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Stevens-Johnson syndrome and toxic epidermal necrolysis: A cross-sectional analysis of patients in an integrated allergy repository of a large healthcare system

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To the Editor

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe cutaneous adverse reactions (SCARs), carrying an associated mortality from 5–40%.^{1,2} Known risk factors for SJS/TEN include HIV infection, female gender, and certain HLA genotypes.^{1,3,4} Various medications have been described to cause SJS/TEN with strongest associations with allopurinol, antiepileptics, non steroidal anti-inflammatory agents (NSAIDs), sulfa-containing antibiotics, β -lactam antibiotics, quinolones, and nevirapine.^{3–6} SJS/TEN are rare, affecting about 2 per million persons per year with SJS three times more common than TEN.^{3,7} However, much of the epidemiologic data on SJS/TEN is limited to national and international reporting networks or cohorts after specialist referral or hospitalization.^{2,5,6} The largest U.S. epidemiologic data identified cases based on ICD-9-CM codes.^{8–9} We aimed to determine the prevalence of SJS/TEN among patients in a large

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health system by searching an electronic allergy repository and to evaluate demographic, allergy, and allergen characteristics of this population.

Methods

We conducted a cross-sectional analysis of patients who have reported allergies listed in the Partners Enterprise Allergy Repository (PEAR) at the Brigham and Women's Hospital or Massachusetts General Hospital between 1983 and 2013. PEAR maintains a record of all allergy information entered into electronic health records (EHRs) by a medical provider and communicates in all of Partners Healthcare both in inpatient and outpatient settings (Online Repository Text). SJS/TEN cases were identified by using keyword search of the free-text reaction field (for entries similar to SJS, Steven, Johnson, Toxic Epidermal Necrolysis, and TEN), followed by manual reaction review of all retrieved cases. Uncertainty of a SJS/TEN diagnosis was defined if the entry included the words "possible" "like," "question" or "?". Uncertainty of a causative agent was defined if the listed agent was an unknown or unrecognizable medication. Agents reported to cause SJS/TEN were manually categorized and frequencies calculated. We compared gender and ethnicity of patients with and without SJS/TEN using χ^2 test, and $p < .05$ was considered statistically significant. SAS statistical software (version 9.3; SAS Institute Inc) was used for statistical analysis. The study was approved by the Partners Human Research Committee.

Results

Between 1983 and 2013, there were 1,877,075 PEAR patients. Of these, 745,813 (39.7%) had at least one allergy recorded in PEAR, with remaining patients having "unknown" or "no known allergies." We identified 704 patients (0.0375% or 375 per million) with an active allergy reporting SJS or TEN.

Of the 704 patients, 66.5% were female (Table 1). The overall PEAR population without SJS/TEN had significantly less women (57.3%, $p < 0.001$) though a similar female predominance was found in those with allergies (67.2%, $p > 0.5$). Patients with SJS/TEN were largely white (83.1%), which was greater than the overall PEAR population without SJS/TEN (75.1%, $p < 0.001$) but similar to those with allergies (78.0%, $p > 0.5$). Of SJS/TEN patients, 23 (3.5%) were Hispanic, which is fewer than the PEAR population without SJS/TEN (8.9% $p < 0.001$) and those with allergies (4.9%, $p = 0.04$), and 35 (5.3%) were Asian, which was a greater proportion than in the PEAR population without SJS/TEN (4.4%, $p = 0.24$) and in those with allergies (2.7%, $p < 0.001$).

Most patients ($n = 652$, 92.6%) had SJS. Only 24 (3.4%) had TEN. Fourteen (2%) had SJS/TEN overlap. Overlap syndromes with other immunologic reactions were rare (2%). Sixty four (9.1%) of reaction entries indicated diagnosis uncertainty. Only three (0.4%) of allergen entries indicated causative agent uncertainty. The majority (92.6%) of patients had only 1 medication listed as the causative drug, 11.6% had 2 causative agents and 5.3% had 3 or more. Patients with SJS/TEN reported an average of 3.1 (SD 3.4) drug allergies, 0.1 (SD 0.6) food allergies and 0.1 (SD 0.4) environmental allergies (Online Repository Table 1).

