Epidemiology of severe cutaneous adverse drug reactions in a University Hospital: a Five-year review

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ABSTRACT

Introduction Severe cutaneous adverse drug reactions (SCAR) is seen in ≤5% of all hospitalized patients. It includes Stevens-Johnson syndrome/toxic epidermal necrolysis spectrum (SJS/TEN), drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms (DIHS/DRESS) and acute generalized exanthematous pustulosis (AGEP).

Objectives The main objective was to determine the epidemiological characteristics of SCAR patients at a tertiary hospital from 2011-2015. Specifically, it aimed to determine the prevalence, demographic characteristics and clinical profile of SCAR patients.

Methods All SCAR patients from 2011-2015 were studied through a single-center, retrospective, descriptive, cross-sectional study.

Results Sixty-eight SCAR cases were diagnosed from 2011-2015 with a prevalence rate of 6.25 per 10,000 people. Majority were 46-55 years old with slight female predominance. The most common SCAR was DIHS/DRESS (50%), followed by SJS/TEN (30%) and AGEP (20%). Eight percent had previous drug reactions, 69% had co-morbidities and 90% were diagnosed clinically without biopsy. The antibiotics was the most common culprit drug category followed by allopurinol and anticonvulsants. Prompt withdrawal of culprit drug/s, supportive therapy, systemic steroids and antihistamine, topical emollients and saline compress were mainstay of treatment. Mortality rate was 4% for all SCAR categories

Conclusion The epidemiology of SCAR in this study is similar to those reported in other literature. The adults were commonly involved; DIHS/DRESS was the most common SCAR with antibiotics being the most common culprit. Prompt withdrawal and supportive therapy were essential. Systemic steroid, antihistamine; topical emollients and saline compress resulted in improvement of patients. In contrast, there was lower prevalence rate with slight female predominance; and lower mortality rate even with the use of systemic steroids.

Keywords severe cutaneous adverse drug reactions, SCAR, drug reaction, epidemiology

INTRODUCTION

Adverse drug reaction, as defined by World Health Organization, is "a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiologic function" (1). Among the common organs affected is the skin, accounting for at least 15% of all adverse drug reactions (1). The spectrum of cutaneous adverse drug reactions includes uncomplicated

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reactions such as urticarial and exanthematous eruptions that have few to no long-term sequelae. On the other hand, severe cutaneous adverse reactions (SCAR) are associated with high morbidity and mortality (1,2).

The Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) (3) is an international project created in order to reduce the medical and economic burden of severe cutaneous adverse reactions on public health and to improve the safety of medication use. It has included three diseases under this type of drug reaction namely, Stevens-Johnson syndrome/ toxic epidermal necrolysis spectrum (SJS/TEN), drug-induced hypersensitivity syndrome or drug reaction with eosinophilia and systemic symptoms (DIHS/DRESS) and acute generalized exanthematous pustulosis (AGEP). SCAR has been reported to comprise around 2 to 5% of cutaneous adverse drug reactions observed in hospitalized patients (1,2).

Available studies on SCAR extensively discussed comprehensive definitions and diagnostic criteria. Most reports showed increased interest in the pathogenesis, specifically at the molecular level and targeted gene in these diseases (4). However, there is still the paucity of data on clinical profile, associated diseases, treatment used and disease outcome. This is due to the rarity of these diseases hence there are few reported cases of such cutaneous adverse drug reaction in our country and worldwide.

At the University of Santo Tomas Hospital (USTH), previous studies which were done described patterns of cutaneous adverse drug reactions and their culprit drugs. The study done by Paliza and Rabe (1993) (5) showed 186 cases of cutaneous drug hypersensitivity reaction among in-patients at the University of Santo Tomas Hospital from January 1985 to June 1992, which showed exanthematous form as the most common cutaneous adverse drug reaction. The algorithm devised by Kramer et al (6) was adopted for more objective reporting of the culprit drug/s of the cutaneous reactions. Their study showed the common culprit drugs included trimethoprim-sulfamethoxazole, phenytoin, ampicillin, paracetamol, nafcillin, allopurinol and amoxicillin-clavulanic acid with trimethoprim-sulfamethoxazole as the most common etiologic agent. In 2012, an unpublished study by one of us, reported 227 of cutaneous adverse drug reactions seen in the USTH. In that study, allopurinol was the most common agent causing vast array of drug reactions as well as life-threatening reactions such as SJS-TEN spectrum. To our knowledge, there has been no study done at the USTH analyzing the epidemiological characteristics and prevalence of the severe forms of cutaneous adverse drug reactions.

Therefore, the main objective of this study was to determine the epidemiological characteristics of patients with severe cutaneous adverse drug eruptions (SJS-TEN spectrum, DIHS/DRESS, AGEP) at the USTH from January 2011 to December 2015. The specific objectives were to determine the prevalence of SCAR, describe the demographic characteristics and clinical profile of patients with SCAR including history of drug reactions, co-morbidities, morphological pattern of the reaction, culprit drug/s, management used, and disease outcome.

