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TITLE: ADVERSE DRUG REACTIONS REPORTED BY HEALTHCARE PROFESSIONALS: REACTION CHARACTERISTICS AND TIME TO REPORTING

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ABSTRACT

We describe adverse drug reaction (ADR) reporting characteristics and factors contributing to length of time to report by healthcare professionals (HCPs). This is a retrospective study of voluntary reports to an Australian healthcare ADR Review Committee over a two-year period (2015-2016). Descriptive and univariate models were used for outcomes, employing standardised ADR definitions. Hospital pharmacists reported 84.8% of the 555 ADRs, 70.3% were hospital-onset and 71.7% were at least moderate severity. Immunologically mediated reactions were most commonly reported (409,73.7%). The median time to submit an ADR report was 3 (IQR 1-10) days. Longer median times to reporting were associated with multiple implicated agents and delayed hypersensitivity reactions, especially SCARs (severe cutaneous adverse reactions). A total of 650 medications were implicated; multiple agents in 165/555 (29.7%) reports. Antimicrobials were most commonly implicated agents. Immunologically mediated reactions were most commonly associated with antimicrobials and radiocontrast agents [p<0.0001, OR 3.6, 95%CI 2.4 – 5.5 and p=0.04, OR 4.2, 95%CI 1.2 – 18.2 respectively]. Opioids and psychoactive medications were more commonly implicated in non-immunological reported ADRs [p=0.0002, OR 3.9, 95%CI 1.9 – 7.9 and p<0.0001, OR 11.4, 95%CI 4.6 – 27.8 respectively]. Due to the predominant reporting of immunologically mediated reactions, a targeted education program is being planned to improve identification and accuracy of ADR reports, with the overall aim of improved management, to ensure quality service provision and patient safety.

KEY WORDS: Adverse drug reactions, pharmacoepidemiology, pharmacovigilance, hypersensitivity, medication safety

MAIN TEXT

INTRODUCTION

Adverse drug reactions (ADRs) pose a significant clinical and economic burden to health systems [1]. In Australia, over 1.5 million people are expected to experience an adverse event from medications annually [2]. Medication-related hospital admissions have previously been estimated to comprise 2–3% of all Australian hospital admissions [3]. Severe ADRs are also a leading cause of hospitalisation and in-hospital deaths, especially in the elderly [4-6].

ADRs are traditionally classified into several types based on underlying pharmacologic and pathogenetic mechanisms [7]. Approximately 75 – 80% of ADRs are non-immunological and occur through direct or indirect pharmacologic mechanisms, whilst immunologically mediated processes account for 20-25% of ADRs [8]. Immunologically mediated ADRs are further classified according to underlying immune mechanisms [9] (Table 1). Medication-related anaphylaxis and severe cutaneous adverse reactions (SCARs) are associated with a high risk of mortality and morbidity [10,11]. Regardless of ADR type, it is estimated that up to 50% of medication-related hospital admissions are potentially preventable [2].

It is therefore essential that healthcare organisations have effective management systems to ensure safer patient care by decreasing harm from medication-related adverse reactions. ADR management is included in the Australian National Health Care Accreditation Standards [2]. Health services are required to have processes for documenting medicine allergies and adverse drug reactions in the healthcare record and in the organisation-wide incident reporting system as well as submitting major or rare adverse drug reactions to the Therapeutic Goods Administration (TGA) of Australia. Central to ADR management is accurate diagnosis and documentation of each episode, timely reporting and evaluation, and risk mitigation through communication to patients, carers and clinicians [2]. The Society of Hospital Pharmacists of Australia's Standards of Practice also states that

the emphasis of ADR management is on preventing ADRs and preventing re-exposure of patients who have already experienced an ADR [12].

