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Five years of a single burn center experience with toxic epidermal necrolysis: retrospective study of causative drugs and the clinical outcome

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ABSTRACT

Introduction: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare, but potentially life-threatening reactions to medications. Both conditions have significant morbidity and mortality. This study aimed to document the epidemiological features, aetiologies, treatment and clinical outcomes of such patients.

Methods: In this retrospective cross-sectional study the records of all patients with TEN treated for5 years in central Hospital, Mashhad, Iran were reviewed.

Results: Thirty-four patients were studied with a mean age of 26.5 years. Mean age in the mortality and survivors groups was 33.6 and 25.3 years, respectively. Drugs accounted for all 34 cases were including Anti-convulsants (%52.9) other the most common implicated drug followed by antibiotics (%26.5), allopurinol (%5.9) and multiple drugs (anticonvulsants plus antibiotics) (%14.7). Antibiotics had the shortest interval between ingestion time and onset of symptoms. The mean ICU length of stay was 12.7 days, with a range of 1 to 30 days. The mean of SCORTEN was 2.3; it was 3.3 and 2.1 in the mortality and survivors group, respectively (P=0.001). All 34 TEN cases were given intravenous immunoglobulins (IVIG). Six patients with TEN died (%17.6). The highest mortality was found in the allopurinol group with %50, whereas anticonvulsants and antibiotics had a mortality rate of %16.6 and %15.3, respectively.

Conclusion: Anti-convulsants especially Lamotrigine were the most frequently implicated drug, followed by antibiotics and allopurinol. IVIG was shown beneficial effects in TEN syndrome.

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Introduction

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare, but potentially fatal disorders. Based on their surface of skin detachment, they are considered as clinical entities within a spectrum of adverse cutaneous drug reactions having increasing severity (1). SJS and TEN manifest with epidermal and mucosal necrosis and differ by the proportion of relative skin detach-

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ment. In SJS, the affected body surface area does not exceed 10%. Epidermal detachment between 10% and 30% is indicative of a transition zone between SJS and TEN and cutaneous detachment over 30% characterizes TEN (2,3).

Incidence rates of SJS/TEN were previously reported to range from 1.4 to 12.7 cases per million person-years (py). In a recent large cross-sectional study in the US during 4 years, this rate was reported as 12.7 cases/million person-years (4,5).

The majority of cases of SJS and TEN are drug induced. Other possible causes include infections, immunization, environmental chemicals and radiation therapy. The most commonly implicated drugs consist of antibiotics, anti-convulsants, non-steroidal anti-inflammatory drugs (NSAIDS) and allopurinol (6). Mortality of SJS, SJS/TEN and TEN have been described to range from 25% to 70% , including a considerable morbidity (2). Prognostic factors for mortality include age, total burn surface area (TBSA), severe anemia, lymphopenia, neutropenia, serum urea nitrogen level and visceral organ involvement (7). These are included in various scoring systems, such as the simplified acute physiology score (SAPS I and SAPS II) and the SCORTEN, a score is of paramount importance for establishing treatment measures must be performed within the first 48 hours of the disease (6, 7).

A similar scoring system is used for burns, the ABSI (abbreviated burn severity index) score. This score includes gender, age, TBSA, inhalation injury, and full thickness burn and allows for the prediction of fatalities (8). In the present study we used SCORTEN and ABSI scores to better evaluate our patient population. There is great variability in the management of patients with SJS and TEN. Basis of treatment involves immediate discontinuation of the offending agent, early referral to a specialty burn unit as well as supportive care (2,6); particularly for patients with large amounts of skin detachment requiring intensive care in specialized units (9). The pathogenesis of SJS/TEN is still unclear and optimal therapeutic options for SJS/TEN are controversial (10). In addition to the supportive care, several immunomodulative therapies are suggested including glucocorticosteroids, cyclophosphamide, plasma-pheresis and intravenous immunoglobulins (IVIG) (11). The aim of this study was to present the epidemiological features, etiologies, treatment and clinical outcomes of TEN patients admitted to Imam Reza Hospital in Mashhad during a 5-year-period.