METHODOLOGY

This was a single center, retrospective, descriptive, cross-sectional study. All hospitalized patients diagnosed with severe cutaneous adverse drug reactions by the Department of Dermatology, USTH from January 2011 to December 2015 were included in the study. Ethical clearance for this review was granted by the Institutional Review Board of the USTH.

Patients were categorized depending on their final diagnosis: Category I (SJS/TEN) Stevens-Johnson syndrome/ toxic epidermal necrolysis spectrum, Category II (DIHS/DRESS): Drug-induced hypersensitivity syndrome/ drug reaction with eosinophilia and systemic symptoms and Category III (AGEP): Acute generalized exanthematous pustulosis

All data were obtained from the medical records and kept confidential. Demographic data such as age, sex and clinical profile including medical history, co-morbidities, drug information, management used (topical, systemic, dressings) and disease outcome were recorded *(Table 1)*. Excluded from this study were severe cutaneous adverse drug reactions not diagnosed by the dermatologists and cases wherein the medical charts were not available.

RESULTS

1. Prevalence of severe cutaneous adverse drug reactions

From January 2011 to December 2015, the Department of Dermatology of the USTH diagnosed sixty-eight (68) patients with severe cutaneous ad-

Table 1. Data Collection Form

Case No.

DEMOGRAPHIC DATA		
Age/Sex:		Date of Admission/Referral:
Occupation:		Date of onset of illness/lesions:
HISTORY		
Chief complaint:		
Constitutional symptoms (if present):		
Distribution of lesions:		
Site of onset of lesions:		
Lesions:		
Evolution of lesions:		
Mucosal involvement:		
Time interval between constitutional symptoms and mucosal involvement:		
Offending drug/s and (generic, brand name) route of administration:	Before the appearance of constitutional symptoms	
Time interval drug intake and skin lesions:		
Current medications (generic, brand name) with route of administration:		
History of drug reactions		
Other co-morbidities:		
Family history of drug reaction:		
GENERAL EXAMINATION		
General survey:		
Vital signs:		
DERMATOLOGICAL EXAMINATION		
Morphology of lesions		
Sites affected		
Mucosal lesions:		
OTHER SYSTEMS		
Cardiovascular		
Respiratory		
Gastrointestinal		
Central nervous system		
Other		
LABORATORY or IMAGING WORK-UPS		
Biopsy Done		
CBC w/ platelet count		
Liver enzymes		
Urinalysis		
Electrolytes		
HIV/Hepatitis screening		
Chest X-ray		
Ultrasound of the abdomen		

Table 1. Continued..

Case No.	
TREATMENT	
Topical	
Systemic	
Dressings	
OUTCOME	
Final diagnosis	
Response to treatment	

* Based on the appendix of Sasidharanpillai S, Riyaz N, Khader A, Rajan U, Binitha MP, Sureshan DN. Severe cutaneous adverse drug reactions: a clinicoepidemiological study. Indian J Dermatol. 2015 Jan-Feb;60(1):10

Table 2. Prevalence rate of severe cutaneous adverse drug reactions per year (2011-2015) at the University of Santo Tomas Hospital

	Total of SCAR (n=68)	**Total admission per year (n=104,192)**	**Prevalence rate per year (per 10,000 patients)**
2011	15	23,934	6.30
2012	20	21,457	9.32
2013	16	20,217	7.91
2014	12	19,777	6.07
2015	5	18,807	2.66

verse drug reactions out of 104,192 total admissions for the years 2011-2015. The prevalence rate was 6.52 per 10,000 patients. The specific prevalence rate per year were 6.30, 9.32, 7.91, 6.07 and 2.66 per 10,000 patients seen during years 2011, 2012, 2013, 2014 and 2015, respectively (*Table 2).*

2. Demographic characteristics

Ages ranged from 9 to 93 years with a mean age and standard deviation of 50 ± 21.29 years. Ninety percent (90%) of the patients were in the adult group followed by the pediatric group (6%) and geriatric group (4%). In the adult group, 24% of the cases were seen in patients aged 46-55 years old followed by 16% in those aged 56 to 65 years old. There was a slight female predominance with a male to female ratio of 1:1.1. Most of the patients were from the Private (Pay) Division (62%) while the remaining were admitted or referred at the Clinical (Service) Division (38%) *(Table 3).*

3. Clinical profile

a. History of drug reaction

Eight percent (8%) of the total patients had history of previous drug reaction or allergy to medications. One of the patient from the SJS/TEN spectrum category had previous cutaneous drug reaction to NSAID and the other patient who died had 2 previous drug reactions: erythema multiforme major caused by NSAID and acute generalized exanthematous pustulosis caused by levofloxacin, prior to having toxic epidermal necrolysis caused by allopurinol. Three patients from the DIHS/DRESS category had previous drug reactions with systemic antibiotics: amoxicillin/clavulanic acid, penicillin/erythromycin and piperacillin-tazobactam respectively and one patient had previous Stevens-Johnson syndrome due to celecoxib. For the AGEP category, one patient had previous Stevens-Johnson syndrome secondary to allopurinol and one patient had erythema multiforme secondary to NSAID. None of them had any family history of such reactions *(Table 4).*

b. Co-morbidities

Sixty-nine percent (69%) of the patients had presence of co-morbidities and twenty percent (20%) of these patients had two or more co-morbidities. Most patients had concomitant cardiovascular disease (29%, hypertension and heart disease), endocrine disease (19%, diabetes mellitus and thyroid disease), and neurologic problems (15%) *(Table 4).*

c. Histologic diagnosis/confirmation

Table 3. Demographic characteristics of patients with severe cutaneous adverse drug reactions at the University of Santo Tomas Hospital from 2011-2015

