Title page

Title

A survey on knowledge gaps in assessment and management of severe drug hypersensitivity reactions: multicentre cross-sectional study of Australian healthcare providers

Authors

Daniel Mazzoni ^{1,2} MD

Hui Wen Tee ² FRACP

Sara Lee de Menezes ² MBBS

Linda Velta Graudins ³ BPharm

Douglas Forsyth Johnson ⁴ FRACP, PhD

Evan David Newnham ⁵ FRACP, PhD

Peter Graham Kelley ⁶ FRACP

Celia Mary Zubrinich ⁷ FRACP

Michelle Sue Yen Goh ⁸ FACD

Jason Anthony Trubiano ^{9,10,11} FRACP, PhD

Ar Kar Aung ^{2,12} FRACP, MPHTM

Affiliations

¹ Department of Medicine, Royal Brisbane and Women's Hospital, Brisbane, Queensland

² Department of General Medicine, Alfred Health, Melbourne, Victoria

³ Pharmacy Department, Alfred Health, Melbourne, Victoria

⁴ Department of General Medicine and Infectious Diseases, The Royal Melbourne Hospital, Melbourne, Victoria

⁵ Department of General Medicine, Eastern Health, Melbourne, Victoria

⁶ Department of Infectious Diseases, Peninsula Health, Melbourne, Victoria

⁷ Department of Allergy, Immunology and Respiratory Medicine, Alfred Health, Melbourne, Victoria

⁸ Department of Dermatology, Alfred Health, Melbourne, Victoria

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1002/jcph.1692](https://doi.org/10.1002/jcph.1692).

This article is protected by copyright. All rights reserved.

⁹ Department of Infectious Diseases and Centre for Antibiotic Allergy and Research, Austin Health, Melbourne, Victoria

¹⁰ The National Centre for Infections in Cancer, Peter MacCallum Cancer Centre, Melbourne, Victoria

¹¹ Department of Medicine, Austin Health, Melbourne, Victoria

¹² School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria

Corresponding author

Dr Ar Kar Aung

Alfred Health

55 Commercial Rd, Melbourne

Victoria, Australia, 3004

Phone: +61 (03) 9076 2000

Email: a.aung@alfred.org.au

Running head

Drug hypersensitivity reactions

Conflict of interest

The authors have no conflict of interest to declare.

Funding statement

The article has no funding source.

Data availability statement

Data available on request from the authors through corresponding author contact details.

Acknowledgements

Special thanks to the Alfred Health Adverse Drug Reaction Committee for assisting in the development of the knowledge survey, survey participants for contributing their responses and site facilitators, who helped coordinate survey distribution.

Word count

Text: 2519

This article is protected by copyright. All rights reserved.

Tables: 3
Figures: 0
Appendices: 3
References: 27

ABSTRACT

Severe drug hypersensitivity reactions (DHRs) are often encountered by healthcare professionals (HCPs). We evaluated knowledge of doctors and pharmacists in the assessment and management of severe DHRs using a structured questionnaire. A cross-sectional study was conducted in four metropolitan hospital networks in Melbourne, Australia. A 13-question, scenario-based, multiple-choice questionnaire to assess specific knowledge domains in drug hypersensitivity syndrome recognition, causality attribution, cross-reactivity patterns, appropriate diagnostic tests and therapy, was administered to HCPs of various vocation and specialty groups. Data was analysed according to profession, self-reported experience and preparedness in managing severe DHRs. 238 participants (45.0% senior doctors, 24.4% junior doctors and 30.7% pharmacists) across a range of sub-specialties achieved an overall median score of 7 (IQR 5 – 8) [overall 55.6% correct responses to all questions], with senior doctors outperforming junior doctors and pharmacists ($p < 0.001$). The best performance by all participants was in DHR syndrome recognition (60.9%), and the poorest was in diagnostics/therapy (52.0%). HCP group and experience levels were significantly associated with better performance in the knowledge domains of cross-reactivity and diagnostics/therapy ($p = 0.003$ and < 0.001 respectively), but not in the domains of syndrome recognition and causality attribution ($p > 0.05$). Levels of self-reported preparedness in DHR management was not associated with performance rates in any of the knowledge domains. This study demonstrated significant knowledge gaps in the recognition and management of severe drug hypersensitivity reactions. Targeted multidisciplinary education of staff caring for these patients is needed to improve knowledge gaps.

