Cutaneous adverse drug reactions in hospitalised patients

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ABSTRACT

Introduction: Serious adverse drug reactions are common in hospitalised patients. There have been few studies examining the clinical presentation, implicated drugs and outcomes in Singapore.

Methods: The clinical and laboratory data of all inpatient dermatology consultations with a diagnosis of cutaneous adverse drug reaction were retrospectively analysed over a one-year period.

Results: A total of 97 patients were diagnosed with cutaneous adverse drug reactions. Eight different clinical reaction patterns were noted, namely drug exanthems (46.4 percent), drug rash with eosinophilia and systemic symptoms (18.6 percent), Stevens-Johnson syndrome/toxic epidermal necrolysis spectrum (14.4 percent), urticaria/angioedema (11.3 percent), acute generalised exanthematous pustulosis (3.1 percent), fixed drug eruptions (3.1 percent), generalised exfoliative dermatitis (2.1 percent) and drug-induced vasculitis (1.0 percent). The putative medications included antibiotics (50.5 percent), anticonvulsants (11.3 percent), allopurinol (8.2 percent), chemotherapeutic agents (7.2 percent), nonsteroidal anti-inflammatory agents (7.2 percent), intravenous contrasts (3.2 percent), complementary medications (2.1 percent) and various other medications (10.3 percent). 30 patients were admitted primarily for their adverse drug reaction, with an average length of hospital stay of nine days, while the remaining 67 patients developed these reactions as a complication of their inpatient stay. A total of five deaths were recorded.

Conclusion: The presentation of cutaneous adverse drug reactions in hospitalised patients is diverse, ranging from self-limiting and benign reaction patterns to those that are life-threatening. Early recognition, accurate diagnosis, withdrawal of putative medications and specific treatments when indicated may improve outcome.

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INTRODUCTION

Serious adverse drug reactions (ADRs) are common in hospitalised patients and occur in 6.7% of all inpatients. In the United States, the incidence of fatal ADRs is 0.32%, and they are estimated to be between the fourth and sixth leading cause of death in inpatients.[1] Cutaneous ADRs are the most common, recognisable and reported form of ADR, representing over 30% of all reported ADRs,[2] and its incidence in hospitalised patients has been estimated to be about 2%.[3] Although the majority of cutaneous reactions are mild and self-limiting, severe cutaneous ADRs, such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) as well as drug rash with eosinophilia and systemic symptoms (DRESS), have been estimated to occur in one out of every 1,000 hospitalised patients and are associated with significant morbidity and mortality.[4]

Few studies have examined the clinical presentation and outcome of cutaneous ADRs of hospitalised patients in Singapore.[5] With the introduction of newer drugs and evolving prescription practices, the risk of adverse reactions and the cutaneous presentation of such drugs remain unclear. The aim of this paper is to report the various reaction patterns of cutaneous ADRs and their putative drugs, as well as the outcome among patients who were managed in a tertiary hospital from 2005 to 2006.

METHODS

A review of all dermatology inpatient consultations received from July 2005 to June 2006 was conducted. The clinical and laboratory data of consultations with a diagnosis of cutaneous ADRs were retrospectively analysed. The diagnosis of cutaneous ADRs was made based on clinical features, exclusion of alternative causes, and was supported by ancillary investigations such as histological and laboratory findings. Drug causality was derived and ranked (World Health Organization [WHO] drug causality criteria: certain, probable, possible,

Table I. Referral pattern classified according to medical specialties and disciplines.

Referral Department	No. (%)
Medical specialties	
Internal medicine	29 (29.9)
Haematology	12 (12.4)
Renal medicine	8 (8.2)
Oncology	7 (7.2)
Infectious disease	6 (6.2)
Neurology	5 (5.2)
Cardiology	4 (4.1)
Respiratory and critical care	4 (4.1)
Gastroenterology	3 (3.1)
Endocrinology	2 (2.1)
Rheumatology & immunology	1 (1.0)
Subtotal	81 (83.5)
Surgical specialties	
Neurosurgery	5 (5.2)
General surgery	3 (3.1)
Ear, nose, throat	2 (2.1)
Orthopaedics	2 (2.1)
Cardiothoracic	2 (2.1)
Plastic & reconstructive	1 (1.0)
Colorectal	1 (1.0)
Sub total	16 (16.5)
Total	97 (100)

Table II. Breakdown of various clinical reaction patterns (n = 97).

