BRIEF OBSERVATION

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Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: An Analysis of Triggers and Implications for Improving Prevention

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ABSTRACT

BACKGROUND: Stevens-Johnson syndrome and toxic epidermal necrolysis are severe mucocutaneous adverse drug reactions characterized by extensive epidermal detachment. The mortality rates have been reported to vary between 1% and 5% for Stevens-Johnson syndrome and 25% and 35% for patients with toxic epidermal necrolysis. Studies have shown that early recognition and prompt withdrawal of the causative agent leads to increased patient survival.

METHODS: A retrospective chart review was conducted on 64 patients admitted to Vancouver General Hospital with a diagnosis of Stevens-Johnson syndrome or toxic epidermal necrolysis from 2001 to 2011. The aim of this study was to identify the medications most often implicated in triggering Stevens-Johnson syndrome and toxic epidermal necrolysis, as well as to delineate the timeline of identification and removal of these triggers.

RESULTS: A trigger was identified in 75% of cases. Allopurinol was the single most common offending agent (20% of cases). Anticonvulsants and antibiotics were common triggers. The offending agent was often removed at time of hospital admission/diagnosis but not at onset of symptoms. A history of prior culprit drug exposure with previous mucocutaneous adverse reaction was noted in 19% of cases with identified triggers. Asians and Native North Americans had a higher mortality than whites, and Asians more frequently had allopurinol as a trigger.

CONCLUSIONS: The onset and high mortality rate of Stevens-Johnson syndrome/toxic epidermal necrolysis may be related to unawareness of the early signs and symptoms of Stevens-Johnson syndrome and toxic epidermal necrolysis, the common drug triggers that cause it, and what investigations (human leukocyte antigen typing in Asians) can be done to prevent it.

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KEYWORDS: Allopurinol; Drug reactions; HLA testing; Phenytoin; Stevens-Johnson syndrome; Sulfamethoxazole-trimethoprim; Toxic epidermal necrolysis

Stevens-Johnson syndrome and toxic epidermal necrolysis are rare, acute, and severe mucocutaneous adverse drug reactions. Initial clinical findings include a prodrome of fever and malaise, followed by the development of a generalized, tender cutaneous eruption consisting of a variety of morphologies including macules, papules, atypical target lesions, and vesicles or bullae. Stevens-Johnson syndrome/toxic epidermal necrolysis are defined

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based upon the amount of epidermal detachment. Stevens-Johnson syndrome involves <10% body surface area detachment, while toxic epidermal necrolysis is characterized by extensive involvement of >30% body surface area. A Stevens-Johnson syndrome/toxic epidermal necrolysis overlap exists when 10%-30% of body surface area is affected.[1,2] The mortality rates vary between 1% and 5% for Stevens-Johnson syndrome and 25% and 35% for patients with toxic epidermal necrolysis.[1,3]

The aims of this retrospective study were to identify the medications most often implicated in triggering Stevens-Johnson syndrome/toxic epidermal necrolysis at our institute, to determine the timelines of withdrawal of these triggers, and to examine whether there were differences in mortality and drug exposure among different ethnicities. The findings from this study may help physicians identify high-risk patients and high-risk medications so that the likelihood of developing Stevens-Johnson syndrome/toxic epidermal necrolysis may be decreased.

CLINICAL SIGNIFICANCE

- Toxic epidermal necrolysis is a life-threatening adverse reaction to drugs. Asians have an increased mortality when compared with whites.
- Allopurinol remains a common trigger in Asians, despite the availability of human leukocyte antigen testing to predict individuals at risk.
- Individuals with a documented cutaneous adverse reaction to antiepileptics or allopurinol should not be re-exposed to these drugs, and patients receiving these drugs developing a cutaneous eruption should have the drug discontinued promptly.