MAIN TEXT

INTRODUCTION

Adverse drug reactions (ADRs) cause significant morbidity and mortality.¹ Serious ADRs occur in approximately 7% of hospital inpatients, leading to unwanted consequences such as complicated care episodes and increased length of hospital stay.² ADRs contribute significantly to healthcare expenditure estimated at AUD 842-million per year.³ Up to half of ADR-related hospital admissions are potentially preventable.⁴ Despite a high burden and impact on health services, training and education in drug allergy and availability of testing services is limited.²

Serious ADRs have been reported to occur in less than 7% of hospitalised patients.⁵ Although comprising less than 15% of severe ADRs,⁶ severe drug hypersensitivity reactions (DHRs) are important ADRs not to miss as they can be life-threatening.⁶ DHRs are immune-mediated reactions to medications, and their classification is based on the timing of onset and underlying pathogenic mechanisms [typically, immediate (IgE mediated or non-IgE mediated) versus delayed (T-cell-mediated) in phenotypes (Table 1)].⁷ Within the hospital environment, severe DHRs are diagnosed and managed by healthcare professionals (HCPs), including medical doctors and hospital pharmacists from a diverse range of specialties. HCPs having appropriate knowledge in the assessment and management of severe DHRs is crucial for timely diagnosis and treatment, referral for definitive testing and post-event medication safety. Previous studies have noted HCP assessment of severe DHRs is suboptimal.^{8,9}

This study seeks to identify knowledge gaps in HCPs involved in the management of severe DHRs, focusing on four main knowledge domains; (i) drug hypersensitivity syndrome recognition, (ii) causality attribution, (iii) cross-reactivity patterns, and (iv) appropriate diagnostic tests and therapy. We propose that by identifying these knowledge gaps, targeted multidisciplinary education and practice improvement programs can be further developed to improve safe medication management and treatment of these potentially life-threatening conditions.

METHODS

Design and Setting

A voluntary cross-sectional questionnaire (Appendix 2) was conducted among HCPs (senior doctors, junior doctors, and pharmacists) in four major metropolitan hospital networks in Melbourne, Australia. For doctors, medical specialties were targeted based on the likelihood of encounter with patients presenting with severe DHR, such as immunology, emergency, dermatology, infectious diseases and general medicine. The questionnaire was developed by a multidisciplinary Adverse Drug Reaction Review Committee (ADRRC) at Alfred Health, with extensive experience in the diagnosis and management of severe DHRs. This committee is comprised of a specialist senior medication safety pharmacist, and medical specialist clinicians including two infectious disease physicians, two clinical immunologists and allergists, one dermatologist and one general physician. Clarity and presentation of the questionnaire was further evaluated and refined by pre-testing of the questionnaire by 15 senior and junior doctors and pharmacists.

The questionnaire was delivered both in person by the researchers at relevant departmental meetings and education sessions, and also electronically via RedCap (version 9.1.0, Nashville, Tennessee, USA) to pharmacists and doctors of the selected medical groups at all four hospital networks. The method of delivery was based on preference by individual units. Data collection occurred non-concurrently at participating sites from December 2016 to March 2018. To prevent duplicate data, repeated participation was not allowed. Ethics approval was obtained from Alfred Health (HREC/17/Alfred/51).

The Victorian metropolitan hospitals involved in the study were Alfred Health (800-bed tertiary teaching hospital), Austin Health (980-bed tertiary teaching hospital), Box Hill Hospital (Eastern Health, 400-bed tertiary teaching hospital), and Frankston Hospital (450-bed tertiary teaching

hospital). The collective services offered by participating hospitals included specialised referral centres with both solid organ transplant (including liver, kidney, lung and heart) and haematopoietic stem cell transplant services, and a state-wide burns service which often is involved in managing certain severe DHRs such as toxic epidermal necrolysis.