Clinical reaction pattern	No. (%)
Drug exanthem	45 (46.4)
DRESS	18 (18.6)
SJS-TEN spectrum (Total)	14 (14.4)
SJS	4 (4.1)
SJS/TEN overlap	3 (3.1)
TEN	7 (7.2)
Urticaria/angioedema	11 (11.3)
AGEP	3 (3.1)
Fixed drug eruption	3 (3.1)
Generalised exfoliative dermatitis	2 (2.1)
Drug-induced vasculitis	1 (1.0)

SJS: Stevens-Johnson syndrome; TEN: toxic epidermal necrolysis; DRESS: drug rash with eosinophilia and systemic symptoms; AGEP: acute generalised exanthematous pustulosis

Table III. Breakdown of SCARs according to demographics and mortality.

	No. (%)		
	SJS/TEN spectrum (n = 14)	DRESS (n = 18)	AGEP (n = 3)
Mean age; range (yrs)	61.5; 39–91	60; 27–88	43; 18–59
Racial distribution			
Chinese	11 (79)	14 (78)	2 (67)
Malays	2 (14)	3 (17)	1 (33)
Indians	1 (7)	1 (5)	0 (0)
Others	0 (0)	0 (0)	0 (0)
Gender distribution			
Male	9 (64)	7 (39)	1 (33)
Female	5 (36)	11 (61)	2 (67)
Mortality	5 (36)	0 (0)	0 (0)

SCARs: severe cutaneous adverse reactions; SJS: Stevens-Johnson syndrome; TEN: toxic epidermal necrolysis; DRESS: drug rash with eosinophilia and systemic symptoms; AGEP: acute generalised exanthematous pustulosis

unlikely) based on the consideration of composite factors such as temporal relationship between the drug ingestion and onset of drug reaction, known epidemiological risk, improvement on withdrawal and exclusion of other causes (Fig. 1). SJS, TEN, DRESS and acute generalised exanthematous pustulosis (AGEP) were considered to be severe cutaneous ADRs, on account of their higher mortality and morbidity.[6,7]

RESULTS

Over the one-year period of the study, there were a total of 73,381 admissions (including electives and emergency) at our hospital. A total of 731 inpatient dermatology consults were recorded, of which 97 patients were diagnosed with cutaneous ADR. The patients' age was 13–88 years, with a mean age of 60 years. The racial distribution consisted of Chinese (85.0%), Malay (12.0%), Indian (2.5%) and other races (0.5%). 53 (54.6%) patients were female and 44 (45.4%) were male. 83.5% of these patients were admitted into the medical disciplines, whereas the remaining 16.5% were surgical patients. The detailed breakdown according to referral department is shown in Table I.

Eight different clinical reaction patterns were noted (Table II). These were drug exanthems, SJS/TEN spectrum (consisting of SJS, SJS/TEN overlap and TEN), DRESS, urticaria/angioedema, AGEP, fixed drug eruptions, generalised exfoliative dermatitis (GED) and drug-induced vasculitis. The top three clinical presentations included maculopapular exanthems (46.4%), DRESS (18.6%) and SJS/TEN spectrum (14.4%). Severe cutaneous adverse reactions (SCARs), comprising SJS, SJS/TEN, TEN (Fig. 2), DRESS (Fig. 3) and AGEP (Fig. 4), made up 36.1% of the cases. The breakdown of SCARs according to demographics and mortality is shown in Table III.

Antibiotics were the most common suspected putative agents affecting 50.5% of patients, followed by anticonvulsants (11.3%), allopurinol (8.2%), chemotherapeutic agents (7.2%), nonsteroidal anti-inflammatory agents (7.2%), intravenous contrasts (3.2%), complementary medications (2.1%) and various other medications (10.3%). The detailed breakdown of the putative drugs and their corresponding reaction patterns are shown in Table IV.

