/TEN overlap | Total        |
|--|--------------|--------------|-----------------|--------------|
| Number of cases                                    | 13 (15.11%)  | 69 (80.23%)  | 4 (4.65%)       | 86 (100%)    |
| Males  | 4            | 29           | 3               | 36 (40.9%)   |
| Females  | 9            | 40           | 1               | 50 (58.1%)   |
| Male: Female ratio                                 | 0.44         | 0.72         | 3               | 0.72         |
| Mean age (years) (SD)                              | 25 (20.62)   | 30.54 (15)   | 35.50(20.14)    | 29.93(16.12) |
| Mean Incubation period (days) (SD)                 | 7.50 (9.82)  | 13.62(12.44) | 16.67(11.15)    | 13.06(12.17) |
| Mean delay between symptoms and rash (days) (SD)   | 2(NA)        | 6.17 (10.09) | 10(NA)          | 6.15 (9.63)  |
| Mean delay between onset and admission (days) (SD) | 11.31(16.49) | 9.58 (13.98) | 11 (8.04)       | 9.91 (14.05) |
| Mean duration of hospital stay (days) (SD)         | 10.69 (6.30) | 12.80 (9.04) | 20.75(12.97)    | 12.85 (8.98) |
| HIV infection                                      | 03           | 30           | 01              | 34 (39.53%)  |
| Number of deaths                                   | 02           | 07           | 00              | 9 (10.50%)   |
| Mean duration of steroid treatment (days)          | 6.50 (3.06)  | 8.33 (5.40)  | 11.25 (3.50)    | 8.25 (5.13)  |

**Table 2** The drugs implicated in SJS/TEN

| <i>Drug</i>           | <i>SJS</i> | <i>TEN</i> | <i>SJS/TENoverlap</i> | <i>Overall</i> |
|-----------------------|------------|------------|-----------------------|----------------|
| <b>Antimicrobials</b> | 04(4.16%)  | 40(41.6%)  | 04(4.16%)             | 48(50.00%)     |
| Nevirapine            | 01         | 24         | 00                    | 25             |
| Cotrimoxazole         | 01         | 07         | 01                    | 09             |
| Ciprofloxacin         | 01         | 02         | 01                    | 04             |
| Rifampicin            | 01         | 02         | 00                    | 03             |
| Levofloxacin          | 00         | 01         | 01                    | 02             |
| Isoniazid             | 00         | 01         | 01                    | 02             |
| Amoxicilin            | 00         | 01         | 00                    | 01             |
| Cefixime              | 00         | 01         | 00                    | 01             |
| Gatifloxacin          | 00         | 01         | 00                    | 01             |
| <b>Antiepileptics</b> | 01(1.04%)  | 20(18.75%) | 01(1.04%)             | 22(22.91%)     |
| Phenytoin             | 00         | 12         | 01                    | 13             |
| Carbamazepine         | 01         | 02         | 00                    | 03             |
| Phenobarbitone        | 00         | 02         | 00                    | 02             |
| Lamotrigene           | 00         | 02         | 00                    | 02             |
| Sodium Valproate      | 00         | 02         | 00                    | 02             |
| <b>NSAIDS</b>         | 04(4.16%)  | 11(11.45%) | 01(1.04%)             | 16(16.66%)     |
| Diclofenac            | 01         | 06         | 00                    | 07             |
| Paracetamol           | 03         | 03         | 00                    | 06             |
| Ibuprofen             | 00         | 02         | 00                    | 02             |
| Nimesulide            | 00         | 00         | 01                    | 01             |
| <b>Others</b>         | 00(00%)    | 09(9.37%)  | 01(1.04%)             | 10(10.41%)     |
| Cetirizine            | 00         | 01         | 00                    | 01             |
| Amlodipine            | 00         | 01         | 00                    | 01             |
| Atenolol              | 00         | 01         | 00                    | 01             |
| Atorvastatin          | 00         | 01         | 00                    | 01             |
| Clopidogrel           | 00         | 01         | 00                    | 01             |
| Multivitamins         | 00         | 01         | 00                    | 01             |
| Olanzapine            | 00         | 01         | 01                    | 02             |
| Aspirin               | 00         | 01         | 00                    | 01             |
| Vicks Action 500      | 00         | 01         | 00                    | 01             |