Data collection

A 13-question, scenario-based, multiple-choice questionnaire (Appendix 2) was developed to assess the knowledge domains of: (i) DHR syndrome recognition – differentiating immediate type reactions (IgE and non-IgE-mediated) from delayed type T-cell mediated reactions (Question 1 i-iii), as well as recognition of a subset of severe cutaneous adverse drug reactions (SCAR), which include Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) (Question 3) and drug rash with eosinophilia and systemic symptoms (DRESS)(Question 4); (ii) assignment of drug causality (Question 3i and 3iii, Question 4i); (iii) cross reactivity patterns of antimicrobials (Question 2b-d and Question 4ii); and (iv) appropriate DHR diagnostic tests (Question 2a and Question 3ii) and management principles, including desensitisation potential (Question 4iii). Responses were analysed only if all questions in the questionnaire were completed.

Outcomes

Questionnaire participants were grouped: senior doctors (specialist physicians including consultant physicians, fellows, and advance training registrars); junior doctors (interns, residents, basic training registrars); and pharmacists (interns, Grade 1, Grade 2, senior pharmacists). In the Australian training system, the basic physician training registrars are doctors in pre-specialist training, and advanced registrars are those who have completed their basic trainee requirements and currently undertaking a physician specialty training program. Participant experience was based on self-report: 'very experienced' (>10 patients with severe DHR seen per year), 'somewhat experienced' (5-10 patients

per year), and 'inexperienced' (<5 patients per year). The self-rated 'preparedness' questions were used as surrogate markers of clinician's confidence in DHR syndrome recognition, cross-reactivity and culprit drug recognition. Three categories of preparedness were analysed ('prepared' category included 'very prepared' and 'somewhat prepared,' and 'unprepared' category included 'somewhat unprepared' and 'very unprepared' on the Questionnaire). The total mark out of 13 was obtained, with each set of questions assessing a different knowledge domain of DHRs.

Statistical Analysis

Statistical analyses were conducted using GraphPad Prism 7 (GraphPad Software 2017, La Jolla, California). Proportions of correct answers were determined by dividing the number of correct responses with the product of total number of questions and total number of respondents in each knowledge domain. Mann-Whitney U tests were used to compare continuous variables of non-normal distribution. Chi-square and Fisher's exact tests were used to determine the associations between discrete variables (e.g. proportions of correct answers). A two-sided p-value of <0.05 was taken as statistical significance for each association.

RESULTS

A total of 238 participants completed all questions on the questionnaire. Of the participants, the majority (107/238, 45.0%) were senior doctors, followed by pharmacists (73/238, 30.7%) and junior doctors (58/238, 24.4%) (Table 2). Clinicians working in 15 specialty areas answered the knowledge questionnaire (Appendix 1). The three most common specialty areas of senior doctors were emergency medicine (23/107, 21.5%), infectious diseases (21/107, 19.6%), and dermatology (19/107, 17.8%).

The majority of senior doctors reported themselves as 'very experienced' (42/107, 39.3%) in diagnosis and management of DHRs, while more than half of the junior doctors and pharmacists reported themselves as 'inexperienced' [32/58 (55.2%) and 37/73 (50.6%) respectively, $p < 0.001$, Table 2]. Dermatologists reported the largest proportion of 'very experienced' responses (15/19, 79.0%), followed by infectious diseases physicians (10/21, 47.6%) and emergency physicians (10/23, 43.5%).

Self-reported levels of preparedness in recognising different drug hypersensitivity syndromes, prescribing alternative beta-lactams and identification of culprit drug (causality attribution) was significantly different amongst the three professional groups (Table 2).

Overall Performance

Out of 13 questions, the median number of questions correctly answered was 7 (IQR 6-8). A significant association was observed between different groups in terms of the number of questions correctly answered amongst senior doctors, junior doctors and pharmacists [8 (IQR 6-9), 6 (IQR 4-7) and 6 (IQR 5-8) respectively, $p < 0.001$]. When stratified according to self-reported experience, the median number of questions correctly answered was 7 (IQR 5-8) for 'inexperienced', 7 (IQR 5-8) for 'somewhat experienced' and 8 (IQR 6-10) for 'very experienced' ($p = 0.005$).