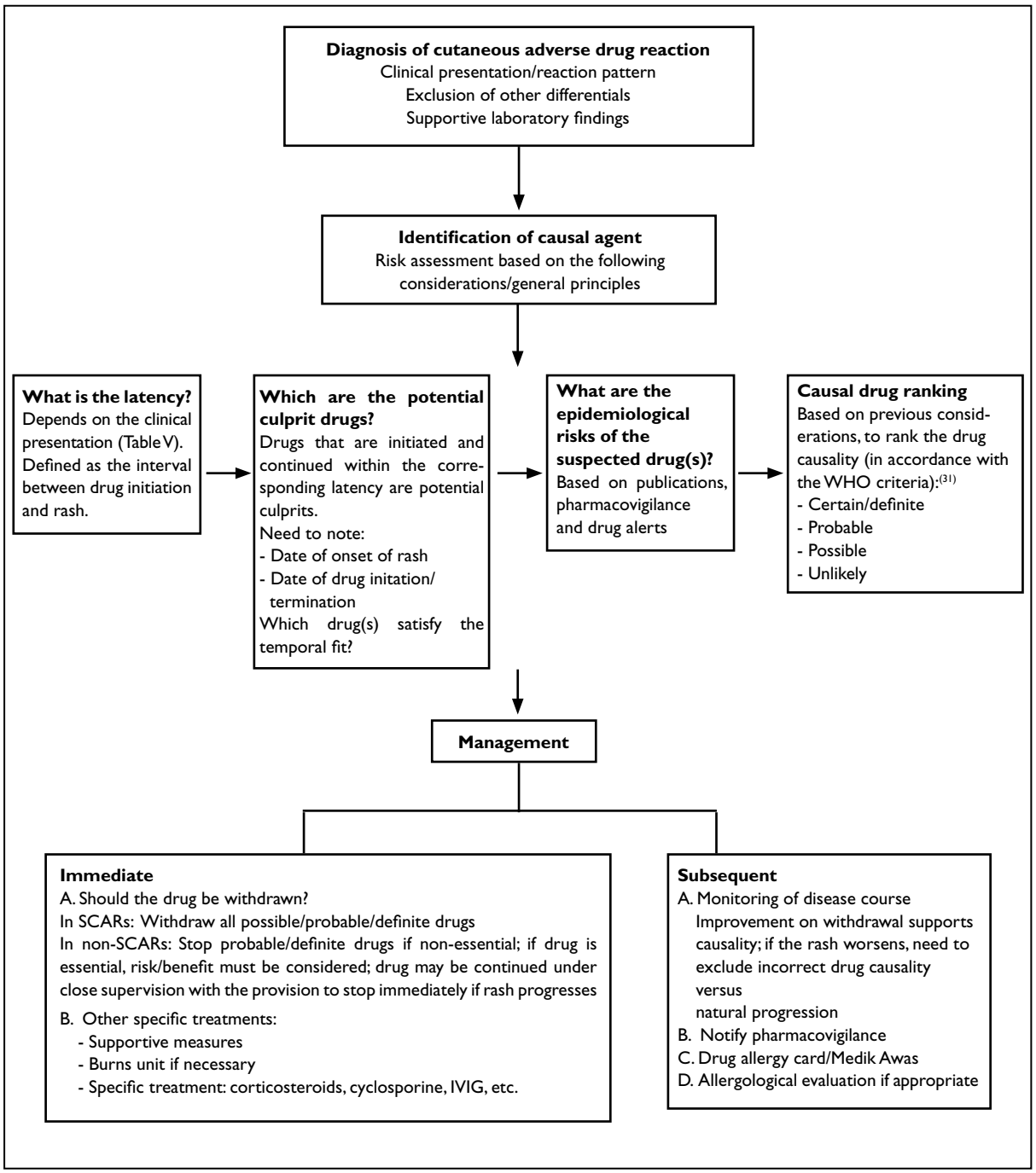

Fig. 1 Practical algorithm in the evaluation of a cutaneous adverse drug reaction.

Among the 97 patients, 30 (31%) were admitted primarily for their cutaneous adverse reaction, and their average length of hospital stay was nine (range 2–24) days. The remaining 67 (69%) patients developed these SCARs as a complication of their inpatient stay. A total of five deaths (5.1%) were reported, two of which were due to SJS/TEN overlap from piperacillin/tazobactam and allopurinol, and the other three were from TEN secondary to meropenem, anti-tubercular medications and omeprazole.

DISCUSSION

In this study, we have highlighted the various patterns of cutaneous drug reactions seen in an inpatient setting, as well as their common putative drugs. The diagnosis of cutaneous ADR is one of the most challenging clinical problems in hospitalised patients. The challenge is two-fold: firstly, to accurately diagnose cutaneous ADR and secondly, to attribute causality to a particular drug, if possible. This is particularly challenging in an acute setting, where the patient is usually on multiple

Fig. 2 Photograph shows extensive epidermal necrolysis and detachment.