	Category I SJS/TEN (n=19)	Category II DIHS/DRESS (n=36)	Category III AGEP (n=13)	Total (n=68) (%freq)
Age				
Pediatric (0-17y/o)	**0**	**3**	**1**	**4 (6%)**
0-8	0	0	0	0 (0%)
9-17	0	3	1	4 (100%)
Adult (18-85y/o)	**18**	**32**	**11**	**61 (90%)**
18-25	1	4	2	7 (11%)
26-35	3	4	2	9 (15%)
36-45	1	6	1	8 (13%)
46-55	8	5	1	14 (24%)
56-65	2	6	2	10 (16%)
66-75	2	2	2	6 (10%)
76-85	1	5	1	7 (11%)
Geriatric (>85)	**1**	**1**	**1**	**3 (4%)**
Sex				
Male	9	16	8	**33 (49%)**
Female	10	20	5	**35 (51%)**
Division				
Clinical (Service)	5	17	4	**26 (38%)**
Private (Pay)	14	19	9	**42 (62%)**

Table 4. Clinical profile of patients with severe cutaneous adverse drug reactions at the University of Santo Tomas Hospital from 2011-2015 per category

	Category I SJS/TEN (n=19)	Category II DIHS/DRESS (n=36)	Category III AGEP (n=13)	Total (n=68) (%freq)
History				
Previous drug reaction or allergy	2	4	2	**8 (12%)**
Family members with drug reaction or allergy	0	0	0	**0 (0%)**
Co-morbidities				
None	6	11	4	**21 (31%)**
One	9	18	6	**33 (49%)**
Two or more	4	7	3	**14 (20%)**
Types of co-morbidities				
Cardiovascular disease	7	11	2	**20 (29%)**
Endocrine disease	3	6	4	**13 (19%)**
Neurologic disease	1	8	1	**10 (15%)**
Genitourinary disease	3	4	1	**8 (12%)**
Other skin disease	2	1	1	**4 (6%)**
Hematologic disease	1	3	0	**4 (6%)**
Psychological disease	1	1	2	**4 (6%)**
Infectious disease	0	3	0	**3 (4%)**
Gastrointestinal disease	1	0	1	**2 (3%)**
Malignancy	0	2	0	**2 (3%)**
Pulmonary disease	0	0	1	**1 (1%)**
Biopsy				
No	19	35	7	**61 (90%)**
Yes	0	1	6	**7 (10%)**

Table 5. Number, percentage and prevalence of severe cutaneous adverse drug reactions per category at the University of Santo Tomas Hospital from 2011-2015

	Number of SCAR	Percentage	Prevalence rate per category (per 10,000 patients) (n=104,192)
Category I SJS/TEN	19	30%	1.82
Category II DIHS/DRESS	36	50%	3.45
Category III AGEP	13	20%	1.25
TOTAL	**68**	**100**	**6.52**

Table 6. The categories of drug culpability implicated in the severe cutaneous adverse drug reactions per category at the University of Santo Tomas Hospital from 2011-2015*

	Category I SJS/TEN (n=29)	Category II DIHS/DRESS (n=52)	Category III AGEP (n=16)	Total (n=97) (%freq)
Certain	19	36	13	**68 (70%)**
Probable/likely	10	7	2	**19 (20%)**
Possible	0	9	1	**10 (10%)**
Unlikely	0	0	0	**0 (0%)**
Conditional/ Unclassified	0	0	0	**0 (0%)**
Unassessable/ Unclassified	0	0	0	**0 (0%)**

* Based on the World Health Organization – Uppsala Monitoring Centre (WHO-UMC) system (7)

Only 7% of the patients had biopsy to establish the diagnosis. Most cases (90%) were diagnosed clinically without doing any skin biopsy. *(Table 4)*

4. Severe cutaneous adverse drug reactions (SCAR) categories and culprit drugs

a. Frequency of SCAR categories

Patients with drug-induced hypersensitivity reaction or drug reaction with eosinophilia and systemic symptoms (DIHS/DRESS) formed fifty percent (50%, n=36) of the study population with the prevalence rate of 3.45 per 10,000 patients. This was followed by Stevens-Johnson syndrome/ toxic epidermal necrolysis spectrum (SJS/TEN) with thirty percent (30%, n=19) and prevalence rate of 1.82 per 10,000 patients. Lastly, the acute generalized exanthematous pustulosis (AGEP) category occurred in twenty percent (20%, n=13) with prevalence rate of 1.25 per 10,000 patients (*Table 5).*

b. Culprit drugs (General and specific)