Specific Knowledge Domains

The performance in each knowledge domain, stratified by different profession groups, level of experience and level of preparedness is summarised in Table 3. Overall, there were 1719/3094 (55.6%) correct responses to all questions in all domains; the best performance was noted for DHR

syndrome recognition (435/714, 60.9%), and the poorest performance in DHR diagnostics/therapy (371/714, 52.0%).

Statistically significant differences in performance between different *profession groups* were noted in the knowledge domains of cross-reactivity and DHR diagnostics/therapy ($p=0.003$ and <0.001 respectively), but not for DHR syndrome recognition and culprit drug recognition. Further sub-group analyses comparing the three profession groups are shown in Appendix 3.

When analysed according to the *level of experience*, statistically significant differences were noted in the knowledge domains of cross-reactivity and DHR diagnostics/therapy. For sub-group comparisons between the levels of experience in each knowledge domain, refer to Appendix 3.

Interestingly, the *level of preparedness* was not associated with performance outcomes in any of the knowledge domains.

DISCUSSION

This unique study examined knowledge gaps in assessment and management of severe drug hypersensitivity reactions. It further examined the relationship between self-rated experience and preparedness, and performance within each knowledge domain. Greater than 50% of the HCPs surveyed correctly answered questions across the four main knowledge domains.

However, significant knowledge gaps and variability in clinical approach by HCPs were observed, irrespective of profession, level of experience or preparedness.

Our study demonstrated that self-perceived preparedness in managing different DHR scenarios did not have any association with the practitioner's actual clinical knowledge, whereas the level of experience and vocations were more predictive. These findings perhaps demonstrated the Dunning-Kruger effect, as health professionals with a more competent understanding of DHRs may underestimate their knowledge, while those with a suboptimal understanding may not be able to recognise their own knowledge gaps.¹⁰

In assessing syndromic recognition, we assessed HCPs' knowledge in recognising different pathogenesis of immediate hypersensitivity reactions, in the form of IgE-mediated anaphylaxis as well as non-IgE mediated hypersensitivity reactions (Question 1 i-iii). IgE-mediated anaphylaxis confers the risk of recurrent reaction upon drug re-exposure due to long-lasting immunological memory.¹ On the other hand, non-IgE-mediated immediate hypersensitivity reactions, such as intravenous contrast allergies and vancomycin rate-dependent infusion reactions also known as "red man syndrome", are caused by IgE independent histamine release due to direct mast cell receptor activation.^{6,8,12} It is essential for HCPs to be able to discriminate the underlying mechanisms, as in the case of IgE-mediated anaphylaxis, re-exposure to the culprit or structurally related agents needs to be avoided, whereas risk mitigation interventions such as premedication with antihistamines or corticosteroids and reducing the infusion rate should minimise non-IgE mediated immediate hypersensitivity reactions.^{6,8}

To assess syndromic recognition of delayed-type DHRs and drug causality attribution, we presented two different clinical scenarios. The first was characteristic of SJS/TEN due to allopurinol (Question 3), and the second was DRESS to trimethoprim-sulfamethoxazole (Question 4). Allopurinol is the most common cause of SJS/TEN, and sulfonamide-containing antibiotics are the second most frequent cause of delayed hypersensitivity reactions, after beta-lactams.^{13,14}

In Question 3, recognising the patient had SJS/TEN was the crucial first step in identifying the culprit drug as allopurinol, accounting for a latency period of at least 2 weeks prior to onset of symptoms due to it being a delayed-type T-cell mediated disorder.^{9,15,16} Those lacking the understanding of this clinical syndrome and associated pathogenic mechanism mistakenly identified the beta-lactams, commenced immediately prior to the onset of symptoms, as the causative drug (protopathic effect). In the second case, respondents who failed to recognise the waxing and waning nature of DRESS syndrome¹³ mistakenly attributed the reaction to other antibiotics that coincided with the flare of symptoms. Incorrect interpretation of the culprit medication in SCAR conditions places the patient at risk for re-exposure in the future, or result in unnecessary avoidance of multiple medications.^{17,18}