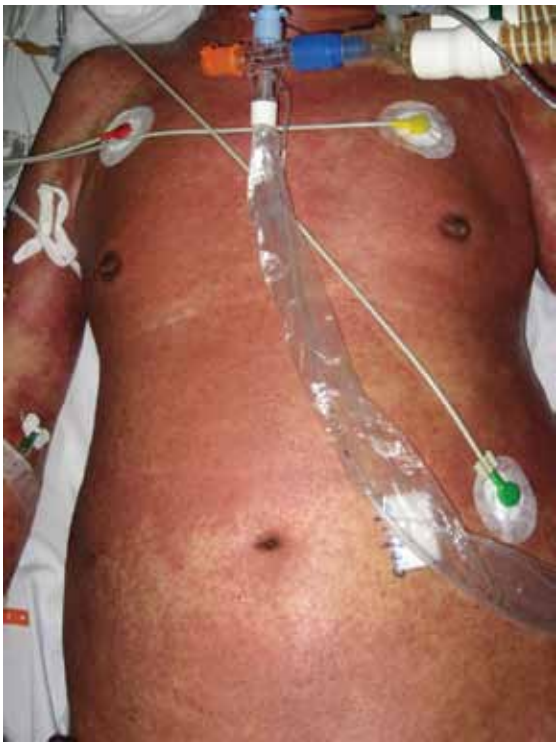

Fig. 3 Photograph shows drug rash with eosinophilia and systemic symptoms (DRESS), with an exanthematous rash requiring ICU care for multiorgan failure.

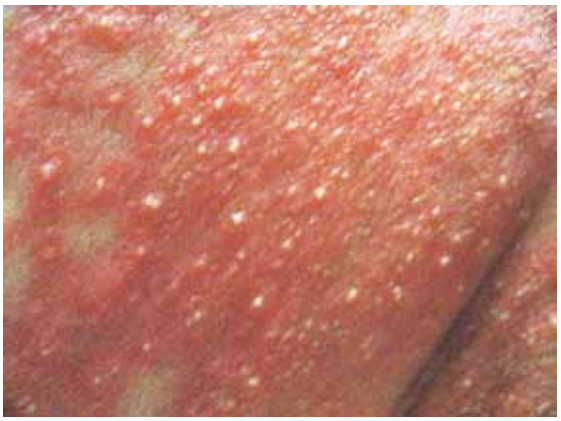

Fig. 4 Photograph shows numerous pinpoint non-follicular pustules on a background of erythema.

medications, some of which may be essential and life-saving. Under-diagnosis and inaccurate attribution of drug causality may expose the patient to life-threatening adverse reactions. Conversely, over-enthusiastic labelling of drug allergy may result in the deprivation of life-saving treatment, less effective therapy or an increase in the healthcare costs with the use of more expensive alternatives.

History and clinical examination form the cornerstone of diagnosis. A practical approach that we have found to be useful is shown in Fig. 1. The recognition of the dermatological reaction patterns and the exclusion of differentials are of primary importance.[4,8] Clinical features of the various reaction patterns and their corresponding differential diagnosis are shown in Table V. These various reaction patterns have different temporal relationships between the time of administration of the medication and the onset of dermatoses, although this latency may be shortened in the event of a re-exposure. Nonetheless, an appreciation of this temporal relationship and the known epidemiological risk of the exposed drugs will facilitate the identification of the probable causal drug, or at least attribute causality probability. The details of the various latency and high-risk drugs associated with the different clinical reaction patterns are shown in Table V. Adjunctive investigations such as skin biopsy can be of value in confirming the diagnosis in certain patterns, or to exclude possible differential diagnoses.[8] Laboratory tests, such as full blood counts, liver function tests, urinalysis and renal panel, are useful for monitoring systemic involvement.

There is no role for skin testing in the acute phase of cutaneous ADRs. Most allergological investigations are performed at between six weeks to six months following the resolution of the ADR,[8,9] and the choice of tests performed is dependent on the clinical reaction pattern and the underlying pathogenesis.[9] Prick tests are used primarily for the evaluation of IgE-mediated reactions such as urticaria,[10,11] whereas patch testing is employed when a delayed Type IV reaction is suspected as the underlying pathogenesis (e.g. maculopapular drug exanthems, fixed drug eruptions, AGEP, DRESS).[10] Although such tests may be useful in confirming the culprit drug, certain pitfalls exist. The sensitivity of patch tests in the evaluation of cutaneous ADR is generally low, with positive results in 50% of drug exanthemas,[12,13] 50% in AGEP, and 9% in SJS/TEN.[14] In addition, the negative predictive value

Table IV. Various putative drugs and their associated clinical reaction pattern.