Although national and international guidelines exist for ADR reporting and management [13,14], no 'gold standard' system has been established at individual healthcare facility level. To date, we found no studies examining the efficiency and effectiveness of institutional ADR management systems nor the characteristics and timing of ADR reporting by health professionals (HCPs). As most healthcare facilities routinely rely on voluntary reporting to capture ADR events, it is important to evaluate these aspects of reporting to benchmark the process measures. This study aims to evaluate the characteristics of reported reactions, medications implicated and factors contributing to time taken for HCPs to report ADRs. The results of this study will a basis forresource planning to improve ADR management and quality care.

METHODS

Setting

This was a retrospective cross-sectional study undertaken at a metropolitan 800-bed tertiary teaching hospital network with an established ADR management system in Melbourne, Australia. The network is an affiliation of four healthcare facilities comprising of a 450-bed tertiary level University-affiliated teaching hospital with general and specialty medical and surgical services, solid organ and haematological transplantation, state-wide burns and trauma, and human immuno-deficiency virus infection services; a 250-bed aged care and rehabilitation hospital; a 100-bed community hospital with general medical and surgical services; and a sexual-health clinic. The institutional ethics committee granted approval to conduct this study (approval number: 179/17).

At participating sites, HCPs (doctors, pharmacists and nurses) are encouraged to report all ADRs encountered to the Adverse Drug Reaction Review Committee (ADRRC) using a standard paper

reporting form (Supplemental Figure 1). Reporting is not mandatory but strongly encouraged on a voluntary basis. The ADRRC is a long-standing hospital committee, comprising a multidisciplinary team including a senior pharmacist and specialist clinicians from at least one of dermatology, immunology, clinical pharmacology, infectious diseases and general medicine. The Committee meets every two weeks to review all ADR reports, verify diagnoses, organise allergy clinics referral if required, and provide further risk mitigation measures through written recommendations to the clinicians involved as well as the patients/carers. Relevant ADR reports are forwarded to the national database at the TGA. Drug causality is assessed by standardised algorithms such as the Naranjo algorithm, ALgorithm for assessment of Drug causality in toxic Epidermal Necrolysis (ALDEN) and the Roussel-Uclaf Causality Assessment Method (RUCAM) in cases of suspected drug- induced liver injury [15-17].

Data collection

All consecutive ADR reports received by the ADRRC over a two-year period, from 1st January 2015 to 31st December 2016, were included in this study. Data regarding the date of onset of reaction, date of reporting, date of ADRRC review, vocation of the reporter, suspected medication(s), strength of causality associations and description of ADR episodes were extracted electronically from the ADR database. Where data was missing, or erroneous, written ADR reports and clinical notes were reviewed to extract a near complete dataset. If multiple reports were submitted for one patient for unrelated ADR episodes, each episode was counted as a separate encounter. The initial diagnosis by the treating clinician was noted, based on clinical, laboratory and/or histopathological findings and was further verified by the ADRRC. Each ADR episode was then retrospectively reviewed and classified into 'immunologically mediated' and 'non-immunologically mediated' reaction by a consensus decision between the authors (AKA, LVG, SLDM and NRA), based on the presumptive underlying pharmacokinetics/pharmacodynamics mechanisms. The immunological reactions were further classified as immediate or delayed hypersensitivity reactions, based on time of exposure to

reaction onset. Delayed hypersensitivity reactions were further categorised into; severe T-cell mediated reactions (SCARs), single organ reactions (e.g. acute interstitial nephritis) and non-SCAR reactions. Where ADRs did not fit into the mechanisms of immunologically or non-immunologically mediated reactions, they were considered 'unclassified'. Definitions used in this study to classify ADR types and severity are provided in Table 1.

Outcomes

Characteristics of ADR reports were evaluated with regards to patients' age distribution, vocation of reporters, place of onset of reactions, reaction types, severity and strength of causality associations. Implicated medications were analysed according to the broad categories of immunologically and non-immunologically mediated reactions. Additionally, the time to ADR report was measured. It was defined as the date of onset of reaction to the date ADR report was submitted to ADRRC. This length of time was taken as a surrogate marker for an ADR management process. All outcomes were analysed using the total number of ADR reports as the denominator, except for the patients' median age, which was based on the total number of patients.

