Stevens-Johnson syndrome/toxic epidermal necrolysis management in the burn intensive care unit: A case series

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Abstract

Background: *Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) comprise a spectrum of severe hypersensitivity skin reactions. Stevens-Johnson syndrome is the least severe on the spectrum of mucosal erosions, and TEN is the most severe. Stevens-Johnson syndrome/toxic epidermal necrolysis is a disease of keratinocytes, and therefore any squamous cell epithelium is at risk. This includes the cornea, conjunctiva, oral mucosa, esophagus, urethra, and anal canal. This skin reaction is typically drug-induced and has a very poor prognosis.*

Methods: *We present four different SJS/TEN patients who were managed solely in the burn intensive care unit (ICU) at our facility. Treatment focused on supportive care with an emphasis on fluid and electrolyte replacement.*

Results: *The age of these patients ranged from 28 years old to 73 years old; three patients were men, and one patient was a woman. The total body surface area involved ranged from 50% to 90%. These patients required 5 to 18 days hospitalization; complications included one case of sepsis and one case of disseminated herpes simplex virus. Two patients died.*

Conclusion: *The cases reported in this series illustrate the types and complexity of SJS/TEN patients managed in our burn ICU. The management of these patients in the burn ICU with a comprehensive interdisciplinary wound care team may improve outcomes.*

Keywords: Stevens-Johnson syndrome, toxic epidermal necrolysis, burn unit ICU

Introduction

Stevens-Johnson syndrome (SJS) is the least severe on the spectrum of mucosal erosions with toxic epidermal necrolysis (TEN) being the most severe. Stevens-Johnson syndrome is characterized by mucosal erosions and dermal detachment involving less than 10% of the total body surface area (TBSA). Total body surface area involvement between 10–30% is classified as SJS-TEN, an intermediate condition that is considered to be an overlap between the two. Full-scale TEN is characterized by ≥30% of TBSA involvement.[1] This disease is often drug-induced, management is difficult, and the prognosis is poor with mortality rates ranging from 25%–70%.[1]

In 2000, a study by Fouchard et al. reported that the risk of mortality can be predicted on admission with the SCORTEN, or Severity-of-Illness Score for Toxic Epidermal Necrolysis. This scoring system identified seven independent risk factors for death: age >40 years, heart rate >120 bpm, neoplasia, initial detachment >10%, serum urea >10 mmol/L, serum bicarbonate <20 mmol/L, blood glucose >14 mmol/L (Table 1). Each additional point increases the risk of mortality (Table 2).[2]

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Case Presentations

Case 1

A 73-year-old man was transferred with concern for SJS. His rash began 3 days prior, and the following

Table 1. SCORTEN Determination

Diagnostic Factors	Points
Age more than 40 years	1
Malignancy	1
Heart Rate >120/minute	1
Initial epidural detachment >10% of BSA	1
Serum urea level >28 mg/dl	1
Serum bicarbonate levels <20 mEq/dL	1
Serum glucose levels >250 mg/dl	1

day, he noticed painful "water blisters" appearing on his trunk, extremities, face, and oral mucosa. He was taking gabapentin and a one-time dose of an unknown antibiotic given to him by his neighbor 2 weeks prior for a cold. On physical examination, there was diffuse epidermal necrosis with dusky, painful, sloughing skin involving greater than 3 mucosal sites. Findings were concerning for SJS/TEN, with a total body surface area (TBSA) of approximately 80%. The Score of Toxic Epidermal Necrolysis score (SCORTEN) was calculated at 4 (age >40, TBSA >10%, BUN >27 mg/dL, bicarbonate <20 mEq/L), with a mortality risk of 58%.

The patient was transferred to the burn intensive care unit (BICU) and started on supportive therapy. He was placed on 3 days of intravenous immunoglobulin (IVIG) for profound leukopenia and daptomycin and cefepime for antimicrobial prophylaxis. His wounds were covered with Opticell silver dressings with overlying elastic bandages. It was concluded that gabapentin was the most likely culprit of his SJS/TEN development. He later developed candidemia, sepsis, and septic shock. The decision was made to transition to comfort care on day 15. The patient expired on day 18.