**Table 3** Table showing associated conditions

| <i>Associated conditions</i>             | <i>SJS</i> | <i>TEN</i> | <i>SJS/TEN overlap</i> | <i>Overall</i>     |
|--|------------|------------|------------------------|--------------------|
| HIV infection                            | 3          | 30         | 1                      | 34 (39.53%)        |
| Epilepsy                                 | 1          | 16         | 1                      | 18 (20.93%)        |
| Tuberculosis                             | 1          | 4          | 1                      | 06 (6.97%)         |
| Chronic kidney disease                   | 0          | 2          | 0                      | 02 (2.32%)         |
| Pneumocystis carinii pneumonia           | 0          | 2          | 0                      | 02 (2.32%)         |
| Esophageal candidiasis                   | 0          | 1          | 0                      | 1 (1.16%)          |
| Cardiovascular accident with hemiparesis | 0          | 1          | 0                      | 1 (1.16%)          |
| Subarchnoid haemorrhage                  | 0          | 1          | 0                      | 1 (1.16%)          |
| Old subarachnoid hemorrhage              | 0          | 1          | 0                      | 1 (1.16%)          |
| Leprosy                                  | 0          | 1          | 0                      | 1 (1.16%)          |
| <b>Total</b>                             | <b>5</b>   | <b>59</b>  | <b>3</b>               | <b>67 (77.90%)</b> |

**Table 4** survival status in patients infected with HIV in comparison with those who were not infected with HIV.

|               |       | <i>Survival_status</i> |           |              | <i>Chi square test</i> |
|---------------|-------|------------------------|-----------|--------------|------------------------|
|               |       | <i>Yes</i>             | <i>No</i> | <i>Total</i> |                        |
| HIV infection | Yes   | 30(88.20%)             | 4(11.80%) | 34(100%)     | P=0.75                 |
|               | No    | 47(90.40%)             | 5(9.60%)  | 52(100%)     |                        |
|               | Total | 77(89.50%)             | 9(10.50%) | 86(100%)     |                        |

P value< 0.05 is considered significant.

## Discussion

Stevens-Johnson syndrome (SJS) was first described in 1922 by two American physicians named Stevens and Johnson. Toxic epidermal Necrolysis (TEN) was first described by Scottish Dermatologist Alan Lyell in 1956.<sup>12</sup> They are severe forms of hypersensitivity reaction mediated by cytotoxic T lymphocytes to a number of noxious stimuli predominantly drugs via perforin-granzyme route, FAS(CD95)-FAS ligand pathway or nitric oxide synthase route in susceptible individuals.<sup>13,14</sup> Both SJS and TEN are devastating and carry a mortality rate of 5% to 12% and more than 30% respectively.<sup>1</sup>

Patients with TEN were more in number (69) when compared to SJS (13). This finding was in contrast with the studies by Yamane et al.<sup>15</sup> and Kim et al.<sup>16</sup> but Barvalia et al.<sup>17</sup> had observed similar finding in their study. For unclear reasons, female predominance is observed in most of the studies done so far<sup>15,16,18-23</sup> albeit there are studies like Naveen K et al.,<sup>(24)</sup> Barvalia et al.<sup>17</sup> which have shown male predominance. The male to female ratio seen in our study (0.72) was in concordance with the former. Adverse events are more commonly seen in extremes of age due to impaired hepatic enzymes and renal functions.<sup>25</sup> Though the age group ranged from 1 year to 70 years, we observed maximum number of patients in 4<sup>th</sup> decade. The mean age was  $29.93 \pm (16.12)$  years and this was similar to the study done by Knight et al.<sup>17</sup>

Drugs constituted the major causative agents in 74 patients (86.04%). The route of administration was oral except in two cases where it was parenteral. Antimicrobials (50.00%), antiepileptics (22.91%) and NSAIDs (16.66%) were responsible in majority of patients. The causative drugs in various studies usually vary according to the type of

prescription given and as per the associated conditions of the patients. Out of varied reasons for taking tablets, HIV constituted the major reason. Accordingly, nevirapine (25/86) was the major offending drug in our study. More than one drug was implicated in 23 cases. While the type of drug consumed was unknown in 6 cases, history of drug intake was not present in 11 cases. Among the latter, herpes gingivostomatitis was seen in 3 cases but we could not find out the cause in the remaining cases.

The duration between exposure to drugs and appearance of symptoms ranged from 1 to 60 days and the mean duration was  $13.06 \pm (12.17)$  days. It was similar to the study done by Chantaphakul et al.<sup>26</sup> However, it was short in SJS [ $7.50 \pm (9.827)$ ] when compared to TEN [ $13.62 \pm (12.44)$ ] and this differed from studies conducted by Yamane et al.<sup>15</sup> and Barvalia et al.<sup>17</sup> where it was short in TEN. It was interesting to note that 3 patients in whom drugs were implicated as offending agents, (phenytoin in 2 cases and Rifampicin and Levofloxacin in one case) the durations seen were 84, 90 and 115 days. These durations were not included in data as they were not within the usual limit (8 weeks) Nevertheless, we could not rule out the possibility of those drugs to be culprit drugs because of their strong propensity to cause SJS and TEN. Prodromal symptoms like fever, myalgia, and sore throat were the major complaints seen in our patients. The mean delay between symptoms and rash was 6.15 days (9.63) and that between onset and admission was 9.91(14.05). The latter was short in TEN [ $9.58 \pm (13.98)$ ] when compared with SJS [ $11.31(16.49)$ ]. This could be because of earlier presentation due to the severity of TEN. Majority (38.40%) had hospital stay in the range of 1 to 2 weeks. The mean duration was  $12.85 \pm (11.00)$  days which was comparable to the study done by Suwarsa et al.<sup>12</sup>

