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Original Article

A clinicoetiological study of Stevens-Johnson syndrome and toxic epidermal necrolysis

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Abstract

Objectives To present the pattern of morbidity associated complications, and causative factors in individual cases of Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN).

Patients and methods This case series descriptive study, using a convenience sampling technique, was carried out in the In-patients department of Dermatology Unit I, Mayo Hospital, King Edward Medical University, Lahore from January 2007 to September 2008. Thirty clinically diagnosed patients, suffering from SJS/TEN, fulfilling the inclusion criteria were included in the study. Patients' demographic data, symptoms, signs and any relevant investigations were recorded and scored. Using an appropriately designed pro forma, symptoms/ and signs were categorized into thirteen variables. The severity of each variable was scored from1-3 (total score range 13 to 39). An association of these variables with patient outcome, in terms of either discharge from hospital or death, was calculated.

Results Pain and gastrointestinal involvement were seen in all 30 (100%) patients. Mortality was found to be 13.3% and was significantly associated with infection, total morbidity score, area of epidermal involvement and respiratory system involvement. Similarly development of wound infection, area of epidermal involvement, fever and total score significantly affected the duration of hospital stay. While the causative drug/s remained unknown in 26.7% cases the most common identifiable drug was trimethoprim-sulphamethoxazole, causing disease in 13.3%.

Conclusions Mortality in cases of SJS/TEN showed significant association with wound infection, area of skin involvement, total morbidity score and respiratory system involvement.

Key words
Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis.

Introduction

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe forms of hypersensitivity reaction to a number of noxious stimuli predominantly drugs. They involve the trunk and limbs with targetoid lesions resembling those of severe erythema multiforme (EM) as well as the mucosae.[1] There are constitutional symptoms of high fever, malaise, myalgia and arthralgia. The onset is usually sudden and numerous organs are affected. SJS may evolve into TEN (Lyell's syndrome) which is characterized by extensive sheet-like skin erosions with widespread purpuric macules or flat atypical target lesions, accompanied by severe involvement of conjunctival, corneal, irideal, buccal, labial and genital mucous membranes. At this point Nikolsky's sign becomes positive.[2]

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Erythema multiforme was first described by Hebra in 1860 as the occurrence of painful erythematous macules and papules due to dermal hypersensitivity. It was named after Stevens and Johnson in 1922 when, additionally, mucous membrane involvement was observed. While EM is now regarded a different entity SJS and TEN are considered to be variations in severity of the same disease.[3]

A potentially life threatening condition, SJS is associated with significant morbidity. Complications of the syndrome, apart from severe pain, include corneal ulceration, anterior uveitis, panophthalmitis and blindness. Gastrointestinal involvement can result in esophageal strictures. Genitourinary involvement can cause renal tubular necrosis and renal failure as well as penile scarring and vaginal stenosis. Pulmonary involvement can cause tracheo-bronchial shedding and respiratory failure. Recurrent infections, septicemia, scarring and cosmetic deformity are other noteworthy complications. Mortality rate varies from 1 to 5% in Stevens-Johnson syndrome (SJS) to 25 to 35% in established toxic epidermal necrolysis (TEN).

Drugs have been causally associated with Stevens-Johnson syndrome and toxic epidermal necrolysis.[4] Vaccination, graft-versus-host disease, lupus erythematosus and infections with the herpes virus, *Mycoplasma pneumoniae* and *Klebsiella pneumoniae* are some of the other well documented causes. Immune-mediated pathogenic interactions involve keratinocytes, T lymphocytes and cells of the monocyte-macrophage lineage. Tumor necrosis factor-α (TNF- α), interferon-γ (IFN-γ), and interleukin-2 (IL2) have a proven role in bringing about keratinocyte necrosis. Furthermore, keratinocytes when stimulated by IFN-γ express the Fas (CD95) antigen which interacts with its Fas ligand expressed on the surface of and secreted by lymphocytes. This interaction leads to apoptosis of keratinocytes which is a prominent feature of SJS/TEN.[5] In addition, cytotoxic T lymphocytes (CTL) and natural killer cell (NK), through perforin-granzyme and granulysin mediated mechanisms, have been shown to cause apoptosis and necrosis.[6] Adequate explanation for the development of such marked immunological reactions in some individuals but not in others is still lacking.