Table 2. SCORTEN and Associated Mortality Rates

SCORTEN	Mortality Rates %
0–1	3.2
2	12.1
3	35.8
4	58.3
>5	90

Case 2

A 42-year-old man was transferred from another facility for possible SJS four days after administration of amoxicillin and ibuprofen for a tooth extraction. Approximately four hours after initiation of amoxicillin, he began to notice a painful, burning, red and blistering rash on his face, which subsequently spread to his mouth and trunk. On examination, there were dusky, non-blanching macules and papules coalescing into patches with some areas of vesiculation and early desquamation involving about 50% TBSA, including his eyes, mouth, face, scalp, neck, thorax, proximal extremities, penis, and scrotum. He was transferred to the burn intensive care unit where supportive care was initiated, and was given a single dose of meropenem.

Stevens-Johnson syndrome/toxic epidermal necrolysis was suspected secondary to amoxicillin or ibuprofen. The SCORTEN was calculated at 2 (age >40, TBSA >10%) with a mortality risk of 12%. The patient was discharged on day 12 with instructions for follow-up with dermatology and ophthalmology and precautions to avoid amoxicillin in the future.

Case 3

A 28-year-old man who was positive for human immunodeficiency virus presented with a 5-day history of ocular itching and 4-day history of rash. The rash first developed around the eyes with redness and crusting, rapidly progressing to involve his face, oral mucosa, bilateral upper extremities, trunk, genitalia, and thighs. It became progressively darker with tense bullae formation and skin sloughing. Estimated TBSA involvement was 80%. The patient had been taking trimethoprim-sulfamethoxazole (TMP-SMX) and azithromycin for one week for acute bronchitis. He had not been taking any antiretrovirals for 5 months. Stevens-Johnson syndrome due to TMP-SMX or azithromycin was suspected. His

SCORTEN index was calculated at 1 (TBSA >10%) with a mortality of 3.2%.

The patient was treated with diphenhydramine and corticosteroids prior to transfer. On day 1, he was taken to the operating room for initial excision and debridement of his bullous wounds with Opticell chitosan dressing. Postoperatively, he was given supportive care with IV fluids, nutrition, pain control, and electrolyte replacement. Petroleum jelly-coated gauze was used for eroded surfaces. Ophthalmic tobramycin-dexamethasone and white petrolatum mineral oil eye drops were started for prophylaxis. The patient had an uneventful recovery course and was discharged on day 5.

Case 4

A 55-year-old woman presented with a 22-day history of rash. The patient was previously being treated for methicillin resistant *Staphylococcus aureus* endocarditis with cerebral antibiotics, including TMP-SMX and daptomycin started 20 and 17 days, respectively, prior to rash onset. The patient was also taking olanzapine and levetiracetam for 12 days prior to presentation. The rash manifested as a pruritic and peeling rash on her arms and trunk then blisters on mucosal surfaces. A tentative diagnosis of drug reaction with eosinophilia systemic symptoms (DRESS) syndrome was made, and daptomycin was switched to ceftaroline fosamil. The rash continued to worsen with extensive desquamation and was unresponsive to steroid therapy. The patient was admitted and TBSA was estimated at 90% with ocular and genital involvement. The SCORTEN was calculated at 3 (age >40, TBSA >10%, BUN >27 mg/dL) with a mortality of 35.3%.

The patient was transferred to the burn ICU and placed on norepinephrine for hypotension. Supportive care with IV fluids, nutrition, and electrolyte replacement was started along with Opticell dressing for wound care. Punch biopsy of the lesions on day 2 demonstrated disseminated herpes simplex virus (HSV), for which the patient was started on acyclovir. Ceftaroline fosamil was added for extended spectrum beta-lactamase *Escherichia coli* which was found on urine culture; all other antibiotics were discontinued. It was concluded that either DRESS syndrome or SJS-TEN secondary to antibiotics allowed the superimposed disseminated HSV infection to develop. The patient continued to deteriorate despite aggressive treatment and expired on hospitalization day 9.

Discussion

Stevens-Johnson syndrome is a life-threatening disease characterized by partial-thickness wounds and the detachment of the epidermis at the dermal-epidermal junction.[3,4] It is associated with an overall mortality rate of 30%.[2] Toxic epidermal necrolysis is on the same spectrum of disease as SJS; the two are distinguished from each other by the percentage of body surface area with epidermal detachment.[5]

Alan Lyell was a Scottish dermatologist who defined TEN in a 1956 case series. In his paper, he differentiated TEN from other dermal disorders, such as erythema multiforme, dermatitis herpetiform, and pemphigoid.[6] In 1990 he wrote a requiem for TEN in which he indicated that it was “a waste of effort to distinguish between what were known as TEN and Stevens-Johnson syndrome, since they represent aspects of the same spectrum of reaction.”[7,8] Clinicians have continued to use SJS and TEN to refer to the same disease but to distinguish severity and involvement of TBSA. This has led to the persistence of this confusing terminology.

