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Treatment of toxic epidermal necrolysis by a multidisciplinary team. A review of literature and treatment results

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ABSTRACT

Background: Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are mucocutaneous hypersensitivity reactions, usually to drugs or their metabolites. TEN is the most severe involving greater than 30% of the total body surface area (TBSA). Management of these patients usually benefits from a large multidisciplinary team for both wound and medical management. Treatment of these patients varies between centers and physicians and there is lack of a standardized treatment protocol in the medical literature.

Objectives: To review the literature and complete a retrospective review of patients treated at Vancouver General Hospital over a 11-year period.

Methods: A retrospective chart review of all patients diagnosed with SJS/TEN and treated at Vancouver General Hospital from 2001 to 2011 was completed. Data collected include patient demographics, time to transfer to a burn center, SCORTEN calculation, suspected cause of TEN, %TBSA involved, length of stay in hospital and ICU, medications, dressings, infections/cultures, fluids, mucosal involvement, teams involved, associated complications, morbidity and mortality. Data is reported quantitatively.

Results: A total of 67 patients were identified (28 SJS, 21 SJS/TEN overlap, 18 TEN). In SJS/TEN overlap and TEN patients, oral mucosa and trunk were the primary sites involved. SCORTEN calculations were highest in the TEN group. Plastic surgery was consulted in 53% of TEN cases, 52% of SJS/TEN cases and 25% of SJS cases. Patients were admitted to a burn unit in 74% of TEN cases, 57% of TEN/SJS cases and 21% of SJS cases. Time from symptoms to diagnosis and transfer to a burn unit was highest for TEN patients. Time from presentation to diagnosis was highest in SJS/TEN overlap. Triggers were identified in 67-82% of cases. Treatment varied widely. Patients were treated conservatively, with steroids, IVIg, and cyclosporine alone or in combination. Observed mortality was higher than predicted by SCORTEN for patients treated with IVIg and lower for those treated with Cyclosporin. Dressings varied greatly and were often changed throughout a patients stay. Total mortality was 20.9% being the highest in the TEN group (35%).

Conclusions: SJS and TEN are a spectrum of severe mucocutaneous reactions that have unclear treatment recommendations within the literature and within our Level 1 hospital. Information gleaned from this research will help educate physicians involved in the

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treatment and management of patients with these diagnoses and has resulted in development of treatment guidelines in our hospital.

1. Background, rationale and review of literature

Toxic Epidermal Necrolysis (TEN) is a severe cutaneous reaction to drugs or their metabolites with multisystem involvements. The mortality rate is approximately 30% [1]. The incidence is reported to be 1–2 per million [2,3]. Pathogenesis is largely unknown, but involves an inappropriate immune response leading to apoptosis of keratinocytes causing separation at the dermoepidermal junction. This results in bullae and epidermal sloughing. The reaction can occur in all age groups but the risk is enhanced in the setting of immunosuppression (HIV, SLE, Collagen Vascular Disease, and malignancy) [3,4].

TEN is part of a group of cutaneous hypersensitivity reactions and is the most severe involving greater than 30% of the total body surface area (TBSA). It is advocated that patients with TEN be treated in major burn centers with support of vital organs, dressing care and infection prevention during the process of re-epithelialization [5]. The largest trial to date showed a decreased mortality rate from 51.4% to 29.8% after transfer to a burns unit within 7 days [6]. Management of these patients usually benefits from a large team of physicians in various specialties [7–9]. It also benefits from the support of nurses, dietitians, occupational therapists and physiotherapists.

1.1. *Clinical manifestations*

The clinical manifestations of TEN often include a prodrome of fever, cough, rhinorrhea, conjunctivitis, anorexia and malaise. This is followed by a painful, non-pruritic macular exanthum with a symmetrical distribution on the face and trunk, spreading to the extremities. The lesions typically have a target appearance but differ from erythema multiforme in that they have only two zones of color. The central area may be vesicular, purpuric, or necrotic with a surrounding macular erythema. Vesicles and bullae may develop from these lesions leading to sloughing of large sheets of epidermis. This leaves exposed, weeping dermis and threat of dehydration, hypothermia and infection. Mucosal involvement may involve the oral cavity, conjunctiva, urethra, vagina, nasal vestibule, tracheo-broncheal tree, gastrointestinal tract and anal canal. Erosive mucosal lesions are described in 97% of cases, with involvement of the mouth being present in almost every case, the eyes in about three quarters and the genital region in more than half of patients [4]. Consequently, stomatitis, conjunctivitis, adhesions, vision loss, urethritis, proctitis, vaginitis, tracheo-bronchitis, pneumonia and enteritis can all occur, complicating the clinical picture. Epidermal detachment may progress for 5–7 days followed by re-epithelialization over 1–3 weeks. Involvement of the gastrointestinal, respiratory and genitourinary mucosa may require months before complete re-epithelialization has occurred.

