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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

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