Among the total of 901 drugs reported to cause SJS/TEN (Table II), antibiotics (n=526, 58.4%) were most commonly implicated, including sulfonamides, β -lactams, macrolides, quinolones, vancomycin, tetracycline, and clindamycin. Antiepileptics were the causative agent for 175 (19.4%) patients. NSAIDs were the causative agent in 55 (6.1%) of patients with ibuprofen, naproxen, and aspirin the most commonly listed specific NSAID trigger. Allopurinol was the causative agent in 19 (2.1%) of patients. Other causative drugs of note included hydroxychloroquine (0.7%) and nevirapine (0.7%). Notable drug classes include the antidepressants (1.6%), beta blockers (0.6%), ACE inhibitors (0.4%), and proton pump inhibitors (0.6%).

Discussion

We assessed an integrated allergy repository of a large health system, and found a prevalence of SJS/TEN of 375 patients per million. The demographics of our cohort showed a female predominance, similar to published data.¹ While patients with SJS/TEN were less likely to be Hispanic, there was a slight overrepresentation of persons from Asian backgrounds, potentially related to HLA associations.³ Compared to SJS, TEN was rare with SJS outnumbering TEN 27 cases to 1, which is greater than the 4 to 1 previously described.⁷ Overlap syndromes were infrequent, similar to previous reports.¹⁰ While almost 93% of patients had their SJS/TEN attributed to one medication only, there were 37 cases with three or more potential causative drugs listed. When a single causative medication cannot be identified, a patient's future treatment may be compromised.

Similar to other reports, antibiotics most commonly causing SJS/TEN were penicillins, cephalosporins, and sulfonamides.³ Macrolides and quinolones were additionally prominent, as described previously.^{3,5} Our data suggest that antibiotics not routinely considered associated with SJS/TEN warrant further consideration, especially vancomycin, tetracyclines, and clindamycin. In addition to commonly implicated antiepileptics,^{2,11} cases from gabapentin, topiramate, and divalproex were present in our cohort though rare in the literature. Many antidepressants were causative drugs, of which the most notable was bupropion. Finally, other drugs were found at lower frequencies that have not been previously been linked to SJS/TEN.

This study has several limitations. First, our data do not contain comprehensive demographic information, making it difficult to discern how this cohort compares to previously described cohorts. However, in terms of gender and ethnicity, our cohort appears similar. Second, we are unable to validate cases and cannot know how many patients were misdiagnosed. However, SJS and TEN are specific medical names that patients seem unlikely to report without a clinician diagnosis, and free-text allergy entries indicated uncertainty in only 64 entries. Third, it is unlikely that causality assessment in SJS/TEN followed recommendations for assessing causality in SJS/TEN. However, 83% of the cohort had only one drug reported to cause, suggesting some degree of certainty. Last, the hospitals in this cohort are in Boston, although both institutions have patients from other parts of the U.S. and abroad.

In conclusion, this report suggests that SJS/TEN, affects 375 patients per million, more than previously reported. There may be new significant causative medications to investigate further. Clinical providers should be aware of this severe hypersensitivity reaction, use evidence-based algorithms to help determine medication causality and document the reaction clearly in the EHR. With the universal mandate of EHRs, it is important to understand drug allergy epidemiology reflected in EHRs and how data compare to previously published reports.

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Abbreviations

SJS	Stevens-Johnson syndrome
TEN	toxic epidermal necrolysis
SCAR	Severe Cutaneous Adverse Reaction
ICD9	International Classification of Diseases, ninth revision
PEAR	Partners Enterprise Allergy Repository

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Clinical Implications

By examining patients electronic allergy record in a large healthcare system, we identify a prevalence of Stevens-Johnson Syndrome or toxic epidermal necrolysis of 375 per million patients. We identify new drugs reported to cause these severe cutaneous adverse reactions that may be emerging causative agents.