The most common cause of death in these patients is infection. Other causes include pulmonary embolism, respiratory distress syndrome, gastrointestinal hemorrhage, cardiac and renal failure. SCORTEN is a validated tool to measure disease severity and is a good prognostic indicator [10]. It includes 7 clinical variables (age, malignancy, TBSA, HR, serum urea, bicarbonate, glucose) and provides a mortality rate.

1.2. *Drugs*

Development of TEN is most frequently associated with the use of certain drugs (aromatic anticonvulsants, sulfonamide antibiotics, allopurinol, oxicam nonsteroidal anti-inflammatory drugs, nevirapine). According to the Euro-SCAR study in 2008, the following drugs are high risk: Nevirapine, Lamotrigine, Carbamezapine, Phenytoin, Phenobarbital, Cotrimoxazole and other anti-infective sulfonamides, sulfasalazine, allopurinol, oxicam-NSAIDs. Low risk drugs include: Sertraline, Acetic acid NSAIDs, Macrolides, Quinolones, Cephalosporins, Aminopenicillins [11].

1.3. *Genetics*

Genetics may also play a role in the disease. Carbamazepine-induced TEN with the HLA-B*1502 allele among Han Chinese has been described [12,13]. This has now been expanded to include HLA-A*3101 and HLA-B*1511 alleles [1,12]. Other alleles have been associated with the disease including HLA-B*1502 with phenytoin, HLA-B*5801 with allopurinol, HLA-B*38 with sulfamethoxazole or lamotrigine and HLA-B*73 with oxicam non-steroidal anti-inflammatory drugs [7,12]. There are multiple proposed mechanisms including fas-mediated apoptosis, granulysin cell-mediated apoptosis, intracellular keratinocyte damage-reactive oxygen species, alternative cell-mediated apoptosis pathways (cytotoxic lymphocytes expressing CD94/NKG2C, activated by HLA-E which is upregulated in TEN), defective regulatory T-cells, and cytokine-induced amplification of apoptotic pathways [1].

1.4. *Management*

Management varies between centers and physicians. Some advocate for a conservative approach with evacuation of blisters and replacement of the detached epidermis. Others advocate for aggressive debridement. Generally, all patients benefit from careful management of fluid balance, electrolyte disturbances, respiratory function, nutrition, infection control, and pain. Consideration must be given to all epidermal and mucosal surfaces including respiratory, gastrointestinal, ocular, vulvovaginal and preputial. The hypercatabolic state necessitates early enteral nutrition. The most common infecting organism is *Staphylococcus aureus* followed by

Pseudomonas aeruginosa after prolonged admission. There is no survival advantage for empiric antibiotics [14]. Additionally, one must avoid unnecessary catheters and invasive devices.

1.5. Medical

Medical management has changed over time. Systemic corticosteroids were historically considered first-line treatment, but have been associated with increased mortality, higher rates of sepsis and prolonged hospital admissions although a recent European study did not detect increased mortality [1]. Studies are currently pending regarding early high dose steroid before epidermal sloughing. The present recommendation is to avoid use of steroids [1,8].

IVIg, on the other hand, has shown success in some studies. It is thought to prevent apoptosis through inhibitory antibodies (anti-Fas activity). The inhibitory antibodies vary between batches making it difficult to study and thus the supporting evidence is controversial. A meta-analysis in 2007 concluded high doses significantly improved survival [11]. Total doses of 2 g/kg or more have shown a 59% reduction in mortality between expected (SCORTEN) and observed mortality, whereas in lower doses there was only a 3% decrease in mortality. Our group previously showed that Cyclosporin has a standardized mortality ratio of 0.43 over the use of IVIg (1.43) [15]. Plasmapheresis is currently being studied. It is thought to clear drug metabolites and cytokines with preliminary results showing potential survival [8]. Lastly, studies are underway for cyclosporin, cyclophosphamide, and anti-TNF-alpha antibodies that may be of benefit by blocking immune activation.

1.6. Dressings

There is currently no gold standard for wound care in patients with TEN, and treatment often follows local trends in burn care. Appropriate wound care is imperative to prevent heat loss, dehydration, secondary infection and scarring (usually associated with infection). In most centers devitalized epidermis is removed and covered with a non-adherent dressing. Frequent dressing changes and aggressive wound debridement are avoided as they interfere with re-epithelialization. Current dressing choices include biological, biosynthetic, silver or antibiotic impregnated dressings.

Biological agents used in wound care include allografts, xenografts, amniotic membrane, cultured human allogenic and autologous epidermal sheets. Cadaver and amniotic membrane dressings may expose patients to infection. Other biologic dressings, such as temporary skin substitutes, are expensive with varying degrees of adherence. A recent survey showed that 38% of North American Burn Centers and Dermatology Departments use bioactive skin substitutes as their topical treatment [16].

