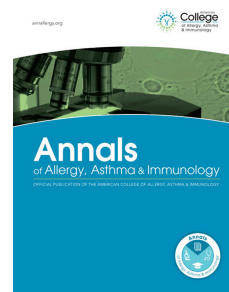


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Title:

Drug-Induced Severe Cutaneous Adverse Reactions (SCARs): Determine the Cause and Prevention.

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1 Introduction

2 Drug-induced hypersensitivity reactions are of major medical concern. Approximately
3 45% of all the adverse drug reactions are manifested in the skin, which occur in 2%-3%
4 hospitalized patients upon drug administration¹. Drug hypersensitivity reactions can be
5 categorized into immediate reactions and delayed reactions. Immediate reactions occur within
6 minutes or hours of drug exposure². The manifestations of immediate-type reactions range from
7 pruritus, urticaria, angioedema to anaphylaxis. The delayed-type reactions are primarily T cell-
8 mediated type IV reactions that usually takes several days or even weeks to manifest after drug
9 exposure. The manifestations of delayed-type drug hypersensitivity range from mild
10 maculopapular exanthema (MPE), and fixed drug eruptions (FDEs) to severe cutaneous adverse
11 reactions (SCARs)^[3]. Most skin reactions are mild, self-limited and usually resolve after the
12 drug is discontinued. However, SCARs are potentially lethal events. Despite the low incidence,
13 SCARs account for a high mortality from 10% to 40% and may incur disability⁴. The most
14 frequent clinical subtypes include Stevens- Johnson syndrome (SJS), toxic epidermal necrolysis
15 (TEN), exfoliative dermatitis, and Drug Rash with Eosinophilia and Systemic Symptoms
16 (DRESS), and acute generalized exanthematous pustulosis (AGEP)⁴. Patients with SCARs may
17 also suffer from fever, mucosal lesions, hematologic abnormalities and in some cases multiple
18 organ involvement⁵⁻⁶.

19 The prevalence and patterns of SCARs differ greatly among different ethnic groups and
20 geographic distributions. It is estimated that the incidence of TEN in Singapore is at least 1.4
21 cases/million population⁷, while the incidence in the United States is 0.5 cases/million
22 population⁴. The rapid development of technologies and current advancements in
23 pharmacogenomics studies have extended our understanding on the genetic basis of

hypersensitivity. Numerous studies have shown that there is a strong association between human leukocyte antigen (HLA) alleles and drug-induced cutaneous reactions⁸. For example, carbamazepine (CBZ) induced hypersensitivity reactions were found to be associated with HLA-B* 15:02 allele among Han Chinese, Taiwanese, Vietnamese and other Southeast Asian descendants. However, these CBZ-induced adverse reactions were found to be associated with HLA-A*31.01 in European and Japanese populations⁸. Interestingly, allopurinol-induced SJS/TEN were found to be strongly linked with HLA-B*58:01 genotype, and this correlation was fairly universal, as the study was successfully replicated in Southeast Asians, Japanese, and European patients^{6,8}. Other HLA-drug associations that have been reported in SCARs include HLA-B* 13:01 with dapsone, HLA-A* 31:01 and HLA-B*15:11 with CBZ, HLA-B*15:02 with phenytoin, HLA-B*57:01 with abacavir, HLA-B*38 with sulfamethoxazole and lamotrigine, HLA-B*73 with oxycam, and HLA-B*59:01 with methazolamide⁸. Another study shows that genetic variants of cytochrome P450 family 2 subfamily C member 9 (CYP2C9) are strongly associated with phenytoin-induced SCARs⁹. Currently, HLA screening, while recommended by US Food and Drug Administration for high-risk groups, is not required.

The aim of this study was to review etiology, demographic, clinical manifestations of patients who were treated with the diagnosis of severe cutaneous adverse reactions (SCARs) at Penn State Hershey Medical Center retrospectively and emphasize the importance of prevention, to include avoiding unnecessary medications, early diagnosis to reduce morbidity and mortality, and treatment, especially removal of offending agent.