METHODS

Ethics approval was obtained from the Clinical Research Ethics Board of the University of British Columbia. A retrospective chart review was conducted on a total of 64 patients who were admitted to Vancouver General Hospital from January 2001 to December 2011. Sixty-two patients were identified as having Stevens-Johnson syndrome/toxic epidermal necrolysis using the International Classification of Diseases codes, and a further 9 patients were identified using the dermatology consult service database, which is a record of all consults seen by the dermatology service. All patients included in this study were evaluated by the dermatology consult team at time of diagnosis and, based on the history and physical examination, fulfilled the signs and symptoms required to make a diagnosis of Stevens-Johnson syndrome/toxic epidermal necrolysis. Seven patients were excluded from the study based on the following exclusion criteria: 1) incompatible clinical assessment, 2) incompatible biopsy results, 3) clinical history of autoimmune bullous disease or other diagnosis that might mimic Stevens-Johnson syndrome/toxic epidermal necrolysis. The primary endpoint of this study was the identification of medications implicated in triggering Stevens-Johnson syndrome/toxic epidermal necrolysis. The identification of culprit drugs was based upon 1) an initiation or change in a medication occurring within the historically validated window of 5-56 days; 2) a history of an adverse reaction to the same medication; 3) the identification of high-risk culprit drugs based on large database analysis such as the European Severe Cutaneous Adverse Reaction study; 4) the presence of other medications or etiologic causes that might make a clear identification difficult or impossible. Secondary endpoints that were evaluated included prior history of exposure to the triggering medication, time from initiation of medication to onset of symptoms, timeline of removal of the offending agent, length of stay in the hospital, and race-specific mortality. Statistical analysis of data included χ^2 test and determination of standard deviations and means using statistical analysis software (Excel; Microsoft Corporation, Redmond, Washington).

RESULTS

Of the 71 patients identified as having Stevens-Johnson syndrome/toxic epidermal necrolysis during a 10-year period from January 2001 to December 2011, a total of 64 patients were included in the analysis, as 7 cases met the exclusion criteria. Twenty-eight patients were classified as having Stevens-Johnson syndrome (43.8%), 17 had toxic epidermal necrolysis (26.6%), and the remaining 19 (29.7%) patients were classified as Stevens-Johnson syndrome/toxic epidermal necrolysis overlap (Table 1). An offending medication was identified in 75% of cases of Stevens-Johnson syndrome/toxic epidermal necrolysis. In a total of 13 cases, patients were on multiple drugs with the potential to cause Stevens-Johnson syndrome/toxic epidermal necrolysis, making it impossible to assign a single culprit drug, with the average being 2.9 drugs. In 19% of cases where an offending medication was identified, the patient had a prior exposure to the identified trigger. Patients developed symptoms, on average, 31.1 days after initiation of the causative drug if

Table 1 Characteristics of Patients Included in Study Analysis

Total number of patients admitted	64
Average age	55.4 y (SD 20 y)
Sex male	43.8% (n = 28)
Disease classification based on maximum body surface area involvement	
Stevens-Johnson syndrome	43.8% (n = 28)
Stevens-Johnson syndrome/toxic epidermal necrolysis overlap	29.7% (n = 19)
Toxic epidermal necrolysis	26.6% (n = 17)

Table 2 Timeframe of Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis Development in Patients with Identified Triggers Correlated with Medication Exposure History

Medication Exposure History	Average Time to Development of Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis
Previous exposure	4.1 d (SD 2.5 d)
No previous exposure	31.1 d (SD 64.9 d)
Unknown	18.5 d (SD 29.2 d)

there was no prior exposure to the medication. However, if there was a previous exposure to the trigger, the time to development of symptoms was significantly shortened to 4.1 days after re-exposure (Table 2).

Anticonvulsants, antibiotics, and allopurinol were the most commonly implicated triggers (Table 3). Anticonvulsants as a group made up the largest percentage of cases (25%); however, allopurinol was the single most common offending medication, implicated in 20% of cases. Triggers were most commonly discontinued at the time of hospital admission, approximately 4 days after onset of symptoms or in the hospital at the time of diagnosis, approximately 5 days after onset of symptoms. In only 19% of cases was the offending medication removed at the time of onset of symptoms (Figure 1).

A total of 14 patients (21.8%) died in the hospital due to complications arising from Stevens-Johnson syndrome/toxic epidermal necrolysis. Caucasian patients made up 44% of the total number of patients diagnosed with Stevens-Johnson syndrome/toxic epidermal necrolysis and exhibited a race-specific mortality of 14%. In contrast, 23% of the patients in this study were Chinese. This reflects the proportion of Mandarin-, Cantonese-, and "Chinese"-speaking individuals in the Vancouver area identified in the 2011 census (22%).[4] However, these patients exhibited a race-specific mortality of 47% (Figure 2). This differed significantly from that for white patients (*P*-value of .02). A correlation between Chinese ethnicity and reactions to allopurinol was evidenced by the fact that 46.2% of all reactions to allopurinol occurred in patients of Chinese ethnicity. Aboriginal North Americans also had a high race-specific mortality, with 2 of 5 patients passing away. Phenytoin was implicated in causing 4 of the 5 cases of Stevens-Johnson syndrome/toxic epidermal necrolysis in Aboriginal North American patients.