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Table 1

Demographic characteristics and allergen information for patients reported to have had Stevens-Johnson Syndrome or toxic epidermal necrolysis (n=704)

All patients in PEAR (n=1,877,075)	With SJS/TEN (n=704)	Without SJS/TEN (n=1, 876,371)	P value ^a
<i>Female No. (%)</i>	468 (66.5)	1,076,485 (57.3)	p<0.001
<i>Race No. (%)^b</i>			
White	549 (83.1)	1,315,209 (75.1)	p <0.001
Black	43 (6.5)	133,612 (7.6)	p = 0.29
Hispanic	23 (3.5)	155,868 (8.9)	p <0.001
Asian	35 (5.3)	76,828 (4.4)	p = 0.24
Other	11 (1.7)	68,105 (3.9)	p = 0.003

Patients in PEAR with allergies ^c (n=745,813)	With SJS/TEN (n=704)	Without SJS/TEN (n= 745,109)	P value ^a
<i>Female No. (%)</i>	468 (66.5)	500,813 (67.2)	p>0.5
<i>Race No. (%)^b</i>			
White	549 (83.1)	581,641 (78.0)	p = 0.9
Black	43 (6.5)	38,844 (5.2)	p = 0.29
Hispanic	23 (3.5)	36,481 (4.9)	p = 0.04
Asian	35 (5.3)	20,076 (2.7)	p<0.001
Other	11 (1.7)	22,072 (3.0)	p = 0.03

Allergy Characteristic	SJS/TEN (n=704)
<i>Hypersensitivity Reaction, No. (%)</i>	
SJS	652 (92.6)
TEN	24 (3.4)
SJS/TEN	14 (2.0)
Overlap syndromes	14 (2.0)
SJS/Drug Rash Eosinophilia and Systemic Symptoms	3 (0.4)
SJS/Erythema Multiforme	2 (0.3)
SJS/Other immune-mediated reactions	9 (1.3)
<i>Medications listed as causative agent</i>	
$\mu \pm SD$	1.28 $\pm$ 0.96
No. (%)	
1	585 (83.1)
2	82 (11.6)
3	21 (3.0)
4	9 (1.3)
5 or more	7 (1.0)

^a P value indicates the race category compared to the sum of the other categories (i.e. white vs. non-white, black vs. non-black, etc.)

^b Determined through patient self-report. Total n's do not match the sum of patients in race groups because of missing race entries including unknown, not given, or refused. All patients in PEAR without SJS/TEN has 126,749 total missing; Patients in PEAR with allergies without SJS/TEN has 45,995 total missing; and 43 patients with SJS/TEN had missing race entries.

^cExcludes patients with “Allergy Unknown” and “No Known Drug Allergies”

Abbreviations PEAR: Partners Enterprise Allergy Repository; SJS: Stevens-Johnson syndrome; TEN: toxic epidermal necrolysis; μ : mean; SD: standard deviation.

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Table 2

Drugs reported to cause Stevens-Johnson Syndrome or toxic epidermal necrolysis among PEAR database entries in a large healthcare system (n=901)

Drug Type	Number (%)
<i>Antibiotic</i>	526 (58.4)
Sulfonamide	283 (31.4)
Penicillins ^a	91 (10.1)
Cephalosporin	42 (4.7)
Macrolides	23 (2.6)
Quinolone	20 (2.2)
Vancomycin	20 (2.2)
Tetracycline	18 (2.0)
Clindamycin	13 (1.4)
Metronidazole	4 (0.4)
Aminoglycosides	3 (0.3)
Trimethoprim	3 (0.3)
Nitrofurantoin	2 (0.2)
Carbapenem	1 (0.1)
Other antibiotic ^b	3 (0.3)
<i>Antiepileptic</i>	175 (19.4)
Lamotrigine	55 (6.1)
Phenytoin	40 (4.4)
Carbamazepine	30 (3.3)
Phenobarbital	20 (2.2)
Oxcarbazepine	8 (0.9)
Gabapentin	4 (0.4)
Topiramate	4 (0.4)
Divalproex	3 (0.3)
Other or unknown antiepileptic ^c	11 (1.2)
<i>Non Steroidal Antiinflammatory Agents</i>	55 (6.1)
Ibuprofen	10 (1.1)
Naproxen	7 (0.8)
Aspirin	4 (0.4)
Sulindac	3 (0.3)
Meloxicam	2 (0.2)
Piroxicam	2 (0.2)
Indomethacin	2 (0.2)
Other ^d	25 (2.8)
<i>Cardiovascular Medications</i>	22 (2.4)
Sulfa-containing diuretic ^e	5 (0.6)
Beta Blockers ^f	5 (0.6)