METHODS

This study is a retrospective review of electronic medical records for patients who developed drug-induced cutaneous reactions and were treated for initial or ongoing care at a University Medical Center between June 4th, 2008 to August 10th, 2018. Search included Stevens-Johnson Syndrome [SJS] (L51.1), Toxic Epidermal Necrolysis [TEN] (L51.2) and TEN/SJS overlap (OL), Drug Rash with Eosinophilia and Systemic Symptoms [DRESS] (L27.0 and T88.7), Acute Generalized Exanthematous Pustulosis [AGEP] (L27.0). Since currently there is no ICD 10 specifically used for DRESS and AGEP, L27.0 (generalized skin eruption due to drugs and medication) and T88.7 (unspecified adverse effect of drugs or medication) were used.

The criteria for the diagnosis of DRESS syndrome is defined by the RegiSCAR criteria which include at least three out of these findings: hospitalization, fever $>38^{\circ}\text{C}$, lymphadenopathy involved at least two sites, internal organ involvement, and hematologic abnormalities 1-8 weeks after the administration of the culprit drug ¹⁰. For the study SJS and TEN are characterized as a rapidly progressing exanthema accompanied by mucosal involvement and skin detachment. SJS involves less than 10% body surface area. SJS/TEN overlap syndrome involves 10-29%. TEN involves more than 30 % ¹¹. Lastly, AGEP is characterized as an acute eruption with the development of numerous non-follicular sterile pustules on a background of edematous erythema with or without fever and neutrophilia ¹². The determination of patients with SCARs was based on reported clinical presentations and corresponding testing when indicated. For each case, the diagnosis was given by a specialized physician (an allergist, a dermatologist, or a pathologist).

69 The study was approved by the local Institutional Review Board in June, 2018. The focus of the
70 assessment was on the causative drug of use, type and duration of adverse reactions, treatments
71 after the skin reactions, and demographics related to age, gender, and ethnicity.

72

RESULTS

Demographics (Table 1)

A total of 1379 cases with drug reactions over the past 10 years was screened, and 596 cases of drug rash were confirmed by screening electronic medical records (43%). Out of these 596 cases of drug-induced rash, a total of 35 (5.9%) cases of SCARS were encountered. The majority of patients were Caucasian (91.4%, n=32) and there were no Asians. There were 17 males (48.6%) and 18 females (51.4%) with ages ranged from 2-81 years. A female preponderance was seen in SJS/TEN/overlap with a female to male ratio of 1 to 0.38. A male preponderance was seen in DRESS with a male to female ratio of 1 to 0.58. The thirty-five cases include 19 (54.3%) of DRESS, 8 (22.8%) of SJS, 6 (17.1%) of AGEP and one each (2.9%) of TEN and SJS-TEN overlap. Twenty-five of the 35 patients with SCARs were hospitalized with the balance treated as outpatients.

Interval between the first drug intake and onset of symptoms

The average intervals between the first drug intake and the onset of symptoms were 14.0 days in DRESS, 6.2 days in SJS/TEN/Overlap, and 4 days in AGEP.

Organ involvement and complications

Two SJS patient developed acute kidney injury. In DRESS (19 cases), acute kidney injury and liver injury were observed in 9 cases (47.4%) and 5 cases (26.3%), respectively. Other complications in DRESS included sepsis (n=1) and hematological abnormalities (lymphocytopenia (n=12); eosinophilia (n=10); anemia (n=5); thrombocytopenia (n=5); leukopenia (n=3); leukocytosis (n=2); and pancytopenia (n=2)).

Implicated Drugs (Table 2)

Causative drugs were determined by considering the history of drug administration. If the patient had taken more than one drug, all of them were considered as causative drugs. A total of 26 drugs were found as suspected causative agents. Multiple causative drugs were indicated in 14 cases (40%) while single drug was responsible in 21 cases (60%). The most common drugs implicated were antibiotics (88.1%). Cephalosporins (23.7 %) and penicillins (16.9 %) were the commonest implicated antibiotics. Other causative drugs included rifampin, lamictal, allopurinol, hydroxychloroquine, lithium, proton pump inhibitors, and tramadol. The most common cause of SJS/TEN/overlap syndrome was trimethoprim/sulfamethoxazole (26.3% of cases). In DRESS, penicillins (23.3% of cases) were the most common causative drug agents. In AGEP, cephalosporins (40 % of cases) were the most common causative drug agents. The detailed list of drugs causing adverse reactions is shown in Table 2.