Table 3 Triggers Implicated in Causing Cases of Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis

Trigger	Number of Patients	Percentage of Total
Allopurinol	13	20
Anticonvulsants	16	25
Phenytoin	10	16
Carbamazepine	5	8
Lamotrigine	1	2
Antibiotics	12	19
Trimethoprim/sulfamethoxazole	4	6
Ceftriaxone	1	2
Cephalexin	1	2
Vancomycin	1	2
Amoxicillin	1	2
Piperacillin-tazobactam	1	2
Ciprofloxacin	1	2
Doxycycline	1	2
Clarithromycin	1	2
Ibuprofen	3	5
Diltiazem	1	2
Terbinafine	1	2
Atenolol	1	2
Mycoplasma	1	2
Unknown	16	25

DISCUSSION

Previous studies of Stevens-Johnson syndrome/toxic epidermal necrolysis have consistently shown that early withdrawal of the offending agent is imperative in improving patient survival.[1,5,6] Our study results show that the trigger was most often removed at the time of hospital admission or at the time of diagnosis in the hospital, and much less commonly at the onset of symptoms. As such, further education for primary care physicians and patients in recognizing the early signs and symptoms of Stevens-Johnson syndrome/toxic epidermal necrolysis is needed. The early signs and symptoms of Stevens-Johnson syndrome/toxic epidermal necrolysis include a painful new skin eruption, sore throat, and fever or malaise.[1] Early clinical recognition of these symptoms in association with the use of high-risk medications may lead to earlier treatment, earlier drug withdrawal, and improved mortality rates.

Perhaps even more telling is that 19% of patients had a previous exposure and reaction to the medication that was triggering their Stevens-Johnson syndrome/toxic epidermal necrolysis. Patients with prior exposure had a much faster timeline for developing Stevens-Johnson syndrome/toxic epidermal necrolysis consistent with a recall response and possibly compounding the harm to these patients.[7] This suggests that better medical histories, particularly focused on previous reactions to medications, and in specific high-risk medications, are needed.

In our study, 23% of patients diagnosed with Stevens-Johnson syndrome/toxic epidermal necrolysis were Chinese, and it was this ethnic group that had the highest mortality rate. To our knowledge, the effects of race on mortality in toxic epidermal necrolysis for White, Chinese, and Aboriginal North Americans have not previously been examined. Differences in ethnicity-related mortality may be due to comorbidities, specific drug effects, or other factors. Strong genetic associations among human leukocyte antigen (HLA) allotypes, adverse drug reactions, and the Han Chinese have been identified.[1,3,8-11] The two strongest