The World Health Organization – Uppsala Monitoring Centre (WHO-UMC) system (7) was used to establish the drug causality. There were six categories based on corresponding assessment criteria that should be fulfilled: certain, probable/likely, possible, unlikely, conditional/unclassified, and unassessable/unclassified. There were ninety-seven (97) drugs implicated in this study. Seventy percent (70%) of these drugs were categorized as certain culpability while twenty percent (20%) as probable/likely and ten percent (10%) as possible culpability (*Table 6).*

Sixty-three percent (63%) of the patients had intake of one drug while thirty-seven percent (37%) had two or more drugs prior to the cutaneous reaction. The mean time and standard deviation from intake of causative drugs to reaction was 11.47 ± 3.41 days for all drug reaction categories. AGEP had the fastest mean onset of lesions with 7.64 days followed by DIHS/DRESS with 12.59 days. SJS/TEN had the slowest mean time to reaction of 14.19 days.

The most common culprit drug category was the antibiotic group accounting for forty-two percent (42%) of all reactions. This was followed by the anti-gout medication which accounted for fourteen percent (14%) then the anticonvulsants with twelve percent (12%). Other causative drugs

were antineoplastic drugs with six percent (6%) and analgesics with five percent (5%). *(Table 7).*

Overall, ampicillin-sulbactam (10%), ciprofloxacin (10%), clindamycin (10%), and quadruple combination of anti-TB medications (10%) had the most number of severe cutaneous adverse drug reactions for the antibiotic class. Allopurinol was the most common (93%) anti-gout drug that caused SCAR but one patient had reaction to febuxostat (7%). Phenobarbital (25%), phenytoin (25%) and lamotrigine (17%) were the top 3 anticonvulsant drugs that caused these reactions *(Table 7).*

Specifically, in DIHS/DRESS, the top 4 drug classes which caused the reaction were the antibiotics (40%), anticonvulsants (16%), anti-gout (10%) antineoplastic drugs (10%). Ciprofloxacin and quadruple anti-TB were the most common antibiotics implicated. Phenobarbital and phenytoin, both anticonvulsants, were only associated with DIHS/DRESS but not identified as a culprit drugs in SJS/TEN and AGEP. Allopurinol was the causative drug identified in four patients and febuxostat in one patient. Cytarabine and doxorubicin were

Table 7. Drug classification of culprit drugs in severe cutaneous adverse reactions at the University of Santo Tomas Hospital from 2011-2015

	Category I SJS/TEN (n=29)	Category II DIHS/DRESS (n=52)	Category III AGEP (n=16)	Total (n=97) (%freq)
ANTIBIOTICS	**9 (31%)**	**21 (40%)**	**11 (70%)**	**41 (42%)**
Fluoroquinolones	2	4	3	9 (22%)
Ciprofloxacin	0	4 (19%)	0	**4 (10%)**
Levofloxacin	1	0	1	**2 (5%)**
Moxifloxacin	0	0	1	**1 (2%)**
Ofloxacin	1	0	1	**2 (5%)**
Penicillin combinations	2	4	2	**8 (20%)**
Ampicillin-sulbactam	0	2	2 (18%)	**4 (10%)**
Piperacillin-tazobactam	1	2	0	**3 (7%)**
Amoxicillin-clavulanic acid	1	0	0	**1 (2%)**
Anti-TB (quadruple combination)	0	4 (19%)	0	**4 (10%)**
Lincosamide	0	3	1	**4 (10%)**
Clindamycin	0	3 (14%)	1	**4 (10%)**
Cephalosporin	0	1	2	**3 (7%)**
Cefuroxime (2nd)	0	0	1	**1 (2%)**
Ceftazidime (3rd)	0	0	1	**1 (2%)**
Ceftriaxone (3rd)	0	1	0	**1 (2%)**
Penicillin	0	1	2	**3 (7%)**
Penicillin	0	0	1	**1 (2%)**
Cloxacillin	0	1	1	**2 (5%)**
Carbapenem	1	2	0	**3 (7%)**
Ertapenem	0	1	0	**1 (2%)**
Meropenem	1	1	0	**2 (5%)**
Macrolide	0	1	1	**2 (5%)**
Clarithromycin	0	1	1	**2 (5%)**
Sulfonamides	2	0	0	**2 (5%)**
Co-trimoxazole	2 (22%)	0	0	**2 (5%)**
Others	2	0	0	**2 (5%)**
Chloramphenicol	2 (22%)	0	0	**2 (5%)**
Glycopeptides	0	1	0	**1 (2%)**
Vancomycin	0	1	0	**1 (2%)**
ANTI-GOUT	**9 (31%)**	**5 (10%)**	**0 (0%)**	**14 (14%)**
Allopurinol	9 (100%)	4 (80%)	0	**13 (93%)**
Febuxostat	0 (0%)	1 (20%)	0	**1 (7%)**

Table 7. Continued..