This study also identified knowledge gaps of drug cross-reactivity pertaining to commonly implicated antimicrobial agents such as beta-lactams (Questions 2b, 2c, and 2d) and sulfonamides (Question 4 ii), particularly amongst the junior doctors.⁸ Over the last decade, significant advances in the understanding of antibiotic allergy have been made. Recent literature suggests penicillin cross-reactivity with cephalosporins specifically can be derived from the similarity of their R1 side chains.^{19,20} Previously, cross-reactivity between penicillins and cephalosporins was thought to be predominantly due to the main beta-lactam ring structure. However, current literature suggests cross-reactivity rates are less than 2% between penicillins and non-R1 cross-reactive cephalosporins, and less than 1% with carbapenems.^{19,20} Selective IgE-mediated reactions to aminopenicillins (i.e. amoxicillin) can involve antibodies directed only at the amino R-group.¹⁹ These antibiotics share a similar side chain structure to aminocephalosporins (e.g. cephalexin), and patients may be allergic to both classes of antibiotics. Dissemination of these advances in our understanding are important due to the high prescribing rates of amino-beta-lactam antibiotic classes in countries such as Australia.²¹ Unlike other beta-lactam antibiotics, aztreonam has negligible cross-reactivity due to its bicyclic-ring structure and therefore would be a safer alternative for penicillin-allergic patients.²⁰

Knowledge of sulfonamide and arylamine group hypersensitivity was also assessed. Non-arylamine group sulphonamides (e.g. frusemide, hydrochlorothiazide, celecoxib) do not cross-react with arylamine sulfonamides (sulfonilamide antimicrobials and sulfasalazine).²² However, as shown in our questionnaire, there is still significant hesitation amongst HCPs in prescribing or recommending medications such as thiazide diuretics and celecoxib to patients with sulfonilamide allergies.²² Non-antibiotic sulfonamides may be prescribed for patients reporting an antibiotic sulfonamide hypersensitivity.

Finally, health professionals demonstrated a poor knowledge of DHR diagnostics and management principles, with both junior doctors and pharmacists scoring below 50% correct responses. We assessed knowledge of the high negative predictive value of penicillin skin testing (Question 2a), which can facilitate the safe use of penicillin in individuals with a previous history of immediate penicillin hypersensitivity reactions.²³ We also assessed appropriate diagnostics in severe cutaneous adverse reactions (i.e. requirement of skin biopsy to diagnose) and criteria for drug desensitisation (Questions 3ii and 4iii), both of which are important for management of hospital inpatients with DHRs.^{16,24,25} Desensitisation is an unsafe management option for most severe delayed reactions. Early referral for immunology or dermatology consult by the treating team when appropriate, can mitigate the delay in diagnosis, and optimise treatment of severe and sometimes life-threatening drug reactions.

The main limitation of our study is that it was performed in teaching hospital networks, hence may not reflect community practice, private hospitals or regional hospital practices. The results nonetheless represent an underestimate of knowledge gaps. Another limitation is that patients' understanding, knowledge and attitudes were not measured as an outcome, which might impact on the HCPs' approach to management of DHRs. It should also be noted that the response rate is unknown as the participants were recruited through convenience sampling during the department meeting or

through department email lists. Accounting for this possible selection bias of respondents, the observed results would likely be an over-estimate.

Our study has shown significant knowledge gaps in the assessment and management of DHRs amongst healthcare professionals in teaching hospital settings, which can potentially impact on the quality of care and patient outcomes. Principles of DHRs are variably taught in undergraduate and graduate courses. This supports a need to develop a robust curriculum on DHRs addressing all key principles, and further design education modules and practice improvement programs to enable providers to deliver optimal care for patients with severe ADRs. Examples of case based e-learning modules, with knowledge assessments, have been published, comparing pre- and post- learning module outcomes showing improvement in levels of knowledge.^{26,27} An e-learning module would be easily adapted for different health services, and the effectiveness of such approach could be evaluated through a multicentre study.