A recent study showed successful wound healing using the application of collagen sheets in 8 patients [17]. Collagen dressings have been found to inhibit the action of metalloproteinases and encourage wound healing through deposition and organization of freshly formed fibres and granulation tissue in the wound bed, thus creating a good environment for wound healing [17]. Moreover, they are easy to apply and have the additional advantage of stopping bleeding, an important property in TEN. Other agents including silver sulphadiazine cream, absorbent dressings like alginates, hydrofibers, cellulose-microfiber biofilm, and synthetic co-polymers have been used but often adhere to wounds causing further trauma and epithelial loss during dressing changes. Nanocrystalline silver dressings combine antimicrobial and anti-inflammatory activity to prevent wound infection. The dressing is widely used in burn wound care but only rare case reports have been reported in treatment of TEN [18]. Further studies are required.

In summary, currently there is the lack of a standardized treatment protocol for patients with SJS and TEN in the medical literature. The difficulties in establishing uniform guidelines are, in part, due to the inherent complexity of the condition and the patients who acquire it.

1.7. Objectives

1. Determine the incidence of Toxic Epidermal Necrolysis, SJS/TEN and SJS at Vancouver General Hospital and their general hospital course.
2. Determine factors that lead to improved survival.

2. Methods

A retrospective analysis of all patients diagnosed with Stevens–Johnson Syndrome (SJS), Stevens–Johnson Syndrome-Toxic Epidermal Necrolysis Overlap (SJS/TEN) and Toxic Epidermal Necrolysis (TEN) treated at Vancouver General Hospital from 2001 to 2011. The Vancouver General Hospital database diagnostic codes were used to find patients treated for these conditions. Chart reviews allowed for a comprehensive evaluation of patient diagnosis and treatment. Data collected included patient demographics (age, sex), comorbid medical illness, allergies, time to transfer to burn center, admission bloodwork (BUN, glucose and bicarbonate to calculate SCORTEN), associated malignancies, heart rate (for SCORTEN calculation), suspected cause of TEN, %TBSA involved, length of stay in hospital, length of stay in ICU, medications, dressings, infections/cultures, fluid resuscitation, ocular involvement/treatment/morbidity, mucosal involvement, teams involved, associated complications, morbidity and mortality.

Inclusion criteria included all adult patients (age >18years) diagnosed with SJS, SJS/TEN and TEN with hospital admission at Vancouver General Hospital. Exclusion criteria included patient's charts with incomplete data pertaining to the factors collected as described above and patients with Erythema Multiforme.

2.1. Statistical analysis

Data analysis is quantitative, reporting trends in TEN care at VGH and any associated increased infections, morbidity or mortality. Quantitative data is reported using basic statistics (e.g. mean, standard deviation and confidence intervals, where appropriate).

Table 1 – Demographics.

	SJS	SJS/TEN	TEN
N	28	21	18
Age (mean)	56.6	49.8	61.5
Gender	14M, 12F	9M, 12F	7M, 11F

3. Results

3.1. General

Out of 71 charts identified, 67 patients met criteria for inclusion by clinical presentation and/or biopsy giving an incidence of 6.1 patients per year. There were 28 patients in the SJS group, 21 patients in the SJS/TEN overlap group and 18 patients in the TEN group. The average age in each group was 56.6, 49.8 and 61.5 years, respectively (Table 1). There were no significant differences between the groups. SCORTEN values were calculated for each patient followed by an average score for each group. In SJS, the average score was 1.3 (mortality rate 3.2%), in SJS/TEN 1.8 (mortality rate 12.1%), and in the TEN group 2.9 (mortality rate 35.3%).

3.2. Co-morbidities

The average number of comorbidities per group was 3. There was no significant difference between types of comorbidities with treatments known to be linked to TEN including gout, cancer, diabetes, immune compromise and seizures (Table 2). There were more diabetics in the TEN group but it was not statistically significant ($p=0.09$). With incorporation of diabetes into the immune compromised group, there was a two-fold increase of patients in the TEN group (data not shown).

3.3. Anatomic involvement

SJS/TEN overlap patients had the highest amount of trunk involvement (Fig. 1). Mucosal surfaces were highly involved in all groups, and the presenting symptom in SJS and TEN groups. Oral mucosa was the most common mucosa to be involved in any group, followed by conjunctiva and perineal involvement (Fig. 2).

3.4. Onset and triggers

The median time frame from symptom onset to presentation to hospital was 96 h in the TEN group, 72 h in the SJS group and 24 h in the SJS/TEN overlap group. Time from presentation to diagnosis was 60 h in the TEN group, 48 h in the SJS/TEN group and 0 h in the SJS group. Time from diagnosis to transfer to a burn unit was 12 h in the TEN group, 24 h in the SJS/TEN overlap group and 2.5 h in the SJS group. There was no significant difference in timing of trigger removal between the groups when comparing removal at symptom onset, admission or diagnosis (Fig. 3).