Materials and Method

We retrospectively reviewed the medical records of 34 patients who suffered from TEN and were admitted in the Burn Unit of Imam Reza Hospital, Mashhad, Iran over a 5-year period. Diagnosis of TEN was based on clinical features as an epidermal detachment of more than 30% of TBSA and involvement of one or more mucosal surfaces. The notes, charts, lab test results and treatment records of these patients were retrospectively reviewed. The collected data included the age, gender, ethnic group, medical history, presenting complaints, inciting drugs, duration between initial drug consumption and the onset of symptoms and SCORTEN and ABSI scores.

Drug taken within four weeks preceding the onset of symptoms were taken as causal drugs. Treatment regimen, duration of hospitalization and mortality were also recorded. All the 34 TEN cases were administered a total of 3 g/kg of IVIG over 3 days. The collected data were analyzed by the SPSS(version 19) and appropriate statistical tests. The significance level was set at $P<0.05$.

Data description was performed with tables, graphs, central indicators, and dispersion. At the inferential level, Chi-square test, independent t-test and Mann-Whitney test were used to evaluate the hypotheses.

Results

In total, 34 cases of TEN were studied with an age range of 1-59 years. Their mean age was 26.5 years. The highest incidence of TEN, independent from gender, was in the age group of 10–19 years and 31-40 years, respectively. Also, 21 out of the 34 patients were female (61.7%) and 13 cases were male (38.3%). Female to male ratio was 1.6. The mean age in the male and female group was 26 and 27.3 years, respectively that are statistically insignificant ($P= 0.26$). Mean age in the mortality group was 33.6 years whereas it was 25.3 years in the survivors' group.

All patients recalled the medication had taken before the incidence of TEN and therefore revealed a good record of the causing agent. Anti-convulsants consumed by 18 cases (52.9%) were the most common implicated drugs, followed by antibiotics in 9 (26.5%) and allopurinol in 2 (5.9%). In the remaining five cases (14.7%), multiple drugs were consumed (anti-convulsants plus antibiotics). The most frequent causative drugs among the anti-convulsants were Lamotrigine in 12 (35.3%) followed by Phenobarbital in 3, Carbamazepine in 2 and Phenitoin in one case. Ciprofloaxacin (3 cases) was the most frequent antibiotic used, followed by Co-amoxiclav (2 cases). Others antibiotics mentioned in the charts were Vancomycin, Penicillin-v, Co-trimoxazol and Amoxicillin.

The mean time-period between ingestion of the drug and onset of symptoms was 7.2 days, with a range of 1 to 20 days. More than half (58.8%) of the patients developed symptoms within the

first week. Antibiotics had the shortest interval between ingestion time and onset of symptoms (4.6 days); it was 3 days for fluoroquinolones and 4 days for Co-amoxiclav. Anti-convulsants had a mean interval of 8.9 days whereas it was 10 days for allopurinol. The mean length of ICU stay was 12.7 days with a range of 1 to 30 days. The mean ICU stay in the anti-convulsants and antibiotics group was 15 days and 12.8 days, respectively. The ICU stay in the mortality group was more than the survivors group (16.8 vs. 10.5 days, P=0.001).

In order to evaluate the prognosis in patients with TEN, the validated SCORTEN disease severity scoring system (Table1 and figure 1) was used. Six (17.6%) patients had a SCORTEN score of 1, 15 (44.1%) had a score of 2, 10 (29.4%) a score of 3, 2 (5.9%) a score of 4 and 1 (2.9%) patient with a score of 5. The mean SCORTEN score was 2.3. The mean SCORTEN score in the mortality and survivors group was 3.3 and 2.1, respectively (P=0.001).

The total mortality rate was 17.6% (6 cases). The highest mortality was found in the allopurinol group with 50% while anti-convulsants and antibiotics had a mortality rate of 16.6% and 15.3%, respectively. When the ABSI score was calculated for each patient, statistical evaluation showed a decrease in mortality with an increase in TBSA. The mean ABSI was 11 (4-16). The mean ABSI in the mortality group was 10 and in the survivors group was 11.5.