	Category I SJS/TEN (n=29)	Category II DIHS/DRESS (n=52)	Category III AGEP (n=16)	Total (n=97) (%freq)
ANTICONVULSANTS	**2 (7%)**	**9 (16%)**	**1 (6%)**	**12 (12%)**
Phenobarbital	0	3 (33%)	0	**3 (25%)**
Phenytoin	0	3 (33%)	0	**3 (25%)**
Lamotrigine	1 (50%)	0	1 (100%)	**2 (17%)**
Carbamazepine	1 (50%)	0	0	**1 (8%)**
Diazepam	0	1	0	**1 (8%)**
Levetiracetam	0	1	0	**1 (8%)**
Zonisamide	0	1	0	**1 (8%)**
ANTINEOPLASTIC DRUGS	**0 (0%)**	**5 (10%)**	**0 (0%)**	**5 (6%)**
Cytarabine	0	2 (33%)	0	**2 (40%)**
Doxorubicin	0	2 (33%)	0	**2 (40%)**
Hydroxyurea	0	1	0	**1 (20%)**
ANALGESICS	**2 (7%)**	**2 (4%)**	**1 (6%)**	**5 (5%)**
Celecoxib	1	1	0	**2 (40%)**
Ibuprofen	1	0	0	**1 (20%)**
Meloxicam	0	1	0	**1 (20%)**
Paracetamol	0	0	1	**1 (20%)**
GI DRUGS	**3 (11%)**	**2 (4%)**	**0 (0%)**	**5 (5%)**
Omeprazole	2	1	0	**3**
Lansoprazole	1	0	0	**1**
Domperidone	0	1	0	**1**
CARDIOVASCULAR DRUGS	**0 (0%)**	**2 (4%)**	**1 (6%)**	**3 (3%)**
Losartan	0	1	0	**1**
Ivabradine	0	1	0	**1**
Diltiazem	0	0	1	**1**
LIPID-LOWERING DRUGS	**2 (7%)**	**1 (2%)**	**0**	**3 (3%)**
Simvastatin	2	0	0	**2**
Nicotinic acid +Laropiprant	0	1	0	**1**
THYROID DRUGS	**0 (0%)**	**2 (4%)**	**0**	**2 (2%)**
Levothyroxine	0	1	0	**1**
Propylthiouracil	0	1	0	**1**
SUPPLEMENTS	**0 (0%)**	**1 (2%)**	**1 (6%)**	**2 (2%)**
Folic acid	0	1	0	**1**
Herbal	0	0	1	**1**
ANTIVIRAL	**1 (3%)**	**0 (0%)**	**0 (0%)**	**1 (1%)**
Acyclovir	1	0	0	**1**
OTHERS	**1 (3%)**	**2 (4%)**	**1 (6%)**	**4 (5%)**
Epoetin alfa	0	1	0	**1**
Salbutamol	1	0	0	**1**
Thalidomide	0	1	0	**1**
Trimipramine	0	0	1	**1**

the most common antineoplastic drugs which caused DIHS/DRESS.

In SJS/TEN, anti-gout (31%), antibiotics (31%) and both anticonvulsants and analgesics (7% each) were the top 4 drug classes identified as culprit. Allopurinol accounted for majority of patients with SJS/TEN spectrum. This was followed by the antibiotics, chloramphenicol and co-trimoxazole.

Table 8. Management used in severe cutaneous adverse drug reactions at the University of Santo Tomas Hospital from 2011-2015

	Category I SJS/TEN (n=19)	Category II DIHS/DRESS (n=36)	Category III AGEP (n=13)	Total (n=68) (%freq)
TOPICAL				
Topical steroid	0	5	5	**10 (15%)**
Topical antibiotics	11	2	2	**15 (22%)**
Emollients	12	13	7	**32 (47%)**
Topical steroid + Emollients	2	6	2	**10 (15%)**
Topical steroid + Topical antibiotics	1	1	0	**2 (3%)**
Saline compress	16	9	10	**35 (51%)**
Potassium permanganate	1	0	0	**1 (1%)**
SYSTEMIC				
Systemic antihistamine	17	35	9	**61 (90%)**
Systemic steroid	17	21	13	**51 (75%)**
Systemic antibiotic	2	6	1	**9 (13%)**
DRESSING				
Low adherent (Melolin)	3	0	0	**3 (4%)**
Hydrocolloid (Duoderm)	1	1	0	**2 (3%)**
Foam (Allevyn)	1	0	0	**1 (1%)**

The anticonvulsants, lamotrigine and carbamazepine triggered reaction in one patient each.

Lastly, in AGEP, the top 3 classes of culprit drugs were the antibiotics (70%), anticonvulsants (6%) and analgesics (6%). Ampicillin-sulbactam was the most common antibiotics that triggered the reaction. Lamotrigine was the culprit anticonvulsant seen in this category. A reaction to paracetamol was seen in one patient with AGEP *(Table 7).*

5. Management and Disease Outcome

Immediate withdrawal of the most likely implicated drugs was done in all the patients. Fifty-one percent (51%) of the patients had saline compress and forty-seven percent (47%) applied emollients. In SJS/TEN spectrum category, eleven patients received topical antibiotics. The combination of topical steroid and emollients was given to 60% in patients with DIHS/DRESS.