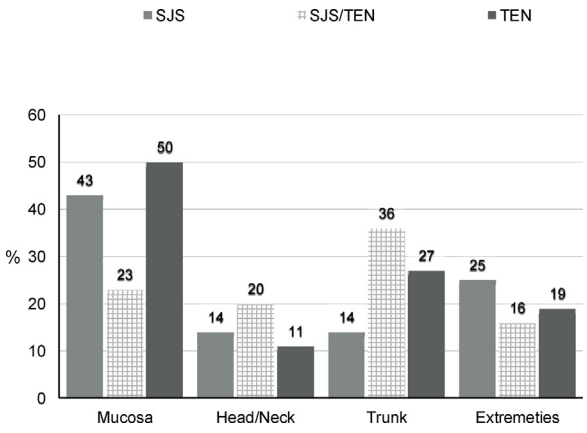

Fig. 1 – Body area involvement.

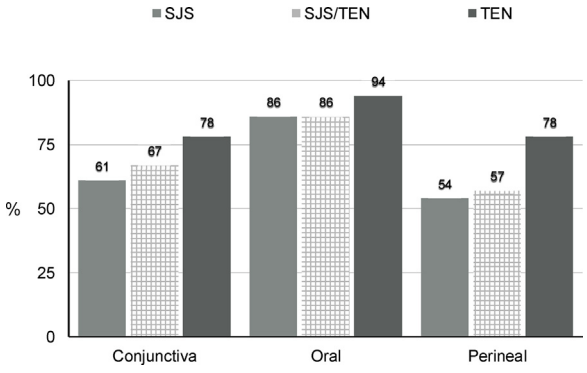

Fig. 2 – Type of mucosa involved.

The cause (or trigger) of the reaction was determined in 82% of the SJS group, 67% of the SJS/TEN overlap group and 79% of the TEN group. The most common triggers where anticonvulsants in 25% of patients followed by allopurinol (20%) of and antibiotics (19%) (Fig. 4). In the anticonvulsant group, phenytoin was the most common cause (16%), followed by carbamazepine (8%), and lamotrigine (2%). In the antibiotic group, sulfamethoxazole-trimethoprim combination was the most common culprit (6%) followed by an even amount of cases for ceftriaxone, cephalexin, vancomycin, amoxicillin, piperacillin-tazobactam, ciprofloxacin, doxycycline and clarithromycin (2% each). The median number of days of exposure to the causative agent was 12 days in the TEN group, 11 days in the

Table 2 – Comorbidities, N (%).

	Number of co-morbidities (mean)	Gout	Cancer	DM	Immune compromised	Seizure
SJS	3.2	7 (25%)	4 (14%)	6 (21%)	4 (14%)	5 (18%)
SJS/TEN	3	2 (10%)	1 (5%)	2 (10%)	6 (21%)	2 (10%)
TEN	3	5 (28%)	2 (11%)	7 (39%)	4 (22%)	1 (6%)

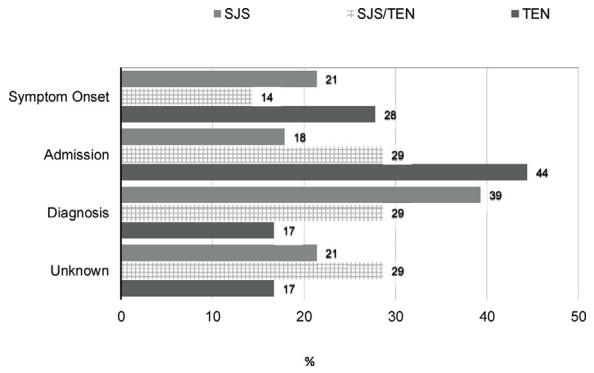

Fig. 3 – Time of trigger removal.

SJS/TEN overlap group and 17.5 days in the SJS group. Previous exposure to the offending agent was found in 15% of TEN patients, 31% of SJS/TEN overlap patients and 21% of SJS (Table 3).

Table 3 – Predicted mortality of patients with Stevens-Johnson Syndrome/toxic epidermal necrolysis using severity-of-illness score for toxic epidermal necrolysis versus observed mortality for patients treated with intravenous immunoglobulin or cyclosporine (with permission from Kirchoff).

	N(patients)	
SCORTEN	IVIg	Cyclosporine
0	2	3
1	12	6
2	11	3
3	6	4
4	5	1
5	1	0
Predicted mortality	7.7	2.4
Observed mortality	11	1
Standardized mortality ratio	1.43 (95% CI 0.71–2.56)	0.42 (95% CI 0.11–2.32)

CI=Confidence interval, IVIg=intravenous immunoglobulin, SCORTEN=severity-of-illness score for toxic epidermal necrolysis.