The incidence of SJS shows regional and age related variation. In France a nationwide survey placed the estimate around 1.2 cases per million per annum. In the USA a study found the incidence of erythema multiforme, SJS and TEN to be 1.8 cases per million patient years for age groups between 20 and 64 years. However, for those less than 20 years and 65 years or more it was 7 and 9 per million person years, respectively and the conditions showed high morbidity and mortality. In Pakistan, though the true incidence remains unknown recent study conducted in Karachi labeled it a rare disease.[7]

In dermatology unit, Mayo hospital, Lahore despite the large patient turnover an attempt to describe the signs and symptoms of the disease had been lacking. This study was conducted to describe the pattern of signs, symptoms and complications regarding the disease in our patients, especially the morbidity, associated with the syndrome.

Patients and methods

This case series descriptive study was conducted in the Department of Dermatology Unit I, King Edward Medical University, Mayo Hospital, Lahore, from January 2007 to September 2008. After informed consent a total of thirty patients

Table 1 Morbidity variables.

1. *Hospital stay* up to three weeks was scored as '1' more than three but less than six weeks as '2' and longer than six weeks as '3'.
2. *Pain* requiring a single analgesic agent either acetaminophen or a non steroidal anti-inflammatory drug (NSAID) for alleviation was scored as '1'. Requirement of both was scored as '2' and need of an opiate analgesic alone or in combination with the above was given a score of '3'.
3. *Fever* (corresponding to sublingual temperature) up to 101°F was given a score of '1' more than 101°F but less than 104°F a score of '2' and 104°F and above , a score of '3', irrespective of the duration.
4. *Area of skin involvement* (using Parkland's rule of 9 for measurement) up to 10% was scored as '1', more than 10% but less than 30% as '2' and 30% and more as '3'.
5. *Ocular involvement* from none to pain and/or inflammation confined to the eyelids or conjunctivae was scored as '1', those involving the cornea as '2' and those causing inflammation of deeper ocular tissues e.g. iridocyclitis was given a score of '3'.
6. *Otitis media* with severity ranging from none to unilateral inflammation with intact tympanum was scored '1', with bilateral involvement was scored '2'and with ruptured tympanum, unilateral or bilateral and discharge was scored as '3'.
7. *Gastrointestinal involvement (GI)* confined to oral mucosa was scored '1', additionally, odynophagia and epigastric pain was given a score of '2', superadded melena or bleeding per rectum in the absence of hemorrhoids was graded '3'.
8. *Respiratory system involvement* No involvement was given a score of '1', involvement of nose and nasopharynx/oropharynx a score of '2' and involvement of the tracheo-bronchial tree and beyond, assessed clinically and/or radiologically was scored as '3'
9. *Cardiac involvement* No cardiac involvement, high output failure and/or 'T' wave changes on ECG, and myocardial infarction of any magnitude was scored 1, 2 and 3 respectively.
10. *Fluid balance* Normal urine 'output', oliguria requiring intravenous fluid administration and acute renal shutdown was given a score of 1, 2 and 3, respectively.
11. *Urinary retention and/or hematuria* No urinary retention, urinary retention of any duration and hematuria was scored as '1', '2'and '3', respectively.
12. *Vaginal involvement* No vaginal involvement or male patient, vulvovaginitis without overt hemorrhage and bleeding per vaginum not due to menstruation was scored 1, 2 and 3, respectively.
13. *Wound infection* No wound infection, infection of one skin lesion and infection of more than one skin lesion was given a score of '1', '2'and '3', respectively.

of any age and either gender with a clinical diagnosis of SJS or TEN were selected using a convenience sampling technique. Those who did not give consent or had co-morbid features like pyrexia of unknown origin, eye, ear disease or any systemic illness prior to the development of SJS were excluded from the study. Similarly, patients on long term glucocorticoid therapy before the development of SJS/TEN were excluded.

A diagnosis of SJS/TEN was made on clinical findings of sudden onset constitutional symptoms associated with tender erythematous wheals, papules/plaques, targetoid lesions, vesicles/bullae and/or sheet-like peeling of skin of any magnitude along with oral and ocular mucosal involvement. Skin biopsies performed in all patients underpinned the clinical diagnosis. A thorough history was taken and detailed clinical examination was carried out in every case.

Patients' demographic data were recorded. Investigations in every case included complete blood count, urine routine examination, chest X-ray, liver and renal function tests.

For measurement of morbidity a system of measurement of thirteen of the most important clinical manifestations of SJS/TEN was devised (**Table 1**) and the data recorded on an appropriately designed pro forma. Once written, it converted the various symptoms and signs of

the disease into numerically calculable morbidity values, each ranging in severity from 1-3. Accordingly, the total score varied from 13 to 39 for each patient and provided a graded index of morbidity.