CONCLUSIONS

This study provided a unique insight into the knowledge gaps for doctors and pharmacists around drug hypersensitivity reaction principles. The performance of HCP groups in the different domains of knowledge will allow development of targeted programs to effectively address knowledge gaps.

REFERENCES

1. Sultana J, Cutroneo P, Trifiro G. Clinical and economic burden of adverse drug reactions. *J Pharmacol Pharmacother*. 2013;4(Suppl1): S73-7.
2. Blumenthal KG, Peter JG, Trubiano JA, Phillips EJ. Antibiotic allergy. *Lancet*. 2019;393(10167):183-198.

3. Pirmohamed M, James S, Meakin S, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. *BMJ*. 2004;329(7456):15-9.
4. Australian Commission on Safety and Quality in Health Care. National safety and quality health service standards. Available from: <https://www.safetyandquality.gov.au> (Accessed 10 July 2019).
5. Lazarou J, Pomeranz PH, Corey PN. Incidence of adverse drug reactions in hospitalised patients. *JAMA*. 1998; 279(15):1200-5.
6. Gomes ER, Demoly P. Epidemiology of hypersensitivity drug reactions. *Curr Opin Allergy Clin Immunol*. 2005;5(4):309-16.
7. Bohm R, Proksch E, Schwarz T, Cascorbi I. Drug hypersensitivity. *Dtsch Arztebl Int*. 2018;115(29-30):501-512.
8. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. *Lancet*. 2000;356(9237):1255-9.
9. Aung AK, Tang MJ, Adler NR, et al. Adverse Drug Reactions Reported by Healthcare Professionals: Reaction Characteristics and Time to Reporting. *J Clin Pharmacol*. 2018;58(10):1332-9.
10. Tan LT. Innovations in Continuing Professional Development — Countering the Dunning–Kruger Effect. *Clin Oncol (R Coll Radiol)*. 2011; 23(10):659-661.
11. Simons FE, Arduoso LR, Bilo MB, et al. World allergy organization guidelines for the assessment and management of anaphylaxis. *World Allergy Organ J*. 2011;4(2):13-37.
12. McNeil BD, Pundir P, Meeker S, et al. Identification of a mast-cell specific receptor crucial for pseudo-allergic drug reactions. *Nature*. 2015;519(7542):237-41.
13. Halevy S, Ghislain PD, Mockenhaupt M, et al. Allopurinol is the most common cause of Stevens-Johnson syndrome and toxic epidermal necrolysis in Europe and Israel. *J Am Acad Dermatol*. 2008;58(1):25-32.
14. Slatore CG, Tilles SA. Sulfonamide hypersensitivity. *Immunol Allergy Clin North Am*. 2004;24(3):477-90.
15. Schrijvers R, Gillisen L, Chiriac AM, et al. Pathogenesis and diagnosis of delayed-type drug hypersensitivity reactions, from bedside to bench and back. *Clin Transl Allergy*. 2015; 5:31.
16. Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. Drug allergy: an updated practice parameter. *Ann Allergy Asthma Immunol*. 2010;105(4):259-73.
17. Trubiano JA, Aung AK, Nguyen M, et al. A comparative analysis between antibiotic- and nonantibiotic-associated delayed cutaneous adverse drug reactions. *J Allergy Clin Immunol Pract*. 2016;4(6):1187-93.