The underlying pathogenesis of SJS/TEN is unclear, but it appears to be very similar to a delayed-type hypersensitivity reaction. It is thought to occur related to medication use but can also be secondary to malignancy or infection.[9] Repeat exposure to the same or similar drug leads to replication of and sometimes more severe reactions. Common offending drugs include allopurinol, sulfonamides, and anticonvulsants. Patients often experience a 1–3-day prodromal phase that consists of fever, rash, conjunctivitis, and pharyngitis. Thereafter, they develop a purpuric, exfoliative rash.[4] Epidermal detachment results in flaccid blisters, resulting in sepsis which is the most common cause of death secondary to loss of skin barrier.[9] Disjunction of keratinocytes and loss of

the dermo-epidermal junction results in Nikolsky sign, in which pressure applied to the skin results in separation of epidermis from dermis.[10]

The rash and subsequent healing of SJS/TEN are similar to uniform superficial partial thickness burns, with an immediate inflammatory response of vasodilation and cellular migration. Replicating epithelial cells subsequently migrate up the skin appendages (hair follicles and ducts of sebaceous and sweat glands) and sheet over the wound. This proliferative phase of wound healing takes 5–7 days and is followed by the remodeling phase in which maturation occurs through fibrous structural proteins.[11] The prognosis of SJS/TEN is variable depending on SCORTEN and time to cessation of the offending agent.

Treatment of SJS/TEN varies among different parts of the world; the most widely accepted treatment is supportive care. This includes cessation of offending drug(s), regulation of body temperature, hydration management, and general wound care. Eyes are extremely sensitive to scarring with vision loss if not protected during the resolving process. This mandates ophthalmology consultation and sometimes protective lenses. The use of corticosteroids, central and peripheral lines, biologic agents, prophylactic antibiotics, and certain types of grafts is debated throughout the literature. The use of corticosteroids is debated because these drugs do not halt progression of disease in the majority of patients. They suppress the immune system and put patients at risk for superimposed infection and sepsis, the most common cause of death.[12] What does seem to arrest progression is debridement of the sloughing keratinocytes either in areas of blistering or of Nikolsky sign and subsequent placement of dressings that adhere to the exposed dermis to act as temporary skin until resurfacing occurs.

Intravenous IgG is an immunomodulator that interferes with apoptosis by blockade of CD95 death ligand.[12,13] Currently, the data regarding IV IgG use are conflicting, with some evidence supporting low-dose (2 g/kg) IV IgG or IV IgG in combination with methylprednisolone. However, other studies report no benefit when compared to supportive therapy alone.[13] Prophylactic antibiotic use has also been debated in the literature. Their use has been controversial since antibiotics can select for resistant organisms and reduce the normal skin microbiome which may result in slower wound healing.[14]

Appropriate wound management is a debated topic and involves using silver coated dressings that adhere and act as temporary skin while the epithelium heals underneath. The management of wounds can use of non-adherent dressings, silver impregnated dressings, non-silver impregnated dressings, and general wrap.[15] A regional burn center study also recommended silver based/non-adherent dressings.[16] Studies in the medical literature also indicate that Biobrane, a biosynthetic dressing, can function as a type of artificial skin which is highly beneficial in SJS/TENS patients.[17]

Conservative management of SJS/TENs uses the detached epidermis as a biological dressing and additional non-adhesive dressings are applied on top. Debridement is used to promote adherence of biological dressings, allografts, or xenografts to the underlying dermis. The two forms of debridement that may be used include sharp debridement at the bedside or debridement with the patient under anesthesia in the operating room. The current literature focuses on use of surgical debridement as the primary form due to the painful nature of debridement and extensive sedation required.[18,19]

Among treatment strategies, the type of hospital unit in which the patient should be treated is also not universally agreed upon. The use of the burn unit in the treatment of SJS/TEN has been debated mostly due to the lack of data and evidence to support its superiority to medical units. In the burn unit in which this case series was managed, even including patients admitted with complex comorbidities, the mortality rate is relatively low.

Recent studies have supported the use of a multidisciplinary team including surgeons, dermatologists, internists, ophthalmologists, and urologists to improve survival and outcomes in SJS/TEN patients. In situations in which patients are promptly transferred to burn units, the outcomes have been favorable. This is likely due to the similarity of SJS/TEN management to that of massive burns and staff familiarity with care of grafts and fluid resuscitation. Burn units allow for more experienced and meticulous care for patients who need to

be closely monitored for infection, dehydration, and graft rejection.

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