Statistical analysis

Statistical analyses were conducted using GraphPad Prism 7 (GraphPad Software 2017, California, United States of America). All categorical data were presented as counts and proportion, and continuous data as median and interquartile ranges (IQR). Univariate analyses were conducted to examine the associations between variables of interest using Mann-Whitney U tests for comparison between two groups (e.g. single vs. multiple agents and median time to reporting) and Kruskal-Wallis tests when one variable has more than two groups [e.g. vocation of reporters (pharmacists vs. medical doctors vs. others) and median time to reporting]. Comparisons between proportions were carried out using Chi-square and Fisher's exact tests, and the associations were also presented as

Odds Ratios (OR). A two-sided p-value of <0.05 was considered statistically significant for all associations.

RESULTS

A total of 555 reports were included in this study, representing 535 patients at median age of 39.5 years (interquartile range [IQR] 19.8 – 63.3). For twenty patients, each had 2 ADR reports submitted. During the study period, the hospital network received 106,683 presentations at both tertiary and community hospitals' emergency departments, with a total of 111,923 episodes of inpatient care at all sites. The majority (471, 84.8%) of reports were submitted to ADRRC by hospital pharmacists, 52 (9.4%) were by doctors and 32 (5.7%) were by other HCPs. With regards to the onset of ADR, 390 (70.3%) episodes occurred during hospitalisation and 165 (29.7%) occurred in the community. Overall, 160 (28.8%) were classified as mild, 232 (41.8%) as moderate, 110 (19.8%) as severe and 53 (9.5%) as life-threatening or fatal episodes. Causality was determined as 'possible' in 233 (42%), 'probable' in 232 (41.8%), 'definite' in 81 (14.6%), 'unlikely' in 1 (0.2%) using standardized algorithms. In 8 (1.4%) reports, causality was unable to be determined.

The types of reactions reported are presented in Figure 1, with the majority (409, 73.7%) being immunologically-mediated, and being delayed type hypersensitivity reactions (61.4%).

Overall, the median time (IQR) from the date of onset of reaction to submitting an ADR report was 3 (IQR 1-10) days. The median time taken from the date of onset of reaction to the ADRRC assessment was 18 (IQR 12 – 29) days. The median time to submitting an ADR report was noted to take longer when multiple agents were implicated [3 (IQR 1-10) vs. 5 (IQR 1-13) days for single vs. multiple implicated agents, p=0.01] and for delayed hypersensitivity reactions [1 (IQR 0-3) vs. 6 (IQR 2-13) days for immediate vs. delayed, p<0.0001]. Compared to other delayed reactions, a longer median time to ADR reporting was significantly associated with SCAR syndromes [4 (IQR 2-9) vs. 9 (IQR 4-18) vs. 12 (IQR 5-18.5) days, p<0.0001, for non-SCARs vs. single organ vs. SCAR ADRs]. Further, median

time to reporting was found to be the longest if reported by the pharmacists [4 (IQR 1-11) vs. 1 (IQR 0-6) vs. 0 (IQR 0-2) days, p<0.0001, for pharmacists vs. medical doctors vs. others]. However, there was no difference in median time to reporting between hospital onset and community onset reactions [4 (IQR 1-10) vs. 3 (IQR 0-10) days, p=0.35]. Of all immunologically mediated reactions, 77 (18.8%) were referred to allergy clinic for further management.

In total, 650 medications were implicated, with multiple agents suspected in 165/555 (29.7%) reactions. Altogether, 475 (73.1%) medications were reported in immunologically mediated reactions, 142 (21.8%) in non-immunologically mediated reactions and the remainder (5.1%) in unclassified ADRs. Antimicrobials were the class most frequently reported; followed by radiocontrast agents, anaesthetic agents, antihypertensives, non-steroidal anti-inflammatory agents (NSAIDs), opioids, antiepileptics and intravenous iron formulations for immunologically mediated reactions (Table 2 and Supplemental Table 1 for complete list of implicated medications). With regards to antihypertensives, all except two ADRs, were angioedema attributed to ACE-inhibitors. For non-immunologically mediated reactions, the most common agents were antimicrobials, opioids, psychoactive medications and anti-emetics (Table 2). The most commonly reported non-immunological ADRs were tendonitis with quinolones (n=7), extrapyramidal/serotonergic symptoms with psychoactive medications (n=9) and altered mental status with opioids (n=6).