Table 1: SCORTEN

SCORTEN Parameter	Individual Score	SCORTEN (Sum of Individual Scores)	Predicted Mortality (%)
Age>40 years	Yes = 1, No = 0	0–1	3.2
malignancy	Yes = 1, No = 0	2	12.1
Tachycardia (>120/min)	Yes = 1, No = 0	3	35.8
Initial surface of Epidermal detachment >10%	Yes = 1, No = 0	4	58.3
Serum urea >10 mmol/L (28 mg/dl)	Yes = 1, No = 0	≥5	90
Serum glucose >14 mmol/L (252 mg/dl)	Yes = 1, No = 0		
Bicarbonate <20 mmol/L	Yes = 1, No = 0		

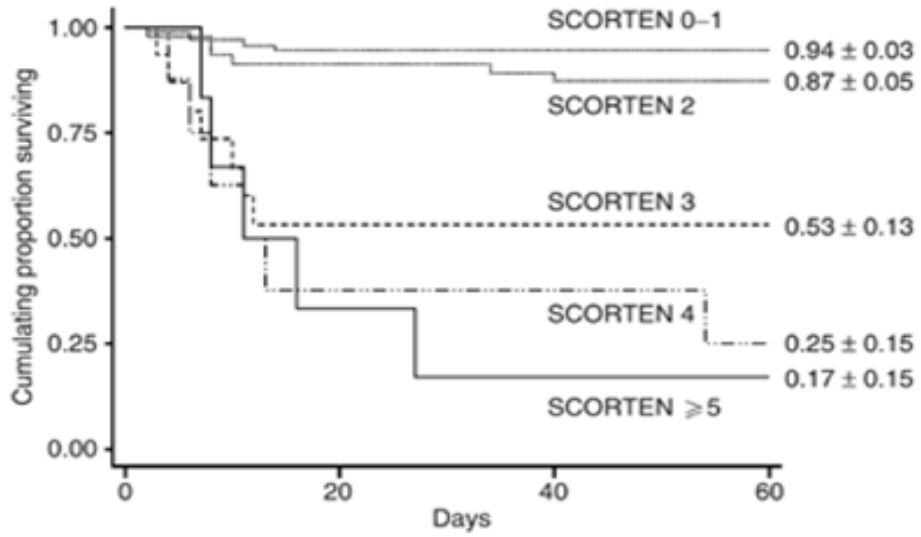

Figure 1: TEN prognosis by SCORTEN

Discussion

TEN still remains a challenge as there is yet no effective treatment known. Mortality described in the literature varies between 16% to 55% (11). In the retrospective chart review by Miliszewski et al. conducted in Canada on 64 cases with SJS and TEN, the mortality rate was 21.8% (13). In our series of 34 cases, the mortality rate was 17.6%. In McCullough et al. study over a 15-year period on 40 patients with SJS and TEN, a mortality rate of only 10% was found. In this study a treatment algorithm consisting of IVIG, fluids resuscitation and nutritional supplementation was used (2).

The onset of SJS/TEN is known to be highest in the adult age group, probably because of the higher intake of drugs in comparison to children and adolescents (9,11). However, in our study, the highest incidence of TEN was in 10-19 years' age group. In a retrospective, cross-sectional and descriptive study in Brazil on 86 cases of hospitalized patients diagnosed with SJS and TEN with a mean age of 23 years, the most affected age group was 0 to 10 years while pa¬tients aged >60 years accounted for 6.98% of cases (6). In a recent large observational study conducted in the UK on 551 SJS/TEN patients during 18 yearss, an overall incidence rate of 5.67 cases/ million person-years was reported. The highest incidence was reported in children aged 1-10 yearss and elderly patients over 80 years (4).

The most common drugs implicated in our hospital were anti-convulsants including Lamotrigine and Carbamazepine (CBZ). Carbamazepine has been reported as the most common causing drug for SJS and TEN in several Asian countries (15-17). In Europe, allopurinol is the most common for these conditions. Daily doses equal to or greater than 200 mg were associated with a higher risk. The risk was restricted to short-term use (≤ 8 weeks) (18).

In the study by Miliszewski et al. in Canada, allopurinol (20%), anticonvulsants and antibiotics were also the most common triggers, respectively (13). The causative drug was antibiotics in 19 (47.5%) anti-epileptics in 8 (20%,), allopurinol in 6 (15%,) in the study by McCullough et al (2).

When calculating the ABSI score for each patient, statistical evaluation showed a decrease in mortality despite an increase in TBSA and despite the predicted increase in mortality by the ABSI score. Inhalation injury is one the major points contributing to mortality prediction when using the ABSI score. In addition, this score was developed to predict the mortality for a burn patient population (8).

However, our results further confirm that the ABSI score should not be used for TEN patients. Nevertheless, no association was found between increased TBSA and a higher mortality in McCullough et al. study (p = 0.17) (2).