Treatment (Table 3)

The treatments for SCARs included supportive care and corticosteroids. Intravenous gammaglobulin was not used. Most of the patients with SCARs were given topical triamcinolone cream and/or antihistamines. Approximately 71.4% (n=25) required systemic corticosteroids. Prompt tapering of the steroid dose was performed along with amelioration of symptoms. Of these, systemic corticosteroid was prescribed in 16 cases of DRESS (84.2%), five cases of AGEP (83.3%), four cases of SJS/TEN/Overlap (40%).

DISCUSSION

Severe Cutaneous Adverse Reactions (SCARs) are rare, but potentially life-threatening with broad clinical features. The estimated incidence of SCARs varies from 1 in 1,000 to 1 in 10,000 drug exposures⁴. Multiple factors have been discovered to be associated with drug-induced SCARs, including gender, age, human-leukocyte antigen-related gene, and defect of drug detoxification¹³.

In terms of demographics in our study, the majority of patients were Caucasian (91.4%, n=32); however, the referral area for the medical center according to the data from US Census (2017), suggests the largest ethnic groups in Hershey are White (82.1%) followed by Hispanic (7.2%), Asian (5.6%), and African American (5.3%). A female preponderance was seen in SJS/TEN/Overlap. A male preponderance was seen in DRESS. The discordance of gender discrepancy is also found in various other literature review¹⁴. SCARs are also associated with increasing age due to the associated comorbidities requiring multiple antibiotics.

Antibiotics were responsible for 88.2% of all cases in our study. The most common culprit drug class were cephalosporins. This finding is different compared to other studies which reported aromatic anticonvulsant to be the most common culprit drugs in Asia⁶. This discrepancy might be due to the different prescribing practices in different countries. In addition, studies have shown that there is a strong association between HLA and drug-induced cutaneous reactions. It was reported that HLA-B* 15:02 allele is associated with carbamazepine (CBZ) induced hypersensitivity reactions among Han Chinese, Taiwanese, Vietnamese and other Southeast Asian descendants. In contrast, the HLA-B12 antigen was significantly increased in Caucasian SJS patients¹⁵.

The youngest patient in our study was a 2-year-old Caucasian female diagnosed with amoxicillin-induced DRESS. Clinical presentations included acute skin rash, fever above 38 °C, bilateral mild lymphadenopathy, and thrombocytopenia. Other complications include transaminitis, atypical lymphocytosis, and elevated inflammatory markers. The onset time was 7 days and the total duration of steroid treatment was 9 days (2 days at hospital).

The oldest patient in our study was an 81-year-old Caucasian female with TEN. She had multiple coexisting medical conditions including infection and chronic kidney disease. She was on proton pump inhibitors, penicillin, and cephalosporin at that time. Clinical features included 80% body surface area (BSA) involvement, hyponatremia, thrombocytopenia, and erythema of both eyes with no loss in vision. The onset time was 14 days, and the hospital stay was 5 days. The total duration of steroid treatment was 21 days. This patient also developed severe anxiety after this incidence and received lorazepam for her anxiety.

All patients were informed to immediately withdraw of the offending drugs. Supportive care, topical triamcinolone cream, and antihistamine were provided as needed. 25 patients (71.4%) were treated with systemic corticosteroids. Systemic corticosteroid use in SCARs remains highly controversial, especially in TENS, SJS and overlap due to the risk of sepsis. From our database, systemic glucocorticoid use reduced skin symptoms and was not complicated by sepsis.

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Figure Legends

Figure 1: Type of SCARs.