3.5. *Subspecialty involvement*

Subspecialty involvement was variable. Dermatology was involved in 100% of cases regardless of diagnosis and dietician in all SJS/TEN and TEN patients. Dermatology service also obtained a tissue biopsy from all patients to confirm diagnosis. Plastic Surgery was involved in about half of the SJS/TEN and TEN patients mainly for wound care. The burn unit was involved in 74% of patients with TEN, 57% of patients with SJS/TEN and 21% of patents with SJS. Ophthalmology and ICU were involved in over 70% of SJS/TEN and TEN patients care. (Fig. 5)

3.6. *Medical treatment*

Treatment varied and changed over the study period. The majority of TEN (77.8%) and SJS/TEN (71.4%) patients received IVIg as part of their treatment strategy. Patients with SJS (71.4%) were more commonly treated with steroid (Figs. 6 and 7). Use of IVIg has been bimodal over the study period with increasing use of Cyclosporin (Fig. 8). The dose of IVIg was 2–5 g/kg/day for 3 days while the dose for cyclosporine varied between 3–5 mg/kg/day orally or intravenously for an average of 7 days. There was no significant difference in age or demographics between each treatment group. Predicted mortality was calculated based on SCORTEN and was compared to observed mortality. The standardized mortality ratio (SMR) was calculated for each patient. The predicted mortality in the group treated with cyclosporin was 2.4. The observed mortality was 1, leaving a standardized mortality rate of 0.42 (survival benefit). The predicted mortality of the patients treated with IVIG was 7.7. The observed mortality was 11 leaving a standardized mortality rate of 1.43 (decreased survival).

3.7. *Dressings, fluid resuscitation and cultures*

Dressings used for wound care were highly variable. Dressings included saline soaked gauze (22%), dressings containing antibiotics (17%), silversulphadiazine (14%), steroid containing

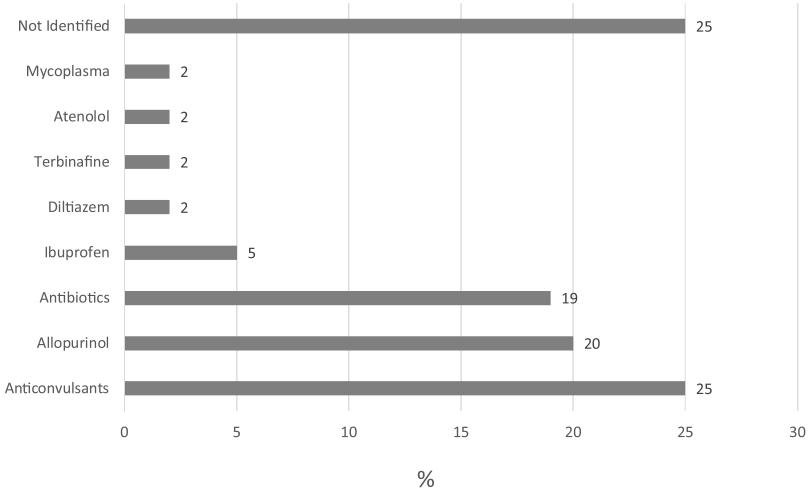

Fig. 4 – Identified triggers.