Amongst the commonly implicated medication classes, antimicrobials and radiocontrast agents were more frequently associated with immunologically mediated reactions [54.1% vs. 24.6%, p<0.0001, odds ratio (OR) 3.6, 95% confidence interval (CI) 2.4 – 5.5 for antimicrobials and 5.7% vs. 1.4%, p=0.04, OR 4.2, 95% CI 1.2 – 18.2 for radiocontrast agents], whereas opioids and psychoactive medications were more frequently associated with non-immunologically mediated reactions [12.7% vs. 3.6%, p=0.0002, OR 3.9, 95% CI 1.9 – 7.9 for opioids and 12.7% vs. 1.3%, p<0.0001, OR 11.4, 95%CI 4.6 – 27.8 for psychoactive medications].

DISCUSSION

This study described the characteristics of voluntarily reported ADRs in a tertiary healthcare setting. The majority of reports were submitted by the pharmacists. Most were inpatient-onset, at least moderate severity, immunologically mediated, and predominantly delayed hypersensitivity reactions. Antimicrobials were found to be the most commonly implicated class for both immunologically and non-immunologically mediated reactions. This study provided a unique insight in that certain medication classes are more likely to be associated with certain reported ADR. SCARs took the longest time to be reported, despite their severity, possibly highlighting the intrinsic challenges associated with accurately identifying and managing these conditions. Overall, this study further emphasised the need to develop strategies to improve recognition, evaluation and timely referrals related to ADRs to ensure patient safety, particularly for SCARs.

Many models of care have been shown to improve ADR reporting and management in both hospital and non-hospital settings [7,18,19]. The multidisciplinary ADRRC approach provides a unique model of care involving both ADR evaluation and patient feedback [20]. Notably, the ADRRC received >500 reports over the two-year study period, a number much higher than a previous study from a hospital of similar size [19], reflecting the established culture of ADR reporting. Our ADR management model allows a centralised and robust approach to the assessment, based on information provided by the treating clinicians, clinical notes and laboratory/radiological results. It also allows subsequent dissemination of risk mitigation measures from a single source through written recommendations to the clinicians, patients and carers [11].

Voluntary reporting is the most widely used low cost and high efficacy method to identify ADRs [21]. As noted in previous studies, pharmacists are an integral part of ADR reporting and management, with the quality of information provided comparable to that of doctors [22,23]. The 2016 TGA national pharmacovigilance data also highlighted that the hospital and community pharmacists are a major

source of ADR reporting, at a much higher rate than doctors (16% vs. 4%) [24]. Similarly, at our institution, ADR reporting is seen as a core clinical activity and responsibility for pharmacists and is integrated into their daily workflow, which resulted in higher reporting rates compared to that of doctors. Although the ADRRC encourages reporting by all professionals, only 6% of reports were submitted by 'other' HCPs, such as nurses and radiographers, mainly for infusion-related or contrast-mediated reactions. Nevertheless, their roles as contributors to ADR reporting need to be acknowledged. Additionally, it is important to note that pharmacists took a longer time than other HCPs to report ADRs. Possible explanations could be that the pharmacists were involved in the assessment of a wider range of ADRs, more complex reactions, or were more thorough in information gathering and evaluation.

Given the above findings, for our ADR management model to effectively function, constant upskilling of both pharmacists, doctors and other HCPs regarding ADR principles is essential. In fact, a recent cross-sectional survey [25] within our organisation revealed that knowledge gaps exist in some areas of ADR management for both pharmacists and doctors, notably in drug causality assessment for delayed hypersensitivity reactions. In collaboration with other departments within the organisation, the ADRRC is developing an institution-wide education module to enhance the accuracy, efficiency and quality of ADR reporting.