Almost all of the patients (90%) from all categories received systemic antihistamine. Seventy-five percent (75%) had systemic corticosteroids given as IV hydrocortisone then tapered and shifted to oral prednisone. Nine patients (13%) received systemic antibiotics for concomitant secondary bacterial infection.

Dressings were mainly used in the SJS/TEN spectrum category. Low adherent dressings were used on three patients while one patient was given hydrocolloid dressing and another patient with foam dressing *(Table 8).*

Forty-three percent (43%) of patients were admitted under the service of Dermatology while most of the patient (57%) were initially admitted under other services due to co-morbidities and subsequently referred to the Department of Dermatology.

Multidisciplinary approach was made in the management of these cutaneous reactions and underlying co-morbidities. Most patients were referred to these top 6 services: cardiovascular (28%), infectious disease (26%), ophthalmology (25%), endocrinology (21%), pulmonology (21%) and neurology/psychiatry (19%).

The mean duration of hospital stay was 6.67 days for all categories. SJS/TEN had the longest mean duration of hospital stay of 10 days while both DIHS/DRESS and AGEP had a mean duration of hospital stay of 5 days. Overall, there was a mortality rate of four percent (4%). Two of the patients from the SJS/TEN spectrum died due to multi-organ failure and septic shock while one patient from the AGEP category died due to previous medical illness leading to myocardial infarction and eventually cardiogenic shock *(Table 9).*

Table 9. Disease outcome in severe cutaneous adverse drug reactions at the University of Santo Tomas Hospital from 2011-2015

	Category I SJS/TEN (n=19)	Category II DIHS/DRESS (n=36)	Category III AGEP (n=13)	Average (n=68)
Duration of hospital stay (days), mean ± SD	10	5	5	**6.67** ± 2.88
Mortality rate (%freq)	2 (11%)	0 (0%)	1 (8%)	**3 (4%)**

DISCUSSION

SCAR are rare disorders that share the following criteria: 1) being severe, needing hospitalization; 2) being non-predictable, idiosyncratic; and 3) most often induced by drugs (2). Few international studies dealing with SCAR discuss the prevalence, clinical patterns and common drugs implicated. In the present study, severe cutaneous adverse drug reactions accounted for around 0.06% of hospitalized patients for the years 2011 to 2015, considerably lower than the reported ≤ 5% in other literature (2). The present study showed a slight female predominance with a male to female ratio of 1:1.1. However, the Philippine Dermatological Society - Health Information System (PDS-HIS) reported more SCAR cases among males than among females with a ratio of 1.2:1 for the years 2011-2015. Similar to the findings in other studies (8), the cutaneous drug reactions were more evident in the adult between 46-55 years old. This may be due to the increased use of drugs for medical illnesses as age advances. The finding in this study that majority of the patients had associated co-morbidities support this possibility. The potential drug to drug interactions with altered drug metabolism and effects in these patients can lead to SCAR. The patients with history of previous drug reactions or allergy were noted to have increased morbidity and mortality in this study. Therefore, knowing the detailed previous medical and drug history is essential in avoiding future drug reactions since repeated exposure to the culprit drug or same drug class may cause more severe manifestations or even lead to death.

The diagnosis of SCAR can be made based on clinical features as shown in this study. Fever, lymphadenopathy, facial swelling, morbilliform to polymorphous lesions, peripheral eosinophilia, atypical circulating lymphocytes, internal organ involvement (particularly liver and/or renal), and a longer lag time between drug exposure and reaction development are features highly diagnostic of DIHS/ DRESS (1). SJS/TEN typically presents with acute onset and rapid progression of painful lesions of the skin and mucous membranes that develop blisters and erosions with severe constitutional symptoms and extensive detachment of the epidermis (2). AGEP clinically presents with an acute fever, generalized small uniform nonfollicular pustules with a tendency for the skin manifestation to be accentuated in the intertriginous and flexural regions, but typically sparing the mucosal membranes (mouth, conjunctivae, genitals) and the palmoplantar surfaces (9,10). On the other hand, the histologic changes in drug reactions usually yield nonspecific to specific changes depending on the lesions being biopsied (11). This may be the reason why biopsy was done only in seven patients in this study. In DIHS/DRESS category, biopsy was done in one patient and diagnosis was made clinically and through laboratory results. The AGEP group had the most number of biopsies done. Three patients from the AGEP group had gram stain of their lesions which showed the sterile nature of the pustules. Both of these tests were done due to the similarities of AGEP with pustular psoriasis and infectious conditions such as folliculitis secondary to staphylococcus aureus (10).