Figure 2: Causative Drugs and SCARs

Figure 3: Antibiotics Use in SCARs Patients

Table 1 Patient Demographics of SCARs

	SJS	TEN	SJS/TEN overlap	AGEP	DRESS	Total
Number	8	1	1	6	19	35
Ethnicity						
- White	7	1	1	4	19	32
- Sephardic Jewish	1	0	0	0	0	1
- Asian	0	0	0	0	0	0
- Black	0	0	0	1	0	1
- Middle eastern	0	0	0	1	0	1
Gender						
- Female	5	1	1	3	7	17
- Male	3	0	0	3	12	18
Age (mean)						

Table 2 Causative Drugs and SCARS

Causative Drug	DRESS	SJS/TEN/Overlap	AGEP	All Cases
Antibiotics, n (%)	28 (93.3%)	16 (84.2%)	8 (80%)	52 (88.1%)
Cephalosporins	6 (20%)	4 (21%)	4 (40%)	14 (23.7%)
- Cephalexin	2	2	1	5
- Cefdinir	2	2	0	4
- Cefepime	1	0	1	2
- Ceftriaxone	1	0	1	2
- Cephazolin	0	0	1	1
Penicillins	7 (23.3%)	2	1	10 (16.9%)
- Amoxicillin	5	1	0	6
- Penicillin	1	1	0	2
- Ampicillin/sulbactam	1	0	1	2
Trimethoprim/sulfamethoxazole	4	5 (26.3%)	0	9
Sulfadiazine (Sulfonamide)	0	1	0	1
Fluoroquinolone	5	1	0	6
- Ciprofloxacin	4	1	0	5
- Moxifloxacin	1	0	0	1
Doxycycline (Tetracycline)	1	0	1	2

Macrolide	1	1	1	3
- Erythromycin (Macrolide)	0	1	0	1
- Azithromycin (Macrolide)	1	0	1	2
Clindamycin (Lincosamide)	0	1	1	2
Metronidazole (Antiprotozoal)	0	1	0	1
Vancomycin (Glycopeptides)	3	0	0	3
Linezolid (Oxazolidinone)	1	0	0	1
Anti-tuberculosis, rifampin	1	0	0	1
Anticonvulsants, Lamictal (Lamotrigine)	0	1	0	1
Antigout, Allopurinol	1	0	0	1
Anti-rheumatic, Hydroxychloroquine	0	0	1	1
Others Lithium	0	1	0	1
Proton pump inhibitor (more than 1 used in the single case)	0	1	0	1
Tramadol	0	0	1	1
TOTAL	30	19	10	59

Number of patients in DRESS, SJS/TEN/Overlap, and AGEP are 19, 10, and 6, respectively.

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Table 3 Treatment with corticosteroids in SCARs Patients

Treatments	DRESS	AGEP	SJS/TEN/Overlap	Total Cases
No steroids	3 (15.8%)	1	6	10
Prednisone alone	11 (57.9%)	5	2	18
Methylprednisolone alone	0	0	1	1
methylprednisolone/prednisone combined	4 (21.1%)	0	0	4
Methylprednisolone/prednisolone combined	1	0	0	1
Prednisone/prednisolone combined	0	0	1	1
Total	19	6	10	35

Figure 1: Type of SCARs.