A morbidity score of 13 was considered as mild while 14 to 26 and 27 to 39 were considered moderate and severe respectively. The effect of these variables on final outcome for the patients, whether in the form of death or discharge from the hospital, was also noted. The routine treatment protocols being observed in the department were recorded for each patient. Abstention from the offending drug, if known, was a ubiquitous practice. Additionally, these were divided into three types which were: general supportive measures alone, in combination with systemic glucocorticoids and in combination with systemic immunosuppressants other than glucocorticoids.

The data were analyzed using SPSS version 11 statistical software. Chi square test was applied to qualitative/categorical variables which were: pain, ocular complications, ear involvement, gastrointestinal complications, respiratory involvement, cardiac involvement, fluid balance, urinary complaints and total score, for calculation of statistical significance. In case of the numerical variables, hospital stay in weeks, total area of skin involvement, number of infected wound sites and fever Student's 't' test was used. A p value of ≤ 0.05 was considered significant.

Results

The sample totaled 30 patients diagnosed with SJS/TEN. The patients' age range was 8 to 65 years and mean age was 30.47 years with a standard deviation of 14.45 and standard error of mean of 2.64. There were 13 (43.3%) females and 17 (56.7%) males**.** The mean age of the females was 30.46 years with a standard deviation of 10.62 and standard error of mean of 2.95 while the mean age of males was 30.47 years with a standard deviation of 17.14 and standard error of mean was 4.16.

All patients (n=30) complained of pain, with 22 (73%) experiencing mild and 8 (27%) having moderate pain. Fever was observed in all patients. Mild fever was experienced by 20 (66.7%), moderate by 7 (23.3%) and high grade by 3 (10%). Less than 10% body surface area was involved in 9 (30%) cases, 10-29% in 10 (33.3%) and 30% or more in 11 (36.7%). All patients except one (3.3%) received corticosteroids along with supportive therapy.

Infection of one skin lesion was observed in 10 (33.3%) patients, infection of more than one lesion was present in 4 (13.3%) while 16 (53.3%) remained free of wound infection.

Ocular complications involving lid and conjunctivae only, were observed in 22 (73%) of patients while 8 (27%) developed corneal involvement. Unilateral aural complications were seen in 25 (83%) patients while 5 (17%) had bilateral involvement. Gastrointestinal involvement was confined to oral mucosa in 10 (33%) while the remaining 20 (67%) complained of odynophagia and epigastric pain. Only in 1 (3.3%) patient was high output cardiac failure seen. Dehydration and oliguria developed in 6 (20%) cases requiring intravenous fluids. Urinary system involvement developed in 2 (6.7%) patients. Out of 13 female patients, 2 (15.4%) developed vulvovaginal involvement.

Frequency data pertaining to total score and causal drugs are presented in **Tables 2** and **3**, respectively.

Table 2 Total score frequency of patients (n=30).

Total score	*N (%)*
13	3 (10.0)
14	4 (13.3)
15	3 (10.0)
16	3 (10.0)
17	6 (20.0)
18	1 (3.3)
19	1 (3.3)
21	2 (6.7)
22	4 (13.3)
23	1 (3.3)
24	1 (3.3)
25	1 (3.3)

Table 3 Causative drugs (n=30).

Causative Drug	*N (%)*
Cotrimoxazole	4 (13.3)
Dipyrone	3 (10.0)
Mefenamic acid	2 (6.7)
Acetaminophen	1 (3.3)
Amoxicillin	1 (3.3)
Levofloxacin	1 (3.3)
Haloperidol	1 (3.3)
Doxycycline	1 (3.3)
Acetyl salicylic acid	1 (3.3)
Carbamazepine	1 (3.3)
Cephradine	1 (3.3)
Clarithromycin	1 (3.3)
Gentamicin	1 (3.3)
Chloroquine	1 (3.3)
Ciprofloxacin	1 (3.3)
Allopurinol	1 (3.3)
Unknown drugs	8 (26.7)

Mortality was 4 (13.3%) and was significantly associated with infection, total morbidity score, area of epidermal involvement and respiratory system involvement. Patients who improved and were discharged from the hospital made up 26 (86.7%) of the total. Their duration of hospitalization correlated significantly with development of wound infection, area of epidermal involvement, fever and total score.