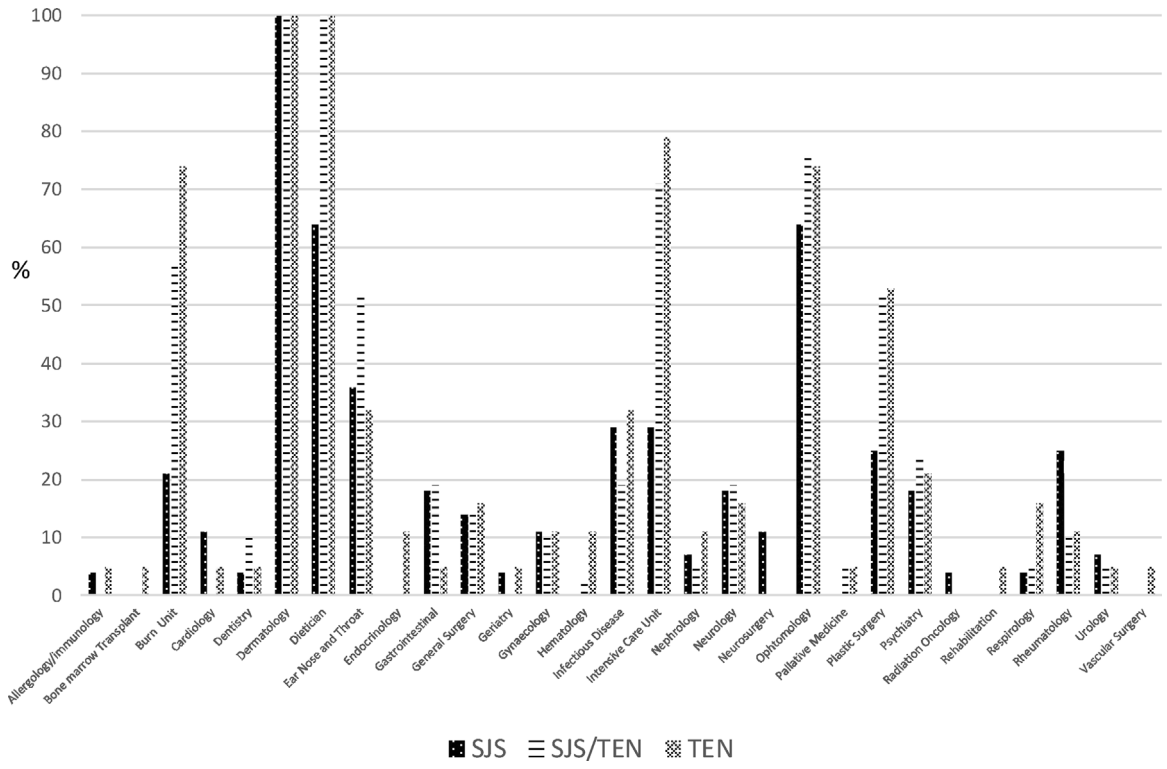

Fig. 5 – Subspecialty involvement.

dressing (15%), vaseline gauze (14%), and silicone coated dressing (7%). Blisters were debrided in 44% of patients with TEN, 14% of patients with SJS/TEN and 7% of patients with SJS. Silversuphadiazine was not used on any patient who had a known sulpha allergy or had sulpha as a trigger.

Fluid resuscitation was very similar regardless of diagnosis. Patients with SJS had an average of 3103 ml of resuscitation fluid in the first 24 h of admission. Patients with SJS/TEN had 3175 ml and patients with TEN had 3714 ml. There was no correlation between time between symptoms to presentation to hospital and the fluids given to the patient. The actual amounts of fluid given the first 24 h did not seem to correlate with hydration status, but was more dependent on the difference in attending physicians, location of admission (burn unit vs medical in-patient unit vs emergency bed).

Various culture results of hospitalized patients were recorded. Positive urine cultures were found in 34.3% of patients during their admission. This was followed by 28.4% positive sputum cultures, 14.9% positive blood cultures, and only 3% with a positive wound culture. Length of hospital stay is presented in Table 4.

3.8. *Mortality*

The total mortality was 20.9% The most common causes of death were multi-organ failure (36%) and bowel perforation (21.4%). Other causes were sepsis, cardiac arrest and ARDS. All patient who had bowel perforation had a TBSA involvement greater than 30%. The deceased patients were older (65.57 vs 53.26 years), had greater TBSA involvement (38 vs 20%) and had a longer length of stay (28.5 vs 20.37 days). Seventy-two percent of patients who died were male and patients with Asian ethnicity had a higher mortality rate than others. (Table 5). The cumulative Kaplan–Meier survival curve is presented in Fig. 9.

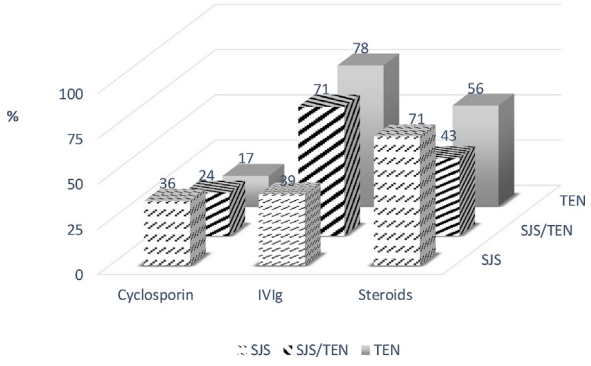

Fig. 6 – Medications used to treat disease.

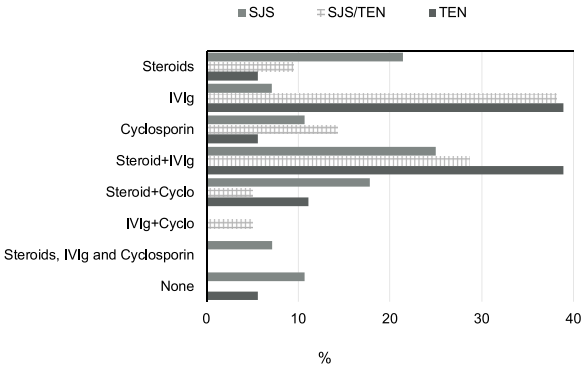

Fig. 7 – Medication combinations by disease severity.