In this study, further classification of ADRs into immunologically and non-immunologically mediated reactions, and subsequently into immediate and delayed hypersensitivity reactions of different sub-types (Table 1) provided a unique insight into the rates at which clinicians differentially reported types of ADRs. Immunologically mediated reactions were reported at a higher frequency than non-immunologically mediated reactions, despite the majority of ADRs being known to be non-immunologically mediated [26]. It may be that immunologically mediated reactions are more readily perceived by the clinicians as causing potential patient harm, thus warranting assessment and risk mitigation through the ADRRC, whereas non-immunologically mediated reactions are due to the

drug's known pharmacological action and hence not worthy of a report. This reporting bias is consistent with previous studies, where physicians tended to report severe or unusual reactions or reactions to new drugs [21,27]. Further, the national TGA database only requires reporting of suspected adverse events to new medications, unexpected adverse events that are not described in the Product Information, and serious adverse events, thereby potentially contributing further to this bias in reporting patterns [13]. . These findings highlight the need to actively promote reporting of non-immunologically mediated ADRs amongst HCPs as they otherwise may not be recognised as drug-related. Routine reporting of ADRs resulting in significant patient harm or hospitalisation would capture the true epidemiology, allowing improvement of systems for risk communication to patients and harm minimisation, thus improving patient safety.

The commonly implicated agents in this study were similar to previous reports [28-30]. In particular, antimicrobials posed the greatest ADR burden. Antimicrobials, radiocontrast agents, anaesthetic agents, NSAIDs and antiepileptics were more likely to be associated with immunologically mediated reactions, implying that further medication allergy assessment in clinics should focus on these classes, by providing *in vitro* and/or *in vivo* causality confirmation, where clinically indicated [31]. For certain medications, especially antimicrobials, further allergy testing not only confirms or refutes causality but may also identify alternate antimicrobials, thereby providing future therapeutic options [32,33].

Severe cutaneous adverse drug reactions are life-threatening, requiring prompt diagnosis, causality assessment and clear risk communication to prevent continued or repeated exposure to offending agents. If clinicians are unfamiliar with these conditions, diagnostic and management delays may result. Supporting this hypothesis, our study found that delayed immunologically mediated reactions were associated with a longer time to report, especially with SCARs, with a median of 12 days. To our knowledge, no previous studies have evaluated the time taken by clinicians to report severe delayed hypersensitivity reactions. The delay in initial clinical recognition of SCAR syndromes, further

time required for diagnostic measures including biopsy, the need to exclude other differential diagnoses, and detailed mapping of complex medication timelines are likely factors contributing to the increased time to reporting. Further studies are required to understand these specific factors to develop innovative ways to improve clinicians' ADR knowledge to facilitate timely assessment and management of these patients. Whilst this is only a descriptive pharmacoepidemiological study, it provides information with sufficient novelty to contribute to an important discussion. Nevertheless, several limitations exist in this study. First, this is a retrospective study with inherent limitations in the quality of information. However, the ADRRC review processes occurred in real-time, and as much accurate information as possible was extracted during the review process. Where important information was missing, the study investigators also revisited the clinical notes. Second, due to complex and heterogeneous nature, no perfect classification system exists for ADRs [7]. We simplified the traditional classification system [7] into two groups, 'non-immunologically' and 'immunologically mediated' reactions. This approach may still be prone to misclassification, yet it provided a simple and clinically meaningful framework to overview ADR episodes for this study. Third, we used the date of onset of reaction to the date of reporting as a surrogate marker for the total time taken to manage an ADR episode. We used the assumption that reporting indicated the completion of a diagnosis and initiation of definitive management plans for each type of ADR. Whilst this methodology provided an approximation, we were not able to accurately ascertain the actual length of time involved nor the specific underlying reasons that contributed to increased length of time for managing of certain ADR types. Lastly, while our organisation has an established ADR management system, this model of care may not be applicable across other institutions.

