The Journal of Clinical Pharmacology
2018, 0(0) 1–8

DOI: 10.1002/jcph.1148

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. This is a retrospective study of voluntary reports to an Australian healthcare ADR Review Committee over a 2-year period (2015–2016). Descriptive and univariate models were used for outcomes, employing standardized ADR definitions. Hospital pharmacists reported 84.8% of the 555 ADRs: 70.3% were hospital onset reactions, and 71.7% were at least of moderate severity. Immunologically mediated reactions were most commonly reported (409, 73.7%). The median time to submit an ADR report was 3 (interquartile range 1–10) days. Longer median times to reporting were associated with multiple implicated agents and delayed hypersensitivity reactions, especially severe cutaneous adverse reactions. A total of 650 medications were implicated that involved multiple agents in 165/555 (29.7%) reports. Antimicrobials were the most commonly implicated agents. Immunologically mediated reactions were most commonly associated with antimicrobials and radiocontrast agents ($P < .0001$, odds ratio [OR] 3.6, 95%CI 2.4–5.5, and $P = .04$, OR 4.2, 95%CI 1.2–18.2, respectively). Opioids and psychoactive medications were more commonly implicated in nonimmunological reported ADRs ($P = .0002$, OR 3.9, 95%CI 1.9–7.9, and $P < .0001$, 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.

Keywords

Adverse drug reactions, pharmacoepidemiology, pharmacovigilance, hypersensitivity, medication safety

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% to 3% of all Australian hospital admissions.[3] Severe ADRs are also a leading cause of hospitalization 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% to 80% of ADRs are nonimmunological and occur through direct or indirect pharmacologic mechanisms, whereas immunologically mediated processes account for 20% to 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]

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Submitted for publication 16 February 2018; accepted 30 March 2018.

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Table 1. Adverse Drug Reaction Definitions Used in This Study

ADR Categories	Definitions
Nonimmunologically 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.
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 reactions (SCARs), and reactions involving a single organ system such as interstitial nephritis, drug-induced liver injury, pneumonitis, and cytopenias with proven or highly suspected immune etiology.
• Immediate hypersensitivity reactions	Immunologically mediated reactions that occur within 2 hours of exposure to a medication and that fulfill the clinical syndromes of anaphylaxis, angioedema, or acute urticaria. Nonspecific 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[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, Stevens-Johnson syndrome, toxic epidermal necrolysis, and acute generalized exanthematous pustulosis.
• 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 semiurgent 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 contributes to death.

ADR indicates adverse drug reactions; SCAR, severe cutaneous adverse reactions.

It is therefore essential that healthcare organizations have effective management systems to ensure safer patient care by minimising 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 medication allergies and ADRs in the healthcare record and in the organization-wide incident-reporting system as well as for submitting major or rare ADRs to the Therapeutic Goods Administration (TGA) of Australia. Central to ADR management are 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 re-exposure of culprit medications in 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 the individual healthcare facility level. To date, we found no studies examining the efficiency and effectiveness of institutional ADR management systems or the characteristics and timing of ADR reporting by healthcare professionals (HCPs). Because 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 aimed to evaluate the characteristics of reported reactions, the medications implicated, and the factors contributing to time taken for HCPs to report ADRs. The results of this study will provide a basis for resource planning to improve ADR management and quality care.

Methods

The institutional ethics committee granted approval to conduct this study (approval number 179/17).

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 4 healthcare facilities comprising a 450-bed tertiary level university-affiliated teaching hospital with general and specialty medical and surgical services, solid organ and hematological transplantation, state-wide burns and trauma, and human immunodeficiency 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.