Drug Type	Number (%)
ACE Inhibitors ^g	4 (0.4)
Calcium Channel Blockers ^h	3 (0.3)
Antiarrhythmics ⁱ	2 (0.2)
Statins (atorvastatin)	2 (0.2)
Angiotensin Receptor Blockers (valsartan)	1 (0.1)
<i>Uricosuric</i>	20 (2.2)
Allopurinol	19 (2.1)
Probenicid	1 (0.1)
<i>Antiretrovirals</i>	15 (1.7)
Nevirapine	6 (0.7)
Efavirenz	3 (0.3)
Other antiretrovirals ^j	6 (0.7)
<i>Antidepressants</i>	14 (1.6)
Bupropion	6 (0.7)
Other antidepressants ^k	8 (0.9)
Other neuro/psych medications ^l	12 (1.3)
<i>Immunomodulators</i>	9 (1.0)
Dapsone	3 (0.3)
Sulfasalazine	3 (0.3)
Other immunomodulators ^m	3 (0.3)
<i>Gastrointestinal Medications</i>	9 (1.0)
Proton Pump Inhibitor ⁿ	5 (0.6)
Antiacids ^o	2 (0.2)
Famotidine	1 (0.1)
Antiemetics ^p	1 (0.1)
<i>Oncology Medications</i>	8 (0.9)
Chemotherapy ^q	7 (0.8)
G-CSF (Pegfilgrastim)	1 (0.1)
<i>Antifungals</i> ^r	7 (0.8)
<i>Antimalarials</i>	7 (0.8)
Hydroxychloroquine	6 (0.7)
Quinine	1 (0.1)
<i>Allergy and Cold Medications</i>	7 (0.8)
Antihistamine ^s	3 (0.3)
Nyquil	2 (0.2)
Pseudoephedrine	2 (0.2)
<i>Pain medications</i>	4 (0.4)
Codeine	2 (0.2)
Hydromorphone	1 (0.1)
Oxycodone + Tylenol	1 (0.1)

Drug Type	Number (%)
Acetaminophen	3 (0.3)
Contrast media	2 (0.2)
Vitamin/Herb ^t	2 (0.2)
Titanium dioxide	1 (0.1)
Unclear	3 (0.3)

^a Includes Beta-Lactam (2)

^b Includes bactitracin/neomycin/polymixin (1), chlroamphenicol (1), and linezolid (1)

^c Includes barbiturates (4) zonisamide (2), rufinamide (1), pregabalin (1), lacosamide (1), and unknown (2)

^d Includes NSAIDS (19), celecoxib (1), oxaprozin(1), rofecoxib (1), tolmetin (1), and valdecoxib (1), nabumetone (1)

^e Includes hydrochlorothiazide (3) and furosemide (2)

^f Atenolol (1), carvedilol (1), metoprolol (1), nadolol (1), propranolol (1)

^g ACE Inhibitor(2), fosinopril (1), lisinopril (1)

^h Diltiazem (1), verapamil (2)

ⁱ Includes procainamide (1) and amiodarone (1)

^j Includes emtricitabine (1), lamivudine (1), lopinavir (1), ritonavir (1), tenofovir (1), zidovudine(1)

^k Includes duloxetine (2), citalopram (1), escitalopram (1), fluoxetine (1), nortriptyline (1) and venlafaxine (1), tricyclic/hertocyclic antidepressants (1)

^l Includes cyclobenzaprine(1), lithium(2), clonazepam(1), tolterodine(1), atypical antipsychotics(1), phenothiazines(1), ziprasidone(1), modafinil(1), zolpidem (1), varencycline(1), and acetazolamide (1)

^m Includes methotrexate (1), MMF (1), and prednisone (1)

ⁿ Includes esomeprazole (1), lansoprazole (1), omeprazole (1), rabeprazole (1), and pantoprazole (1)

^o Includes maalox (1) and methoscopolmonbromide (1)

^p Includes prochlorperazine (1), scopolamine (1), trimethobenzamide (1)

^q Includes imatinib (2), cyclophosphamide/doxorubicin (1), paclitaxel (1), docetaxel (1), experimental drug GDC0980 (1), lenalidomide (1)

^r includes fluconazole (2), voriconazole (2), itraconazole (1), nystatin (1) and griseofulvin (1)

^s Includes terfenadine (1), diphenhydramine (1), and dimenhydrinate (1)

^t Includes chinese herbs (1) and ascorbic acid (1)

Abbreviations PEAR: Partners Enterprise Allergy Repository