Discussion

This study showed that in the patients examined, there was a male to female patient ratio of 1.3:1. According to a study by Stephen Foster the proportion of females had been estimated to be 33-62%.[8] In a ten year retrospective study in India, Sanmarkan *et al*. found the male to female ratios to be 1.63:1 and 1:2.57 for the SJS and TEN groups, respectively.[9] The largest series reported 39.9% of females in a group of 315 patients with SJS.[6] Where a preponderance of females was seen, it was attributed to generally a greater consumption of drugs by women.[10]

A definite history of intake of medication preceding the onset of the syndrome was invariably present in 100% of the patients (n=30) included in this study. This finding was in keeping with the generally accepted causal association of this syndrome with drugs. Noteworthy was the finding that the identity of by far the most often implicated drug remained unknown. Levi *et al.* found that intake of medications, mostly sulfonamides and the anticonvulsants phenobarbital, carbamazepine and lamotrigine, was associated with all 80 cases of SJS and TEN they studied.[11] In the present study the exact identification of the causative drugs remained latent in 8 (26.7%) cases. A sulphamethoxazole-trimethoprim (Co-trimoxazole) was the etiological agent in 4 (13.3%). The remaining 18 cases showed predominantly a single agent as having caused the disease. Dipyrone for the control of fever had been taken by 3 (10%) cases. Except for mefenamic acid to which 2 (6.7%) cases owed their disease the rest were attributed equally to the drugs mentioned in **Table 3**. This is congruent with a study by Barvalia *et al*. which showed antimicrobials as the most frequent cause followed by non-steroidal anti-inflammatory agents and antiepileptics in that order.[12] In Asian countries traditional herbal remedies have a causal role to play in severe cutaneous adverse reactions including SJS/TEN.[13] Whether these were operative in the

26.7% cases in which the identity of the drug remained unknown is debatable.

This study differs, however, in its finding of dipyrone as one of the offending drugs. Dipyrone use is seldom found in studies conducted outside Pakistan, owing perhaps to its rare use as an antipyretic, a fact which emphasizes its importance in our setting. The other drugs mentioned have at one time or another found their place as factors in the causation of SJS/TEN all over the world.

All patients experienced pain with 73% experiencing mild pain and 27% of moderate intensity, based on the scoring system devised (**Table 1**). Pain was associated with denuded skin and mucosae and was also complained of in the joints. Pain is considered to be a universal finding in most of the studies conducted.[8] It is now considered a very important part of the symptom complex. There was no way of measuring as subjective a variable as pain. The scoring system therefore indirectly extrapolated it from the patients' need for analgesia.

Hospital stay lasted up to three weeks in 26 (86.7%) and between three and 6 weeks in 4 (13.3%) cases. Again, this is not too different from findings of Parillo *et al.* in which re-epithelialization began in a few days except in cases where the disease activity went into a protracted phase and mostly completed in three weeks time.[14] In the present study the duration of hospital stay as a variable correlated significantly with fever, area of skin involvement, the total score and most importantly, with the development of wound infection. The latter occurred in 46.6% of patients and significantly affected mortality. Infection (p=0.02) and total score (p=0.03) were, both found to have a significant correlation with mortality. Infection occurred at one wound site in 10 (33.3%) of patients and at two sites in 4 (13.3%). Skin of the remaining 16 (53.4%) cases remained free of infection. The total area of epidermal separation was significantly related to the frequency of infection (p=0.01). This was an expected finding. Any disruption in the barrier function of the skin facilitates microbial invasion. The lack of cleanliness in our public hospitals also helps promote wound sepsis. According to Pierre Wolkenstein and Jean Revuz the predominant cause of death during TEN was sepsis from *Staphylococcus aureus* and *Pseudomonas aeruginosa*, in their study.[10] Similarly, in a French retrospective study, conducted by de Prost *et al*. sepsis was the main cause of mortality and occurred in 48% of their 179 patients, studied.[15] As expected, it also strongly highlighted the association between area of epidermal detachment and blood stream infection.

The case definition in this study did not take into account the area of skin involvement to classify this severe cutaneous drug reaction into its various subtypes, which was a potential source of bias. In order to control it the mortality was calculated according to the international area-based definitions taking into account the three grades of severity of the variable 'area'. The mortality figures thus calculated were 27.3% for TEN, 10% for SJS/TEN overlap and none for SJS. According to a study from Switzerland by French the mortality rates mentioned for TEN ranged between 25 and 35% while for SJS they were 1 to 5%.[16] Again in a study conducted at the Agha Khan University Hospital, Ahmad *et al*. found mortality rate was 10.1% for SJS.[5] Patients with a total skin area involvement of more than 30% made up 36.7% (n=11). In three out of 4 (75%) cases with a fatal outcome the area of involvement exceeded 30% and in only one did it remain between 10-30%. This increase

in mortality once the area of epidermal detachment exceeded 30% of body surface area was again expected keeping in view the above mentioned figures.