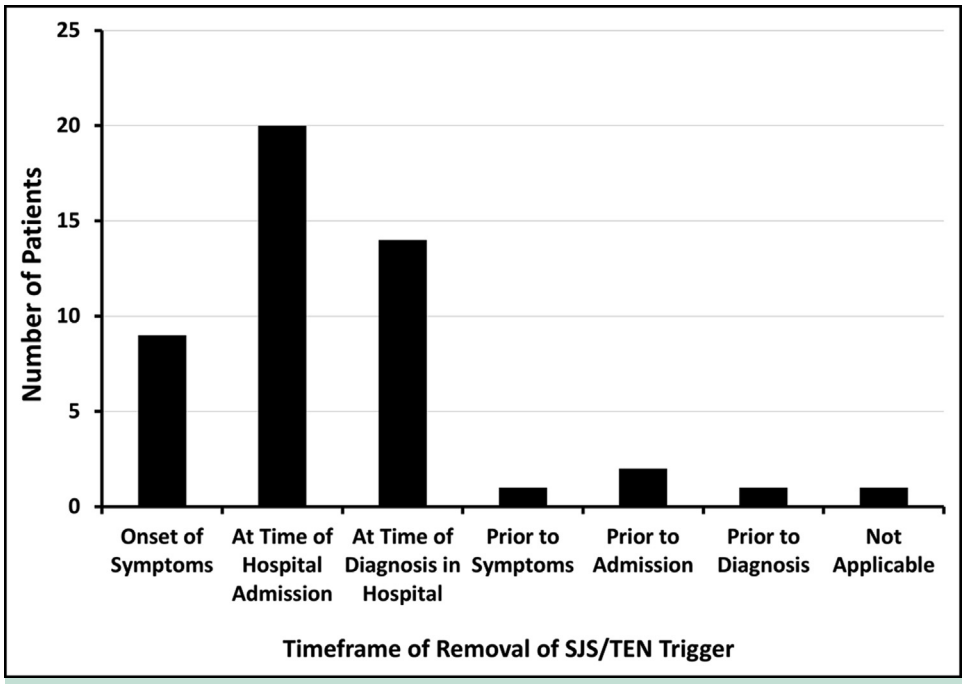

Figure 1 Time-frame of removal of triggers in patients with Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN).

HLA-drug adverse reaction associations for the Han Chinese are HLA-B*1502 and carbamazepine, as well as HLA-B*5801 and allopurinol.[1,3,8-11] The US Food and Drug Administration currently recommends genotyping all East Asian patients prior to commencing treatment with carbamazepine.[1,12] Our study suggests that HLA testing is not routinely being carried out prior to commencement of high-risk offending medications in high-risk populations. Data obtained from our provincial HLA laboratory showed that in a single year (2013), HLA-B*1502 testing was ordered for 8 individuals and HLA-B*5801 for only 3 individuals. A cost-effectiveness analysis of HLA-B*5801 screening in preventing allopurinol hypersensitivity was conducted by Zhu et al.[13] The study concluded that HLA

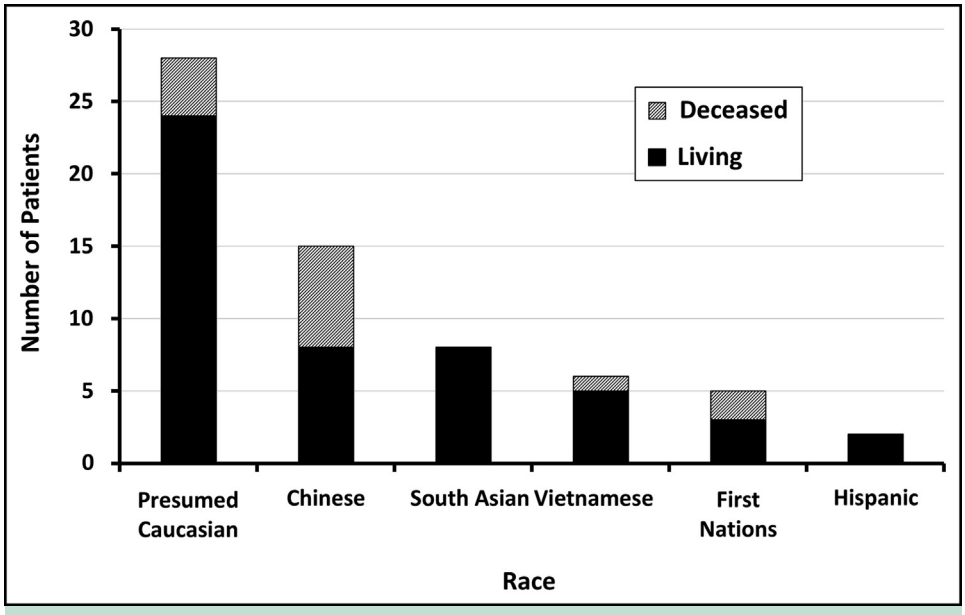

Figure 2 Race-specific mortality. Total number of patients with Stevens-Johnson syndrome/toxic epidermal necrolysis admitted based on race and associated mortality.

testing was cost-effective when conducted prior to the initiation of allopurinol therapy, particularly with regard to Asian patients.[13]

CONCLUSION

Given the potential for significant morbidity and mortality, we recommend that all patients of Asian ancestry be tested for HLA-B*1502 prior to starting carbamazepine, and HLA-B*5801 prior to starting allopurinol. This message should be urgently transmitted to family practitioners, rheumatologists, and other individuals who often prescribe this medication and pharmacists who dispense the medication. We also observed a high mortality rate amongst Aboriginal North Americans. Whether Aboriginal North Americans carry HLA alleles that predispose to severe drug reactions will require further investigation.

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