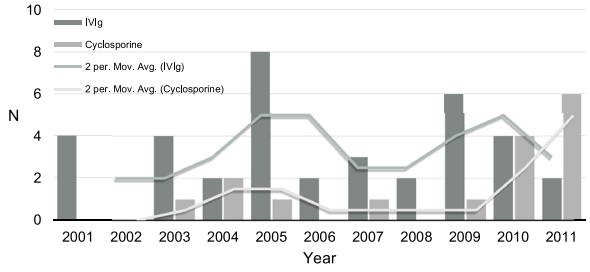

Fig. 8 – Number of Patients Receiving IVIg or Cyclosporine by Year of Admission.

Table 4 – Length of hospital stay by diagnosis.

	SJS	SJS/TEN	TEN
Max	159	71	51
Min	2	3	1
Avg	21	27	18
Median	13	24	18

4. Discussion

Stevens-Johnson Syndrome (SJS), Stevens-Johnson Syndrome-Toxic Epidermal Necrolysis Overlap (SJS/TEN) and Toxic Epidermal Necrolysis (TEN) are mucocutaneous hypersensitivity reactions, usually to drugs or their metabolites. TEN is the most severe involving greater than 30% of the total body surface area (TBSA). Management of these patients usually benefits from a large multidisciplinary team of physicians for both wound and medical management.

Table 5 – Mortality demographics. Data presented as mean (range).

		All	Deceased	Alive
Age (years)		55.79	65.57 (28-88)	53.26 (16-84)
TBSA (%)		24	38 (3-90)	20 (2-80)
LOS (days)		22.04	28.5 (1-159)	20.4 (4-71)
Male (%)		44	72	48
Ethnicity (%)	Asian	36.7	57.1	31.5
	Caucasian	47	28.6	51.8
	First nations	7.4	14.3	5.6
	Southeast Asian	7.4	0	9.3
	Middle Eastern	1.5	0	1.8

Mucosal surfaces are highly involved in all groups warranting a thorough examination and multidisciplinary involvement as indicated. The mucosal involvement in conjunctiva (78%), perineal region (78%) and intraorally (94%) in the TEN patients in our study correlate well with the numbers reported in the literature, with involvement of the mouth in 93%, the eyes in 78% and the genital region in 63% [4]. Dermatology is involved in all cases, with plastic surgery, the burn unit and other services increasingly involved with the increasing severity of disease. This is in accordance to the general

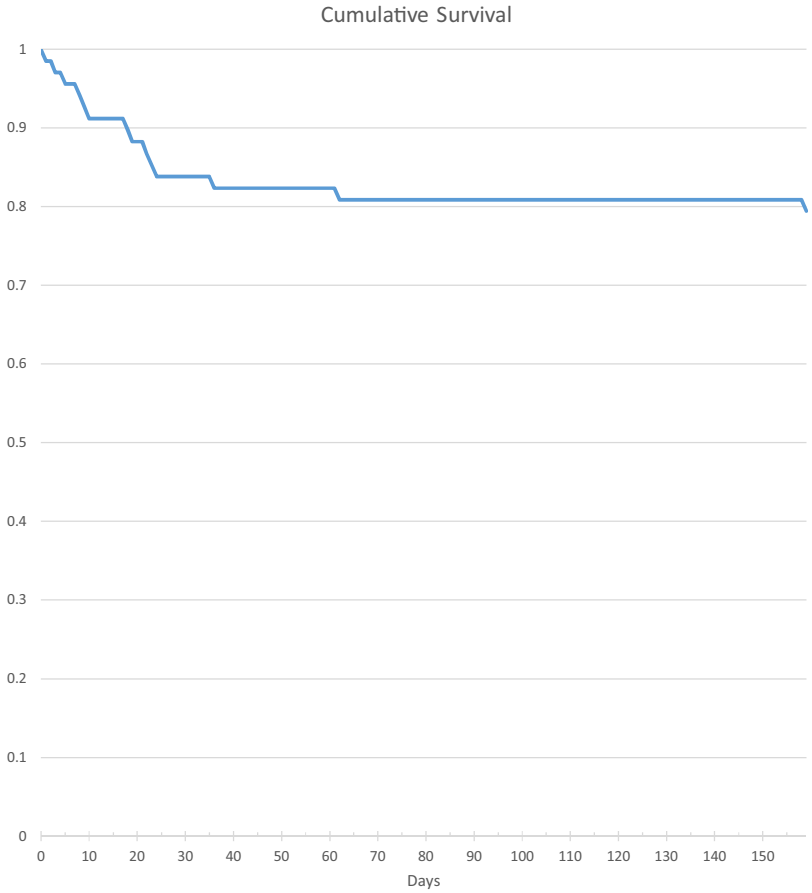

Fig. 9 – Kaplan-Meier cumulative survival curve.

guidelines that the burn unit should be involved in all cases with TEN due to mortality benefit [6].