The gender distribution for TEN in literature shows that woman have an almost equal or slightly higher incidence than men (11,19). This is not consistent with our study findings. The mean number of days between ingestion of the drug and onset of symptoms for our patients was 7.2 days. For many drugs, the risk of SJS and TEN was highest in the first weeks of use, particularly for antibiotics, as approved in our study. For most high-risk drugs that are intended for long-term use, the risk of developing TEN is elevated during the initial 2 weeks of use (14). In the study from Canada, patients developed symptoms, on average, 31.1 days after initiation of the causative drug if there was no prior exposure to the medication. It decreased to 4.1 days in those with a previous exposure (13).

The overall mortality in our study was 17.6% and the most important complication causing death was sepsis; this is in accordance with the available literature (9). The agent causing the highest mortality was allopurinol with 50%, however, in our studied population of this group involves from a very small number. In the Brazilian study, anticon¬vulsants also accounted for the majority of mortalities, followed by analgesics and antibiotics (6); a similar result was found in the study conducted in the US in which despite antibiotics being the most common class of medications implicated, allopurinol was associated with a higher mortality (33.0% vs. 10.5%) (2).

A few years ago, the EuroSCAR study was published, a large case control study for risk evaluation of drugs causing SJS/TEN (20). Nevertheless, this study evaluated the relative risk of agents causing SJS/TEN and did not correlate mortality to different drugs or drug groups. Therefore, it is of limited value for comparison. Accordingly, there are very few articles in the literature comparing the mortality caused by different drugs (21).

The mean length of ICU stay was 12.7 days with a range of 1 to 30 days, being higher in the mortality group compared to the survivors group (16.8 vs. 10.5 days, P=0.001). The same figure was 15.1 days in McCullough et al. study, the mean length of stay in the deceased group being shorter than the survivors (2). The mean SCORTEN score was 2.3; as 3.3 and 2.1 in the mortality and survivors group, respectively (P=0.001). SCORTEN on admission ranged from 1 to 5 with an average of 2.06 in the latter mentioned study, while higher in the deceased group (2).

To date, the pathogenesis of SJS and TEN is still not fully understood. SJS and TEN are characterized by massive keratinocyte apoptosis. Fas-Fas ligand (FasL)-induced apoptosis in keratinocytes is one of the most thoroughly studied immune mechanisms in SJS/TEN. It was first proposed in 1998 that the death receptor Fas/CD95 plays a key role in the apoptosis

of keratinocytes leading to epidermal necrolysis (22). Subsequently, numerous possible mediators of keratinocyte apoptosis have been suggested, such as peripheral cytotoxic T cells, inflammatory cytokines, nitric oxid, granzyme B, perforin and granulysin (23). The strong association found between HLA-B*1502 with CBZ-induced SJS/TEN (14-18,24) and HLA-B*5801 with allopurinol-induced SJS/TEN (25-28) suggests that genetic predisposition may play a role in the pathogenesis of SJS/TEN.

No treatment modality has yet been established as the gold standard for such patients. There are no randomized controlled trials of pharmacological agents in the treatment of SJS and TEN. However, there are case reports of successful treatment using IVIG, systemic corticosteroids, plasmapheresis, cyclosporine, cyclophosphamide, anti-tumour necrosis factor-α (TNF-α) and haemodialysis (29).

IVIG contains anti-Fas antibodies that can abrogate the Fas-mediated keratinocyte apoptosis. Most studies on IVIG in SJS and TEN reported improvement in arresting disease progression and reduction in time to skin healing (30).

In general, mortality varies from 0% to 12% in studies that support the use of IVIG; it is 25% to 41.7% in those that did not demonstrate a beneficial effect (31,32). Mortality was associated with a lower dose of IVIG, longer time of onset before IVIG use, co-existing underlying chronic conditions, older age and greater involved body surface area (33).

Conclusion

Here, we retrospectively reviewed the medical records of 34 patients who suffered from TEN over a 5-year period. The highest incidence was in 10-19 years' age group with anti-convulsants as most frequently implicated drug, followed by antibiotics and allopurinol. In our case series, IVIG was administered to all patients with a dosage of 3 g/kg over 3 days which resulted in lower mortality and mean length of stay. Therefore, IVIG can be used as a beneficial treatment in TEN syndrome.

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Conflict of interest

None of the authors had any conflict of interest to disclose.

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