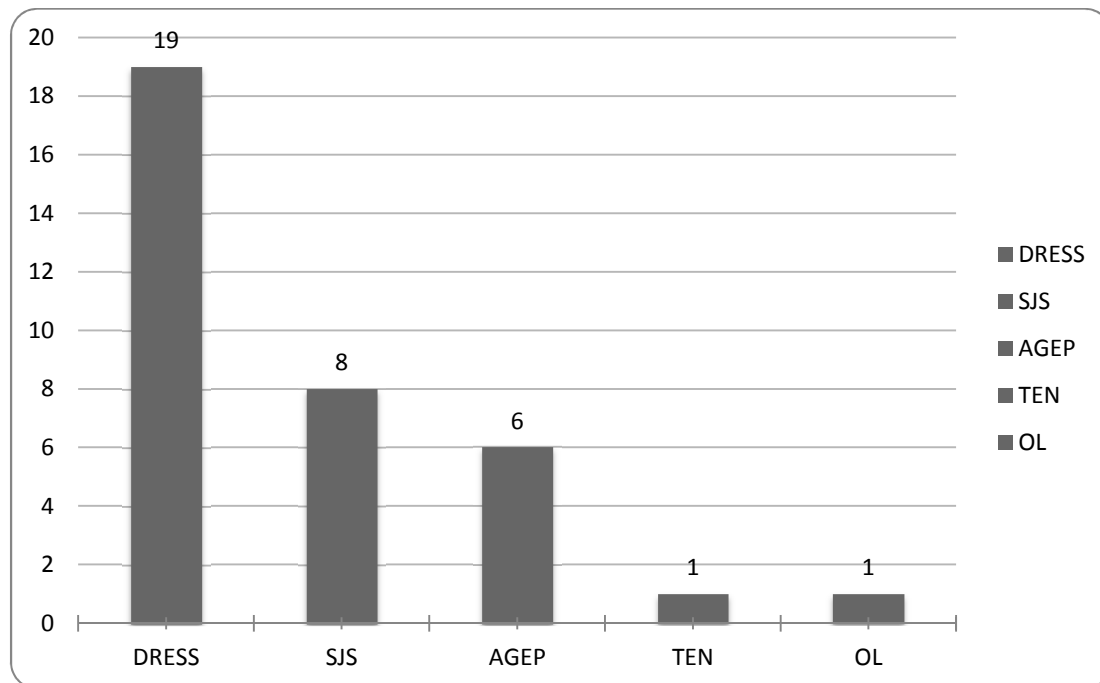


Figure 2: Causative Drugs and SCARs

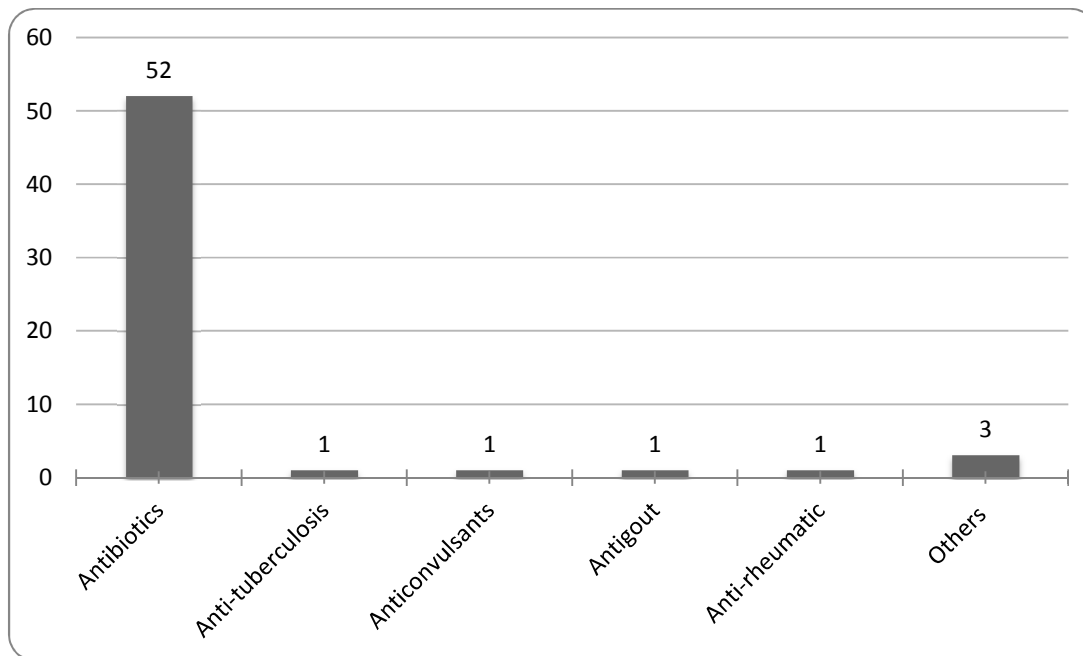


Figure 3: Antibiotics Use in SCARs Patients