A limitation of the measurement lay in categorizing the area involved into the three broad types as mentioned under the head 'patients and methods'. Inclusion of exact measurements of the body surface area would have engendered a more precise inference.

In this setting mortality rates for cases involving >30% area reached close to the upper limit of the internationally recognized area-specific mortality rates. Certainly, this could be improved, for only steroids were invariably given in all cases where immunosuppression or control of inflammation was needed. Of the more sophisticated immunological therapies, monoclonal anti-TNF-α or pooled human intravenous immunoglobulins have shown dramatic improvement and reduction in mortatility.[17] Unfortunately, in this study, their potential remained untapped even for the more sick patients. Steroids rank among the established therapies for SJS/TEN. Here, the almost universal use of steroids makes their efficacy in treating SJS/TEN elusive to all comment.

Involvement of vital systems like the respiratory and cardiac is certainly expected to have an important bearing on death and disability/morbidity of every patient, especially where multi-system involvement is present, as in these patients. However, cardiac involvement failed to correlate significantly with outcome with a *p* value of 0.133. High output cardiac failure was noted in only one patient out of thirty. Application of significance testing to a single case could not be expected to yield any other result. This patient was among the four who died. She had cardiac, gastrointestinal and respiratory involvement of moderate degree, a total area of dermal involvement/epidermal detachment more than 30% and infection involving multiple sites on her skin and a total score of 22. Hence, cardiac complication in its own right could not be labeled as the only cause of her death.

On the other hand, a fatal outcome correlated very significantly with respiratory system involvement ($p<0.001$). According to a study by Burk *et al*. respiratory involvement occurred mostly in the acute phase of the illness in TEN patients.[18] In their study patients developed dyspnea, bronchial hypersecretion, and hypoxemia within 48 hours of admission, and this was within 4 days of onset of mucocutaneous symptoms. Subsequently, in 9 out of 10 patients ventilatory support was needed. Despite this, only three patients survived underscoring the prognostic value of this dreaded complication.

There was no provision in the scoring system to show a total lack of abnormality in certain variables, like body temperature/fever, ocular involvement and ear involvement. This was certainly a source of observation bias which could not be corrected. Towards the calculation of the total score the same proved to be a limitation.

This study emphasizes the need for educating physicians of all levels of expertise about the potential hazards of giving drugs such as co-trimoxazole and dipyrone. It also underscores the importance of normal, ethical medical practice whereby patients are given written prescriptions of their medicaments. This will ensure that drugs they have taken for any reason do not remain unknown and hence do not

predispose them once again to a second episode of SJS/TEN.

Also noteworthy is the significant association between such variables as respiratory involvement, wound infection and a high total score with a fatal outcome. Such complicated cases require a more aggressive treatment approach. These patients will benefit from frequent and early interventions by the relevant subject specialists. Very important was the finding of contribution of a number of independent as well as dependent variables towards mortality and morbidity from SJS/TEN. This implies that any modification, however small, in any of the variables that show significant correlation with morbidity or mortality is likely to improve disease prognosis.

Limitations

The study was conducted to observe the pattern of clinical manifestations of SJS and was limited in scope in that it was conducted at only one tertiary care hospital. A multi-center approach involving a large sample size would go a long way in educating us about the causal associations, the morbidity patterns, and the associated mortality rates; as well as about the most appropriate management of the syndrome in our setting.

Conclusion

This study showed that mortality in cases of SJS/TEN showed significant association with respiratory system involvement, with the development of wound infection and with the total morbidity score. Better treatment of these parameters/variables could have reduced morbidity and/or mortality.

The area of skin involvement, as an independent variable, significantly affected the development of infection and fever as well total duration of hospital stay. Besides helping to have a direct 'area specific' measurement of disease outcome it also added to the total score and therefore indirectly affected the prognosis.

In future, case-control studies comparing the use of standard steroid based therapies with some of the more modern ones using intravenous immunoglobulins and/or TNF-α inhibitors are needed. In order to prevent this life threatening illness better education needs to be imparted to all the health care professionals. Special emphasis needs to be laid on accurate identification of patients with severe cutaneous adverse reactions and their prompt referral to appropriately equipped hospitals.

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