	Exanthems	SJS	SJS/TEN	TEN	DRESS	AGEP	Urticaria/ angioedema	FDE	GED	Vasculitis	Total no. (%)
Antibiotics											49 (50.5%)
Penicillins	9		1				1	1			12
Cephalosporins	8				1	1	1				11
Quinolones	2						1			1	4
Macrolides	2										2
Carbapenems	2		1								3
Vancomycin	5										5
Clindamycin	1			1							2
Metronidazole	1				1						2
Bactrim					1			2			3
Dapsone					1						1
Anti-tuberculosis	2			1					1		4
Anticonvulsant											11(11.3%)
Phenytoin	1	1			6	1					9
Carbamazepine		1									1
Valproate		1									1
Allopurinol			1	1	6						8 (8.2%)
NSAIDs				1			6				7 (7.2%)
Chemotherapeutics											7 (7.2%)
VP-16				1							1
Cytarabine	4										4
Thalidomide	1										1
Capecitabine	1										1
Complementary	1			1							2 (2.1%)
IV contrast	2						1				3 (3.2%)
Others											10 (10.3%)
Omeprazole		1		1							2
Plavix					1						1
Griseofulvin					1						1
Buscopan	1										1
Carbimazole	1										1
Clexane	1										1
Enalapril							1				1
Transexamic acid						1					1
Fenofibrate									1		1
Total	45	4	3	7	18	3	11	3	2	1	

SCARs: severe cutaneous adverse reactions; SJS: Stevens-Johnson syndrome; TEN: toxic epidermal necrolysis; DRESS: drug rash with eosinophilia and systemic symptoms; AGEP: acute generalised exanthematous pustulosis; FDE: fixed drug eruptions; GED: generalised exfoliative dermatitis; NSAIDs: nonsteroidal anti-inflammatory drugs

of skin tests is unknown, and the rate of positive oral challenges following negative prick, patch and intra-dermal tests was about 13%–17%.[15,16] Drug challenges are not routinely recommended due to their inherent risks and ethical considerations, and they are absolutely contraindicated in severe cutaneous adverse reactions such as SJS, TEN, DRESS.

In the current study, while the majority of cutaneous reactions were minor and self-limiting, 36.1% of cases were severe cutaneous ADRs (consisting of SJS/TEN spectrum, DRESS and AGEP) that were potentially life-threatening. The mortality rate of SJS and TEN is reported to be < 5% and about 30%, respectively,[4] and these conditions are frequently associated with long-term ocular, mucosal and cutaneous sequelae. Similarly, DRESS may have systemic complications, such as hepatitis, renal failure, myocarditis, pneumonitis and haematological involvement,[6] and

Table V. Summary of drug reactions, common features, differentials, latency period and common putative drugs. Table is adapted from references 4–6, 27–30 and the current study.

Diagnosis	Clinical Features	Latency	Common responsible drugs*	Differential diagnosis
SJS/TEN (Fig. 2)	Small blisters on dusky purpuric macules, atypical targets, confluent erythema, sheet-like detachment; usually 2 or more mucosal sites are affected BSA < 10% : SJS BSA 10-30% : SJS/TEN BSA > 30% : TEN	1–4 weeks	Allopurinol, anticonvulsants (phenytoin, carbamazepine, phenobarbital, lamotrigine), infective sulphonamides, oxicam NSAIDs	Immunobullous diseases HSV-associated EM, mycoplasma SJS, connective tissue diseases – SLE, multi-focal bullous fixed drug eruptions
DRESS (Fig. 3)	Exanthematous rash, exfoliative dermatitis, associated with eosinophilia, fever, lymphadenopathy and multisystem involvement	2–8 weeks	Allopurinol, anti-infective sulphonamides, anticonvulsants, minocycline	Cutaneous lymphoma/ pseudolymphoma, viral infections (e.g. EBV, CMV, dengue)
AGEP (Fig. 4)	Extensive, non-follicular pustules	1–7 days	Aminopenicillins, quinolones, pristinamycin, sulphonamides, antimalarials, terbinafine, diltiazem	Pustular psoriasis
Drug exanthem	Erythematous macular/ maculopapular/papular	1–2 weeks	Aminopenicillins, sulfonamides, cephalosporins, anticonvulsants	Viral exanthem
Urticaria/angioedema	Wheals and flares	Minutes to 1–2 days	Penicillins, cephalosporins, sulfonamides, tetracyclines#	Dermographism, other forms of urticaria
Fixed drug reactions	Sharply demarcated erythematous, oedematous plaques, occasionally with central blister/epidermal detachment	First exposure: 1 week Subsequent exposures: 24–48 hours	Tetracyclines, sulphonamides, NSAIDs, barbiturates, carbamazepine, paracetamol phenolphthalein	Generalised FD may mimic SJS/TEN, mucosal FDE: herpes infection
Drug-induced vasculitis (cutaneous small vessel vasculitis & ANCA positive vasculitis)	Purpuric papules, haemorrhagic blisters, pustules, erosions	1–3 weeks	CSSV: Penicillins, NSAIDs, sulfonamides, cephalosporin, fluoroquinolones, thiazide diuretics, frusemide, ANCA +VE: Propylthiouracil, hydralazine, minocycline	Non-drug causes of cutaneous vasculitis, pigmented purpuric dermatoses, scurvy, viral exanthems (parvovirus B19, enterovirus), coagulopathy