In a tertiary hospital in Malaysia, Choon et al (2012) (12) did an epidemiological and clinical analysis of cutaneous drug reactions which showed that SJS/TEN spectrum and DRESS were the most common reaction pattern while the drug culprits were from the antibiotics, anticonvulsants and anti-gout groups. In a Brazilian study by Grando et al (2014) (13), DRESS was the most frequent presentation and anticonvulsants, antibiotics and analgesics/ anti-inflammatory drugs were the drugs most commonly implicated. An epidemiological study done in India by Sasidharanpillai et al (2015) (8), showed that among the severe forms of cutaneous drug reactions, SJS/TEN spectrum was the most common reaction pattern and aromatic anticonvulsants were

the most common offending drug group. In the Philippines, the Philippine Dermatological Society – Health Information Systems (PDS-HIS) recorded one thousand twenty-three (1023) SCAR patients among its institutions out of 315,759 patients from the year 2011 to 2015. SCAR comprised 0.32% of all cases seen in all institutions accredited by the Philippine Dermatological Society (PDS). DIHS/DRESS had the most number of cases, accounting for sixty-seven percent (67%) of all patients followed by SJS/TEN spectrum with twenty-percent (22%) and AGEP with only eleven percent (11%) of all severe cutaneous adverse reactions during the same period. The findings in the present study are therefore, similar to these foreign studies and the collated findings of the PDS-HIS. For all the SCAR categories, the mean time to reaction from start of drug intake in this study was between 1-2 weeks. This supports the idea that, in general, drugs taken within the immediate 2 weeks prior to reaction should be considered in determining the possible culprit drug in a cutaneous reaction. However, studies have shown that SJS/TEN has mean time to reaction of 1-3 weeks (1) and DIHS/DRESS usually begin 2 to 6 weeks after exposure to the offending drug (2,9,14). There are also certain drugs that may induce severe reactions even after 8 weeks (15,16). This signifies that drugs taken for a longer duration of more than 8 weeks prior to the SCAR may still be considered for possible culpability. As expected, the onset of the cutaneous manifestation in the AGEP category, was more rapid as compared with the SJS/TEN spectrum and DIHS/DRESS categories. However, compared with other reports (1,9,14,17) our study showed that the mean time to reaction onset in SJS/TEN group was longer than the DIHS/DRESS category.

Antibiotics were the most common culprits in all categories, specifically the fluoroquinolones and penicillin combinations. These findings are similar to most international (2,9,18) and local studies (5) done. Moreover, it was noted that sulfonamides and chloramphenicol were seen as causative agents in the SJS/TEN spectrum category only. On the other hand, clindamycin was a common culprit in the DIHS/DRESS category. Lastly, penicillin and cephalosporins were frequently seen as culprits in the AGEP category. Aromatic anticonvulsants were also common to all categories but more commonly seen as a trigger factor in the DIHS/DRESS category. Allopurinol and NSAIDs were causative agents seen in both the SJS/TEN spectrum and DIHS/DRESS categories but not in the AGEP group. These findings in our study are similar compared to other reports (2,9,18), (*Table 10)*. In this present study, it is noteworthy that paracetamol and febuxostat were implicated as causative drugs for some severe cutaneous adverse drug reactions. Paracetamol is thought to be a common and safe antipyretic, over the counter drug usually given among pediatric patients. However, Chen et al (2015) (19) reported AGEP in a 4-year-old due to paracetamol. Febuxostat is a selective inhibitor of xanthine oxidase which is recommended as urate-lowering alternative for gout who have allopurinol hypersensitivity. However, Chou et al (2015) (20) reported a febuxostat-associated DRESS in an 81-year-old. Paschou et al (2016) (21) described a case of a chronic kidney disease who developed DRESS with febuxostat. This study also recorded an herbal drug and folic acid as culprits of AGEP and DIHS/DRESS, respectively. Hence, it is critical to have a high index of suspicion for these drugs as culprit so as to withdraw their use as early as possible to prevent further serious complications.

Withdrawal of the causative drugs was the initial management in all severe cutaneous adverse drug reactions included in this study. Prompt recognition was important in such reactions to prevent further disease progression. Once the diagnosis was established, systemic therapy was given such as corticosteroid and antihistamine. Topical treatments such as saline compress and emollient were given to aid in faster healing of the skin. Dressings were used more on the SJS/TEN spectrum due to the characteristic lesions with extensive detachment of the skin. Multidisciplinary care was also vital in the management of these drug reactions. Ophthalmology had the most referrals mainly in the SJS/TEN group due to the common eye involvement seen in this category. Medical management of pre-existing co-morbidities and internal organ complications were also important as seen in this study. Cardiovascular medicine had the most referrals for pre-existing hypertension and heart disease. Infectious disease had increased number of referrals for management of concomitant infections and prevention of sepsis which is a common cause of mortality of SCAR patients especially in cases of SJS/TEN. Some cases like AGEP have been initially diagnosed with underlying infectious cause of the pustules prior to referral to dermatology. These just prove the need for multispecialty management in

Table 10. Comparison of common culprit drugs of severe cutaneous adverse drug reactions