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 that includes a senior pharmacist and specialist clinicians from at least 1 of dermatology, immunology, clinical pharmacology, infectious diseases, and general medicine. The Committee meets every 2 weeks to review all ADR reports, verify diagnoses, organize allergy clinic 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 standardized 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 2-year period, from January 1, 2015 to December 31, 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 were missing or erroneous, written ADR reports and clinical notes were reviewed to extract a near complete data set. If multiple reports were submitted for 1 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 as either an immunologically mediated or a nonimmunologically mediated reaction by a consensus decision among the authors (A.K.A., L.V.G., S.L.D.M., and N.R.A.) based on the presumptive underlying pharmacokinetic/pharmacodynamic and immunological mechanisms. The immunological reactions were further classified as immediate or delayed hypersensitivity reactions, based on time from exposure to reaction onset. Delayed hypersensitivity reactions were further categorized into severe cutaneous adverse reactions (SCARs), single-organ reactions (eg, acute interstitial nephritis), and non-SCAR reactions. Where ADRs did not fit into the mechanisms of immunologically or nonimmunologically 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 regard to patients' age distribution, vocation of reporters, place of onset of reactions, reaction types, severity, and strength of causality associations. Implicated medications were analyzed according to the broad categories of immunologically and nonimmunologically mediated reactions. Additionally, the time to ADR report was measured. It was defined as the date of onset of reaction to the date an ADR report was submitted to ADRRC. This length of time was taken as a surrogate marker for an ADR management process. All outcomes were analyzed 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, La Jolla, California). 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 2 groups (eg, single versus multiple agents and median time to reporting) and Kruskal-Wallis tests when 1 variable has more than 2 groups (eg, vocation of reporters [pharmacists versus medical doctors versus others] and median time to reporting). Comparisons between proportions were carried out using chi-squared and Fisher exact tests, and the associations were also presented as odds ratios (OR). A 2-sided P value of $<.05$ 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 (IQR 19.8–63.3). For 20 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%) by doctors, and 32 (5.7%) by other HCPs. With regard to the onset of ADR, 390 (70.3%) episodes occurred during hospitalization, 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%), and "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 submission of 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 be longer when multiple agents were implicated (3 [IQR 1–10] versus 5 [IQR 1–13] days for single versus multiple implicated agents, $P = .01$) and for delayed hypersensitivity reactions (1 [IQR 0–3] versus 6 [IQR 2–13] days for immediate versus delayed, $P < .0001$). Amongst the delayed reactions, a longer median time to reporting was significantly associated with SCAR syndromes (4 [IQR 2–9] versus 9 [IQR 4–18] versus 12 [IQR 5–18.5] days, $P < .0001$, for non–SCARs versus single-organ versus SCAR ADRs). Further, median time to reporting was found to be the longest if reported by the pharmacists (4 [IQR 1–11] versus 1 [IQR 0–6] versus 0 [IQR 0–2] days, $P < .0001$ for pharmacists versus medical doctors versus others). However, there was no difference in median time to reporting between hospital-onset and community-onset reactions (4 [IQR 1–10] versus 3 [IQR 0–10] days, $P = .35$]). Of all immunologically mediated reactions, 77 (18.8%) were referred to the 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 nonimmunologically mediated reactions, and the remainder (5.1%) in unclassified ADRs. Antimicrobials were the class most frequently reported, followed by radiocontrast agents, anesthetic agents, antihypertensives, nonsteroidal anti-inflammatory agents, opioids, antiepileptics, and intravenous iron formulations for immunologically mediated reactions (Table 2 and Supplemental Table 1 for complete list of implicated medications). With regard to antihypertensives, all except 2 ADRs, were angioedema attributed to ACE-inhibitors. For nonimmunologically mediated reactions, the most common agents were antimicrobials, opioids, psychoactive medications, and antiemetics (Table 2). The most commonly reported nonimmunological ADRs were tendonitis with quinolones (n = 7), extrapyramidal/serotonergic symptoms with psychoactive medications (n = 9), and altered mental status with opioids (n = 6).

Among the commonly implicated medication classes, antimicrobials and radiocontrast agents were more frequently associated with immunologically mediated reactions (54.1% versus 24.6%, $P < .0001$, OR 3.6, 95%CI 2.4–5.5 for antimicrobials and 5.7% versus 1.4%, $P = .04$, OR 4.2, 95%CI 1.2–18.2 for radiocontrast agents), whereas opioids and psychoactive medications were more frequently associated with nonimmunologically mediated reactions (12.7% versus 3.6%, $P = .0002$, OR 3.9, 95%CI 1.9–7.9 for opioids and 12.7% versus 1.3%, $P < .0001$, 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.