Our study highlighted an ADR management system which focuses on early reporting of major reactions through engagement with clinicians, especially pharmacists, and providing a comprehensive multidisciplinary assessment. To benchmark and improve the quality and efficiency of this ADR management system, we suggest that several process measures and outcomes need to

be continually monitored and evaluated. They include evaluation of reporter characteristics, reporting patterns and biases, implicated medications, time to reporting of severe reactions and HCPs' knowledge. There is no established 'gold standard' for ADR management systems and there exists significant inter-institutional variability with respect to the timing and nature of ADR reporting. However, organisations may adapt our multidisciplinary ADR management model to provide a system optimised for local needs through available resources.

CONCLUSIONS

This study provided us with a unique insight into the characteristics of voluntary reports and time taken to report ADRs, highlighting potential gaps in ADR management. Targeted education programs to promote the understanding of ADR principles, identification and accurate reporting of ADRs may lead to improvements in appropriate prioritisation of resources to deliver effective management. There is a need to expand existing clinical allergy services to provide further comprehensive evaluation and testing, especially for the complex and antimicrobial-related reactions, to ensure quality service provision and patient safety.

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Figure 1 Legend: ADR: adverse drug reactions, SCAR: severe cutaneous adverse drug reactions

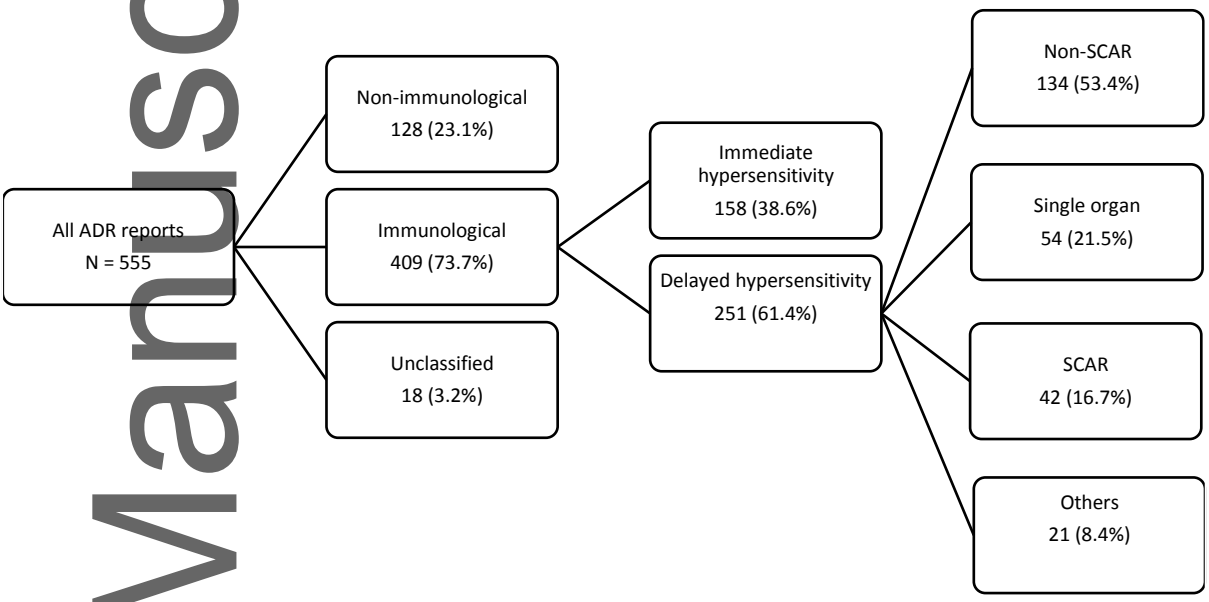

Table 1: Adverse drug reaction (ADR) definitions used in this study

ADR Categories	Definitions
Non-immunologically mediated	Reactions caused by the direct dose-related pharmacological effects of the drug, side-effects or intolerances, for example, akathisia due to metoclopramide, ketoacidosis due to sodium-glucose transport protein 2 inhibitors, etc.
Immunologically mediated	Reactions presumed to be caused by activation of any effector component of the immune system, in accordance with mechanisms described in revised Gell and Coombs classification [9]. Descriptions included anaphylaxis, urticaria, angioedema, maculopapular rashes, severe cutaneous adverse drug reactions (SCARs) and reactions involving single organ system such as interstitial nephritis, drug-induced liver injury, pneumonitis and cytopenias with proven or highly suspected immune aetiology.