Triggers were identified in approximately 70–80% of patients. The top 3 triggers where phenytoin, carbamezapine and sulfamethoxazole-trimethoprim. All anticonvulsants were aromatic which the literature has shown to be high risk for this type of reaction [18]. Phenytoin may be showing the highest link out of the aromatic anticonvulsants purely because it is the most prescribed. Attempts to examine this link at our center were unsuccessful. Recent evidence has shown that these reactions may be predicted with genetic testing [3,6,9,13,19,20]. In the future, physicians may be able to test for genetic factors that would be linked to this severe reaction prior to prescribing certain medications.

Interestingly, two of the top three dressings used contained agents that are known to cause the disease (Flamazine® which contains sulpha and certain antibiotic containing agents). There currently is no gold standard for wound care in the literature, and treatment often follows local trends in burn care. Appropriate wound care is imperative to prevent heat loss, dehydration, secondary infection and scarring. In this case series 14% and 17%, respectively, got silversulphadiazine cream (Flamazine®) or an sulpha based dressing despite sulphamethoxazole-trimethoprim (Septra®) being the highest associated antibiotic to cause the reaction. A second hypersensitivity reaction could be catastrophic thus the choice of dressing may need to be looked at in more detail. Additionally, the most common dressing used was saline soaked gauze. This dressing requires frequent changes that can interfere with re-epithelialization and hence could be delay wound healing. None of our patients had a skin substitute such as Biobrane® or cadaver skin used, which have their own inherent risks although have shown promise in the literature with faster epithelialization, mobilization and improved pain control [4,15,21–23]. The burn literature has been highly supportive of Acticoat® dressings due to it's low risk of hypersensitivity reaction, ease of application, anti-infective properties of silver, and its longevity thus decreasing the number of dressing changes required [18,24]. The low number of positive wound cultures in our material (3%) speaks for appropriate wound care.

We could not find a link with infection and blister debridement. Most wounds were not cultured, which is appropriate, as most of them would be colonized with normal skin flora [25]. We noticed an increase in blister debridement with increasing severity of disease. Similarly to burn literature, the role of blister debridement is TEN is unclear.

Surprisingly, despite TBSA or SCORTEN values, the amount of fluid administered to patients in the first 24 h was quite similar in all groups. From the burn literature, we know that fluid over-resuscitation can lead to severe complications [26]. This includes edema, increased burn depth and compartment syndromes. As this was a retrospective chart review, it was difficult to assess the indications for the amount of fluids used. It is possible that co-morbid illnesses where a factor.

As expected, mortality increased with increasing disease severity. TEN patients had the highest scores on the SCORTEN validated system. It is interesting that patients in the TEN group also took longer to present to hospital and longer to diagnose. Our mortality rate in TENS patients, 35%, is in accordance to mortality reported in literature [1]. Increased length of time to treatment is associated with a higher mortality rate [14]. Guillaume et al. calculated a mean time from initiation of drug treatment to onset of TEN of 13.6 days [27]. This was similar in our group (12 days), although we had a much higher proportion of patients who had been exposed to the drug in the past (15–30%).

For treatment, IVIg was the most commonly used agent in patients with TEN and SJS/TEN. SJS patients were more often treated with steroid. Cyclosporin was less commonly used, but it's use increased over the study period with a bimodal variation in IVIg use. It is interesting that we found increased mortality with the use of IVIg versus a mortality benefit with cyclosporine, a finding we published earlier [15]. The literature has remained controversial about the benefit of IVIg and steroids [28–30]. Additionally, the evidence to support cyclosporin comes from small case series [8]. A recent meta-analysis of IVIg use for SJS/TEN did not show a mortality benefit, except amongst pediatric patients [31]. None of our patients received therapeutic plasma exchange, although the literature has seen some benefit [30]. Etanercept may have benefit, in theory, due to higher levels of TNF alpha found in biopsy specimens and blister fluid, but this will require further studies [32].

We acknowledge there are multiple limitations of this study. This study is longitudinal and retrospective. Due to the rarity of this disease (1–2 per million per year), it is difficult to gather a large sample size or prospectively study these patients. Additionally, treatment paradigms have changed over the study period. This makes conclusions about treatment difficult.

In summary, SJS, SJS/TEN and TEN is a multifactorial disease group with multiple algorithms for treatments proposed in the literature [5,33]. Due to the rarity of this condition and huge variety in treatment modalities used it is difficult to back them with evidence. By reviewing the literature and undertaking this study we have created treatment guidelines by a multidisciplinary team. From these guidelines, we will be able to standardize care and continue to revisit and make changes to the guidelines when indicated.

Conflict of interest

The authors warrant that they have no conflicts of interest.

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