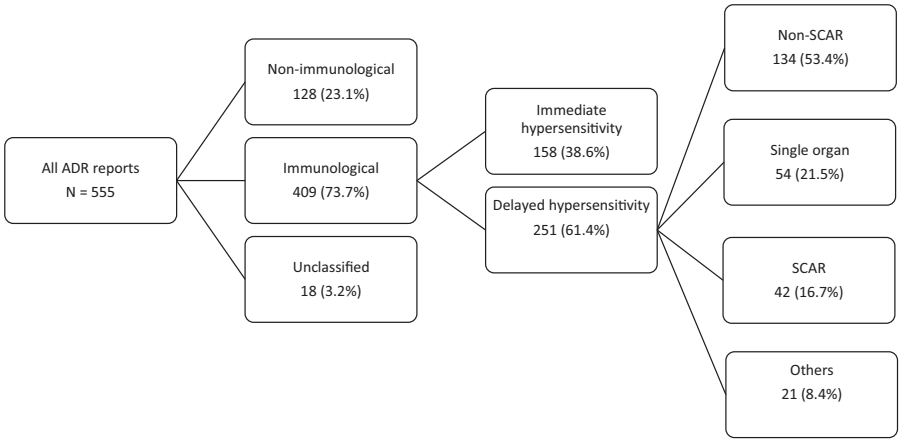

Figure 1. Subjects. ADR indicates adverse drug reactions; SCAR, severe cutaneous adverse reactions.

Table 2. Top 10 Implicated Medications Overall and According to Immunologically and Nonimmunologically Mediated Reactions

Rank Order	Overall (N = 650)	n (%)	Immunologically Mediated Reactions (N = 475)	n (%)	Nonimmunologically 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)	Anesthetic agents	19 (4.0)	Psychoactive medications	18 (12.7)
4	Antiepileptics	25 (3.8)	Antihypertensives	19 (4.0)	Antiemetics	14 (9.9)
5	Psychoactive medications	25 (3.8)	NSAIDs	19 (4.0)	Antiepileptics	7 (4.9)
6	Anesthetic agents	24 (3.7)	Opioids	17 (3.6)	Iron formulations	7 (4.9)
7	NSAIDs	24 (3.7)	Antiepileptics	16 (3.4)	Anesthetic 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)

NSAID indicates nonsteroidal anti-inflammatory agent.

Most ADRs were inpatient onset, of 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 nonimmunologically mediated reactions. This study provided a unique insight in that certain medication classes are more likely to be associated with certain reported ADRs. 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 emphasized 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 nonhospital 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 2-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 centralized 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% versus 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 education of pharmacists, doctors, and other HCPs regarding ADR principles is essential. In fact, a recent cross-sectional survey [25] within our organization 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 organization, 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 nonimmunologically mediated reactions, and subsequently into immediate and delayed

hypersensitivity reactions of different subtypes (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 nonimmunologically mediated reactions, despite the majority of ADRs being known to be nonimmunologically 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 nonimmunologically 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 in which 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 nonimmunologically mediated ADRs by HCPs because these ADRs otherwise may not be recognized as drug related. Routine reporting of ADRs resulting in significant patient harm or hospitalization would capture the true epidemiology, allowing improvement of systems for risk communication to patients and harm minimization, thus improving patient safety.

The commonly implicated agents in this study were similar to those in previous reports.[28–30] In particular, antimicrobials posed the greatest ADR burden. Antimicrobials, radiocontrast agents, anesthetic agents, nonsteroidal anti-inflammatory drugs, and antiepileptics were most 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. In support of 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, and to facilitate timely assessment and management of these patients.

Although 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, because of their complex and heterogeneous nature, no perfect classification system exists for ADRs.[7] We simplified the traditional classification system[7] into 2 groups, nonimmunologically 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. This methodology provided an approximation, but we were not able to accurately ascertain the actual length of time involved or the specific underlying reasons that contributed to increased length of time for managing of certain ADR types. Last, although our organization has an established ADR management system, this model of care may not be applicable across other institutions.

Our study highlighted an ADR management system that focuses on early reporting of major reactions through engagement with clinicians, especially pharmacists, and provides 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. These 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 interinstitutional variability with respect to the timing and

nature of ADR reporting. However, organizations may adapt our multidisciplinary ADR management model to provide a system optimized 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 prioritization 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.

Funding Source

None.

Data Sharing

The authors are unable to share the data included in this manuscript.

Conflict of Interest

None to report.

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