SJS and TEN often involves mucous membranes of eyes, oral cavity and genitals.<sup>27</sup> Oral mucosal involvement was most common (59) followed by eye (47) and genitalia (11). While involvement of both oral and ocular mucosa was seen in 37 patients, all 3 mucosae including genital mucosa were involved in 6 patients with TEN. Pregnant women who develop SJS/TEN are a unique subset, possibly with different risk factors and outcomes for both the mother and foetus.<sup>28</sup> We observed 3 pregnant patients with TEN in our study. The causative drugs were paracetamol and nevirapine in two each and no drug was implicated in 1 patient. All 3 responded to treatment and survived. However, information pertaining to pregnancy outcome was not available.

We came across 14 (16.27%) pediatric patients (5 with SJS and 9 with TEN) in our study. Paracetamol (3/14), Nevirapine (2/14), Phenobarbitone (2/14), Phenytoin (2/14) were the major offending drugs. Mortality rate was higher (14.30%) than that seen in adults (9.70%), though was not statistically significant. (P value=0.61)

Sixty seven (77.90%) patients had associated conditions like chronic kidney disease, cerebrovascular accident with hemiparesis, hepatitis, oesophageal candidiasis, subarachnoid haemorrhage, PCP, TB, leprosy, HIV, epilepsy few of which were the reasons for taking the drugs which caused SJS and TEN. HIV (39.53%) and epilepsy (20.93%) were the most common. There were totally 9 deaths seen in our study, 7 with TEN and 2 with SJS. The mortality rate was 10.50%. This was comparable to the study done by Suwarsa et al.<sup>12</sup> and Kim et al.<sup>16</sup> Immediate discontinuation of causative agent and supportive medical care might have been the reason for lower mortality rate. The complications seen were septicaemia and DIC

which were the causes of deaths in 8 cases. In one case cause of death was TEN.

HIV/AIDS increases the risk of SJS/TEN by 1000 folds.<sup>9</sup> There were 34 patients (39.50%) infected with HIV (thirty with TEN, three with SJS and one with SJS/TEN overlap) in our study amongst which 29 were on antiretroviral therapy. The incidence of 39.50% was comparable to the studies done by Barwalia et al.<sup>17</sup> and Chantaphakul et al.<sup>26</sup> CD4 counts were available in 16 patients and it ranged from 4 to 1107. The causative drugs were nevirapine 17/29, nevirapine and cotrimoxazole 8/29, Rifampicin 1/29 and cotrimoxazole along with ciprofloxacin and Isoniazid 1/29. The causative drug was not known in 2 cases. Four patients who had TEN succumbed. While Knight et al.<sup>18</sup> observed significant impact of HIV infection on mortality; we did not observe any statistically significant difference between mortality seen in HIV infected patients and those who did not have HIV (p value=0.75). In other words, this study implied that survival rate seen in patients with HIV (88.20%) was almost similar to the patients who did not have HIV (90.40%) (p value=0.75).

Treatment with steroids for SJS/ TEN is like a double edged weapon. While few studies favour its use for its beneficial effects, others argue for its detrimental side effects. Amidst the unresolved controversies, the general consensus adopted in most of the studies is to start with high dose steroids (pulse therapy) at the time of presentation and taper it at the earliest.<sup>5,29</sup> In our study, almost all were treated with initial high dose steroids (2mg/kg in majority) and was tapered soon. The mean duration was  $6.50 \pm (3.06)$  days in SJS and  $8.33 \pm (5.40)$  in TEN. The use of cyclosporine in SJS/TEN began very recently in our institution. It was given in 4 cases in addition to the steroids.

We could review the reports of 53/86 among which 50 were anaemic, 33/86 patients among which 4 had raised transaminases and 52/86 among which 7 had abnormally raised creatinine and urea values. SCORTEN was not done in majority due to incomplete documentation of the required parameters. The information on blood culture and skin culture reports was limited. These were the limitations in our study since it was a retrospective analysis.

## **Conclusion**

While inadvertent drug intake definitely causes serious side effects, appropriate drugs taken as per the prescription for genuine health ailments can also lead to life threatening adverse reactions like SJS and TEN. The study revealed drugs as the major causative agents for SJS and TEN. Although no statistically significant difference was observed between mortality in patients infected with HIV and those without HIV infection, more studies are required to validate this finding. Dermatologists and treating physicians should have an eagle's eye on the slightest symptom and sign in the patients who present with a history of drug intake. Patients should also be counseled and educated regarding unpredictability of drug behaviour and the importance of early presentation to doctors in order to minimise the morbidity and mortality associated with it.

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