18. Trubiano JA, Worth LJ, Urbancic K, et al. Return to sender: the need to re-address patient antibiotic allergy labels in Australia and New Zealand. *Intern Med J.* 2016;46(11):1311-7.
19. Terico AT, Gallagher JC. Beta-lactam hypersensitivity and cross-reactivity. *J Pharm Pract.* 2014;27(6):530-44.
20. Pichichero ME. Use of selected cephalosporins in penicillin-allergic patients: a paradigm shift. *Diagn Microbiol Infect Dis.* 2007;57(3 Suppl):13S-8S.
21. Cairns KA, Roberts JA, Cotta MO, et al. Antimicrobial stewardship in Australian hospital and other settings. *Infect Dis Ther.* 2015;4(Suppl 1):27–38.
22. Lehmann DF. The metabolic rationale for a lack of cross-reactivity between sulfonamide antimicrobials and other sulfonamide-containing drugs. *Drug Metab Lett.* 2012;6(2):129-33.
23. Fox S, Park MA. Penicillin skin testing in the evaluation and management of penicillin allergy. *Ann Allergy Asthma Immunol.* 2011;106(1):1-7.
24. Rzyany B, Hering O, Mockenhaupt M, et al. Histopathological and epidemiological characteristics of patients with erythema exudativum multiforme major, Stevens-Johnson syndrome and toxic epidermal necrolysis. *Br J Dermatol* 1996;135(1):6-11.
25. Solensky R. Drug desensitization. *Immunol Allergy Clin North Am.* 2004;24(3):425-43, vi.
26. Schneider AT, Albers P, Muller-Mattheis V. E-Learning in Urology: Implementation of the Learning and Teaching Platform CASUS(R) - Do Virtual Patients Lead to Improved Learning Outcomes? A Randomized Study among Students. *Urol Int.* 2015;94(4):412-8.
27. Oliveira AC, Mattos S, Coimbra M. Development and Assessment of an E-learning Course on Pediatric Cardiology Basics. *JMIR Med Educ.* 2017;3(1)

Table 1: Classification of Drug Hypersensitivity Reactions⁶

Reaction type	Mechanism	Clinical example(s)	Timing of reaction after drug exposure
Type I (immediate)	IgE mediated, mast-cell histamine release	Anaphylaxis, urticaria, angioedema	Within minutes to 1 hour
Non-IgE mediated immediate hypersensitivity	Still poorly understood Non-IgE mediated histamine release from degranulated mast cells	Red man syndrome, contrast medium reaction, reaction to neuromuscular blocking agents	Within minutes to hours
Type II	IgG/IgM mediated, complement	Haemolytic anaemia	Variable
Type III	Immune complex mediated, IgG, complement	Serum sickness, glomerulonephritis	1 - 3 weeks
Type IV (delayed)	T cell mediated, activate macrophages	Allergic contact dermatitis, cutaneous drug eruption (DRESS, SJS, AGEP)	2 days – 6 months

Table 2: Distribution and characteristics of respondents

		Overall (n=238)	Senior doctor (n=107)	Junior Doctor (n=58)	Pharmacist (n=73)	P-value
Health Service	Alfred	100 (42.0%)	57	18	25	N/A
	Austin	51 (21.4%)	27	10	14	
	Eastern	53 (22.2%)	11	24	18	
	Peninsula	34 (14.3%)	12	6	16	
Level of experience	Inexperienced	102 (42.9%)	33 (30.8%)	32 (55.2%)	37 (50.7%)	0.002*
	Somewhat experienced	67 (28.2%)	32 (29.9%)	21 (36.2%)	14 (19.2%)	
	Very experienced	69 (29.0%)	42 (39.2%)	5 (8.6%)	22 (30.1%)	
Preparedness in recognising DHR syndromes	Unprepared	59 (24.8%)	12 (11.2%)	21 (36.2%)	26 (35.6%)	<0.001*
	Neutral	37 (15.5%)	11 (10.2%)	13 (22.4%)	13 (17.8%)	
	Prepared	142 (59.7%)	84 (78.5%)	24 (41.4%)	34 (46.6%)	
Preparedness in prescribing alternative beta-lactam to penicillin allergic patient	Unprepared	64 (26.9%)	28 (26.1%)	23 (39.7%)	13 (17.8%)	0.03*
	Neutral	34 (14.3%)	17 (15.9%)	9 (15.5%)	8 (11.0%)	
	Prepared	140 (58.8%)	62 (57.9%)	26 (44.8%)	52 (71.2%)	
Preparedness in identifying culprit drug in a drug reaction	Unprepared	47 (19.7%)	16 (15.0%)	24 (41.4%)	7 (9.6%)	<0.001*
	Neutral	35 (14.7%)	13 (12.1%)	10 (17.2%)	12 (16.4%)	
	Prepared	156 (65.5%)	78 (72.9%)	24 (41.4%)	54 (74.0%)	

NB: The numbers (%) within each cell denotes the proportion of correct answers in each knowledge domain, derived by the formula [Total number of correct responses for each domain/(total number of questions x total number of respondents)].