* Commonly implicated drugs based on local and overseas data are listed. # Other drugs such as aspirin, NSAIDs, may induce non-immunological mediated urticaria.
SJS: Stevens-Johnson syndrome; TEN: toxic epidermal necrolysis; DRESS: drug rash with eosinophilia and systemic symptoms; AGEP: acute generalised exanthematous pustulosis; BSA: body surface area; EM: erythema multiforme; SLE : systemic lupus erythematosus, CSSV: cutaneous small vessel vasculitis; FDE: fixed drug eruptions; NSAIDs: nonsteroidal anti-inflammatory drugs; EBV: Epstein-Barr virus; CMV: cytomegalovirus; HSV: herpes simplex virus; ANCA: anti-neutrophil cytoplasmic antibodies; SLE; systemic lupus erythematosus

is also associated with autoimmunity in survivors.[17,18] All the mortality in our cohort of patients arose from the SJS/TEN spectrum. It is therefore imperative for clinicians to recognise such severe adverse reactions as an early withdrawal of drugs, particularly those with short half-lives,[19] and prompt access to burn unit care[20] have been shown to improve the survival of such patients.

In addition to mortality and morbidity risks, cutaneous ADRs also constitute a sizeable healthcare cost. In the United States, it is estimated that ADRs contribute to an additional US$1.56 to 4 billion in direct hospital costs per year,[21] and it is estimated that 5%–9% of hospital costs in the United Kingdom[22] are related to ADRs. Similarly, 31% of all our patients were admitted solely for their cutaneous complications and required nine days of hospitalisation on an average, while the remaining 69% developed these complications as an inpatient, potentially resulting in a longer period of hospital stay.

In their earlier report in 1984, Fong et al[5] found that the commonly implicated drugs in cutaneous ADRs in local inpatients were antimicrobials (51.4%), anti-inflammatory/analgesics (17.8%), allopurinol (8.4%), Chinese herbs (3.7%) and anticonvulsants (3.7%). Despite the introduction of newer medications and evolving prescription practices over the last 25 years, similar findings were noted in our current study, where the three most commonly implicated drug groups/ drugs observed were antibiotics, anticonvulsants

and allopurinol, although there has been an increase in reactions attributed to anti-epileptic agents and a corresponding decrease in those attributed to NSAIDs. Similar trends have been borne out in our local Health Sciences Authority pharmacovigilance[23,24] as well as in other centres,[25] highlighting the need for caution when such "high-risk" drugs are prescribed. Unique to our demographics, complementary/traditional medications may be an important, albeit often overlooked offending agent.[26]

In our study, 0.1% of inpatients developed cutaneous ADRs during the study period. This appears significantly lower compared to a previous report of 2%.[3] Several factors could explain this finding. Firstly, our study only included cases that were referred for dermatological opinion. It is likely that many cases of cutaneous ADRs, particularly those that were mild, were managed by the primary physicians. Secondly, there may have been an underreporting or under-recognition of cutaneous ADRs. Lastly, patients with a shorter duration of stay (e.g. elective surgery or delivery) are more likely to develop these reactions post discharge and hence, are more likely to have been managed as outpatients. Adequate reporting of such adverse events and further prospective studies may clarify the actual incidence of cutaneous ADR.

In summary, the presentation of cutaneous ADRs in hospitalised patients is diverse, ranging from self-limiting and benign reaction patterns to those that are life-threatening. Despite medical advances, cutaneous ADRs remain a clinical diagnosis. Appreciation of the varied clinical presentations and the common putative drugs will enable clinicians to recognise, diagnose and institute timely measures, such as withdrawal of drugs, specific treatments and specialised care, so as to improve the outcome of these iatrogenic events.

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