		Category I SJS/TEN	Category II DHS/DRESS	Category III AGEP
2009	Roujeau JC, Allanore L, Liss Y, Mockenhaupt M (2).	Antibacterial Sulfonamides Anticonvulsant agents NSAIDs Allopurinol Chlormezanone Corticosteroids	Antiepileptic Allopurinol Sulfonamides Gold salts Dapsone Minocycline	Antibiotics Aminopenicillins Pristinamycine Diltiazem Terbinafine Chloroquine Hydroxychloroquine
2013	Ahmed AM, Pritchard S, Reichenberg J (9).	Antimicrobials Aminopenicillins TMP-SMX Sulfa containing Anticonvulsants Allopurinol NSAIDs	Sulfonamides Dapsone Minocycline Aromatic antiepileptics Allopurinol Gold salts	Antibacterials Aminopenicillin Macrolides Vancomycin Allopurinol Griseofulvin Enalapril Itraconazole
2014	Pavlos R, Mallal S, Ostrov D, Pompeu Y, Phillips E (18).	Sulfa antimicrobials Allopurinol Aromatic amine anticonvulsants Anti-retrovirals (nevirapine) NSAID	Antimicrobial Sulfonamides Beta-lactam Aromatic amine anticonvulsants Allopurinol Anti-retrovirals (nevirapine) NSAID	Antibiotics Beta-lactam Pristinamycin Sulfonamides Quinolones Hydroxychloroquine Diltiazem Terbinafine
Present study	Guzman, Paliza	Antibiotics Fluoroquinolones Penicillin combinations Sulfonamides Chloramphenicol Aromatic anticonvulsants Allopurinol NSAIDs	Antibiotics Fluoroquinolones Penicillin combinations Clindamycin Aromatic anticonvulsants Allopurinol NSAIDs	Antibiotics Fluoroquinolones Penicillin combinations Penicillin Cephalosporins Aromatic anticonvulsants Paracetamol

cases of SCAR to prevent unnecessary workups and initiate prompt management. According to previous studies (9,14,22), the use of steroid in DIHS/DRESS was acceptable, however in SJS/TEN spectrum, it remains controversial and might be indicated only in the first 48 hours of the disease. In this study, eighty-nine (89%) percent of patients with SJS/TEN received IV corticosteroids and the results showed that seventy-nine percent (79%) who received IV corticosteroid improved. Overall, the mortality rate was four percent for all categories. These may suggest the need for a large controlled prospective study to investigate the role of systemic steroid in the management of these severe cutaneous adverse drug reactions. In our study, the hospital stay ranged from 5-10 days with a mean of 6.67 days. This suggests that all aggressive measures and therapy should be initiated at once within this time period.

The present study showed the common severe cutaneous adverse drug reactions seen among hospitalized patients, together with their clinical profile, co-morbidities and common culprit drug/s. A knowledge of these information will help clinicians recognize these severe cutaneous drug reactions, identity possible culprit drugs that need to be immediately withdrawn and promptly provide the proper management to prevent further morbidity and mortality of patients.

CONCLUSION

Sixty-eight cases of severe cutaneous adverse drug reactions diagnosed by the Department of Dermatology of the USTH from January 2011 to December 2015 were studied. These cases formed 0.06% of the total hospital admission for the said period.

The most common severe drug reaction pattern was DIHS/DRESS followed by SJS/TEN and AGEP. The mean age for all categories was 50 years old

with slight female predominance. Eight percent (8%) of the total patients had history of previous drug reaction or allergy to medications and sixty-nine percent (69%) had presence of co-morbidities. Most had concomitant cardiovascular diseases (hypertension and heart disease), endocrine diseases (diabetes mellitus and thyroid disease) and neurologic problems. Diagnosis was based on clinical features in most patients without the need for biopsy. The culprit drugs were identified in all of the patients. Thirty-seven percent (37%) had two or more drugs identified as trigger factors. The most common culprit drugs for DIHS/DRESS were ciprofloxacin, quadruple anti-TB drugs, clindamycin, phenobarbital, phenytoin and allopurinol. For SJS/TEN the most common culprits were cotrimoxazole, chloramphenicol, allopurinol, lamotrigine, carbamazepine, celecoxib and ibuprofen, and for AGEP they were ampicillin-sulbactam, lamotrigine and paracetamol.

The prompt withdrawal and initiation of supportive therapy were the mainstay of treatment. Additional management of systemic therapy with steroid and antihistamine as well as topical treatment with saline compress and emollients had a major role in the improvement of patients. There was a mortality rate of four percent (4%) mostly seen in patients with SJS/TEN but 96% of patients were discharged improved.

RECOMMENDATIONS

A more comprehensive study should be done to include more subjects on a national level with the participation of other institutions that manage such severe cutaneous adverse drug reactions. Additional studies may be conducted to establish whether certain co-morbidities can make patients more susceptible to have these severe cutaneous adverse drug reactions. This study can be a basis for a standardized report system that can be used for severe cutaneous adverse drug reaction in our country. Further studies should be done to determine the role of systemic steroid and antihistamine as standard therapies of these severe cutaneous adverse drug reactions.

Disclosure and Conflict of Interest

This study is investigator-initiated and not industry funded or company sponsored. There is no potential conflict of interest.

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