* represents the denominator value.

P-values are determined by Chi-square tests for 3x3 group interactions.

Table 3: Comparison of proportion of correct answers in each DHR knowledge domain between groups of interest

		DHR syndrome recognition (n=714)*	Culprit Drug Recognition (n=476)*	Cross reactivity (n=1190)	DHR diagnostics/therapy (n=714)*
	Overall	435 (60.9%)	265 (55.7%)	648 (54.5%)	371 (52.0%)
Profession group	Senior doctor	204 (63.6%)	124 (57.9%)	306 (57.2%)	200 (62.3%)
	Junior doctor	98 (56.3%)	65 (56.0%)	133 (45.9%)	82 (47.1%)
	Pharmacist	133 (60.7%)	76 (52.1%)	209 (57.3%)	89 (40.6%)
	P-value	0.29	0.54	0.003	<0.001
Level of experience	Inexperienced	183 (59.8%)	116 (56.9%)	268 (52.5%)	137 (44.8%)
	Somewhat experienced	123 (61.2%)	76 (56.7%)	165 (49.3%)	117 (58.2%)
	Very experienced	129 (62.3%)	73 (52.9%)	210 (60.9%)	117 (56.5%)
	P-value	0.85	0.74	0.007	0.004
Preparedness in recognising DHR syndromes	Unprepared	110 (62.1%)			
	Neutral	67 (60.4%)			
	Prepared	258 (60.6%)			
	P-value	0.93			
Preparedness in identifying	Unprepared		50 (53.2%)		

culprit drug in a drug reaction	Neutral		45 (64.3%)		
	Prepared		170 (54.5%)		
	P-value		0.28		
Preparedness in prescribing beta-lactam to penicillin allergic patient	Unprepared			165 (52.3%)	
	Neutral			100 (58.9%)	
	Prepared			383 (54.7%)	
	P-value			0.30	
Preparedness in DHR diagnostics/therapy	Unprepared				63 (44.7%)
	Neutral				60 (57.1%)
	Prepared				248 (53.0%)
	P-value				0.12

NB: The numbers (%) within each cell denotes the proportion of correct answers in each knowledge domain, derived by the formula [Total number of correct responses for each domain/(total number of questions x total number of respondents)].

* represents the denominator value.

P-values are determined by Chi-square tests for 3x3 group interactions.

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Mazzoni, D;Tee, HW;de Menezes, SL;Graudins, LV;Johnson, DF;Newnham, ED;Kelley, PG;Zubrinich, CM;Goh, MSY;Trubiano, JA;Aung, AK

Title:

A Survey on Knowledge Gaps in Assessment and Management of Severe Drug Hypersensitivity Reactions: Multicenter Cross-Sectional Study of Australian Health Care Providers

Date:

2020-07-10

Citation:

Mazzoni, D., Tee, H. W., de Menezes, S. L., Graudins, L. V., Johnson, D. F., Newnham, E. D., Kelley, P. G., Zubrinich, C. M., Goh, M. S. Y., Trubiano, J. A. & Aung, A. K. (2020). A Survey on Knowledge Gaps in Assessment and Management of Severe Drug Hypersensitivity Reactions: Multicenter Cross-Sectional Study of Australian Health Care Providers. JOURNAL OF CLINICAL PHARMACOLOGY, 61 (1), pp.25-31. <https://doi.org/10.1002/jcph.1692>.

Persistent Link:

<http://hdl.handle.net/11343/276005>