• Immediate hypersensitivity reactions	Immunologically mediated reactions that occur within 2 hours of exposure to a medication and fulfil the clinical syndromes of anaphylaxis, angioedema or acute urticaria. Non-specific histamine release type reactions, such as diffuse rash and hypotension caused by opioids [34], or anaphylactoid reactions caused by radiocontrast agents or infusion of parenteral iron formulations [35,36] are also

	considered as immediate immunologically mediated reactions.
• Delayed hypersensitivity reactions	Immunologically mediated reactions that occur >2 hours after medication exposure consistent with the diagnoses of maculopapular exanthems, SCAR syndromes or single organ involvement. Due to the underlying pathogenesis, bradykinin mediated angioedema secondary to angiotensin converting enzyme inhibitors [37] and heparin induced thrombocytopenia caused by formation of IgG antibodies directed against platelet factor 4 (PF4) [38] are also included under delayed immunologically mediated reactions.
• Severe cutaneous adverse reaction (SCAR)	A subset of delayed hypersensitivity reactions including Drug rash with eosinophilia and systemic symptoms (DRESS), Stevens Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis (AGEP).
• Non-SCAR	A subset of delayed hypersensitivity reactions including maculopapular exanthema or any cutaneous reactions not consistent with the full diagnosis of SCAR syndrome.
ADR Severity	Definitions
Mild	Asymptomatic, no treatment or a short course of

	oral/topical treatment only required.
Moderate	Symptomatic, causes some physical morbidity and requires semi-urgent medical care or Emergency Department presentation.
Severe	Symptomatic, causes significant physical morbidity and requires urgent medical care or hospital admission.
Life threatening/fatal	Results in significant disability, potentially fatal if not treated promptly or directly contributed to death.

Table 2: Top ten implicated medications overall and according to immunologically and non-immunologically mediated reactions

Legend: NSAIDs: non-steroidal anti-inflammatory agents

Rank order	Overall (N=650)	n (%)	Immunologically mediated reactions (N=475)	N (%)	Non-immunologically mediated reactions (N=142)	n (%)
1	Antimicrobials	309 (47.5)	Antimicrobials	257 (54.1)	Antimicrobials	35 (24.6)
2	Opioids	38 (5.8)	Radiocontrast agents	27 (5.7)	Opioids	18 (12.7)
3	Radiocontrast agents	30 (4.6)	Anaesthetic agents	19 (4.0)	Psychoactive medications	18 (12.7)
4	Antiepileptics	25 (3.8)	Antihypertensives	19 (4.0)	Anti-emetics	14 (9.9)
5	Psychoactive medications±	25 (3.8)	NSAIDs	19 (4.0)	Antiepileptics	7 (4.9)
6	Anaesthetic agents	24 (3.7)	Opioids	17 (3.6)	Iron formulations	7 (4.9)
7	NSAIDS	24 (3.7)	Antiepileptics	16 (3.4)	Anaesthetic agents	5 (3.5)

8	Iron formulations	23 (3.5)	Iron formulations	16 (3.4)	Lipid lowering agents	5 (3.5)
9	Antihypertensives	22 (3.4)	Antimetabolites	12 (2.5)	NSAIDs	5 (3.5)
10	Antimetabolites	16 (2.5)	Antineoplastics	9 (1.9)	Osteoporotic agents	5 (3.5)