

Improving drug allergy label accuracy by supervised safety- and protocol-driven evaluation

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ABSTRACT

Introduction: Drug allergies are often self-reported but of unknown accuracy. We carried out a prospective study to examine the utility and safety of formal allergology evaluation, and to identify factors associated with accurate drug allergy labels.

Method: All patients who underwent drug allergy evaluation in our clinic during the study period were recruited. Baseline demographics, characteristics of index hypersensitivity reaction and outcomes of evaluation were recorded.

Results: A total of 331 patients from March 2019 to June 2021 completed drug allergy evaluation to index drugs of concern. There were 123 (37%) male patients, and the mean age was 49 years (standard deviation 17). There were 170 beta-lactam antibiotics, 53 peri-operative drugs, 43 others, 38 non-steroidal anti-inflammatory drugs, and 27 non-beta-lactam antibiotic evaluations. Index reaction occurred within 5 years in 165 (50%) patients, with latency of less than 4 hours in 125 (38%) patients. The most common index reactions were rash, angioedema and urticaria. There were 57 (17%) evaluations stratified as low risk, 222 (67%) moderate risk, and 52 (16%) high risk based on multidisciplinary consensus. Allergy label was found to be false (negative drug evaluation) in 248 (75%) patients, while 16/237 (7%) skin tests, 44/331 (13%) in-clinic graded challenge, and 23/134 (17%) home prolonged challenges were positive (true drug allergy). The most common evaluation reactions were rash and urticaria. No cases of anaphylaxis were elicited.

Conclusion: Seventy-five percent of drug allergy labels are inaccurate. Risk-stratified, protocolised allergy evaluation is safe. Prolonged drug challenge increases the sensitivity of drug allergy evaluation and should therefore be performed when indicated.

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Keywords: Drug allergy, drug hypersensitivity, graded challenge, prolonged drug provocation, skin testing

INTRODUCTION

Self-reported drug allergies¹ are common, and the majority of these have been shown to be inaccurate. Recording of drug allergy details is also often incomplete and inaccurate.² Consequences of inaccurate drug labelling include unnecessary avoidance of effective medications, restricted access to appropriate antibiotics, impact on antimicrobial stewardship, and public health consequences of health economics and utilisation. Beta-lactam allergy labelling results in the use of

broad-spectrum antimicrobials that are more costly and potentially less effective, as well as increase the rates of antimicrobial resistance and susceptibility to *Clostridium difficile* infection.³⁻⁶

Various interventions have been proposed to address these issues. Measures include: (1) access to formal allergological evaluation; (2) reducing inappropriate drug allergy labelling through physician- and pharmacist-led multidisciplinary teams;⁶⁻⁹ and (3) point of care direct challenge to penicillin. Formal

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CLINICAL IMPACT

What is New

- Seventy-five percent of drug allergy labels in an outpatient allergy clinic were found to be inaccurate on evaluation.
- Prolonged drug provocation increases the sensitivity of drug allergy evaluation and should be considered where appropriate.
- A stepwise relationship between pre-evaluation risk prognostication and the likelihood of accurate drug allergy labelling was observed.

Clinical Implications

- Prolonged drug provocation should be considered if the latency of reaction is delayed or unknown.
- A formal risk prognostication framework should be adopted.
- Drug allergy evaluation is safe, improves therapeutic options, and has important public health consequences.

allergological evaluation of drug allergies includes skin tests, patch tests and graded drug challenges in monitored settings.¹⁰⁻¹⁴ Controlled drug provocation testing to penicillin has been successful in 70.9 to 94.4% of patients^{15,16} and alternative drug challenges can also be performed to increase therapeutic options. Although a significant number of drug allergy labels can be removed upon evaluation, the clinical or historical factors associated with a true drug allergy remain unclear.

The primary aim of our study was to examine the outcomes and safety of allergological evaluation of drug allergies in Singapore General Hospital. Our secondary aim was to determine if there are underlying factors that can predict accurate drug allergy labels.

METHOD

Over the period of March 2019 to June 2021, all patients above 18 years old who attended the Singapore General Hospital's Allergy Centre for drug allergy evaluation were recruited into a prospective observational study. In general, all patients underwent, if appropriate, skin testing consisting of skin prick test and intra-dermal testing as per published protocols according to drug classes.^{13,17,18} Specific immunoglobulins for beta-lactam allergy were determined via ImmunoCAP whole

allergens testing (ThermoFisher Scientific Inc, Waltham, US). For reactions that are delayed or of unknown latency, additional patch tests and delayed intra-dermal reading were also performed. If skin tests are negative or unnecessary as per protocol, patients will proceed on to an in-clinic graded challenge under supervision. In patients with delayed/unknown reactions, an additional step of prolonged drug provocation (at home) of 5 days' duration was instituted. Prior history of severe cutaneous adverse drug reactions and pregnancy were contraindicated from any drug testing in our centre.

For certain drugs such as non-steroidal anti-inflammatory drug (NSAID) hypersensitivity, patients were offered either evaluation to index NSAIDs, or alternative evaluation to cyclooxygenase-II inhibitors such as etoricoxib. Shared decision-making was undertaken based on physician and patient preferences.

Prior to evaluation, all patients were risk-stratified during a multidisciplinary meeting consisting of specialty doctors, nurses and pharmacists. Patient stratification was based on consensus and a composite of clinical factors: (1) likelihood of reaction in terms of symptoms, latency, prior reactions and re-exposure post-event; (2) severity of reaction e.g. systemic reactions versus cutaneous; (3) age and underlying comorbidities; and (4) evaluation of responses to index drug versus alternative drug. High-risk patients were assigned to receive continuous monitoring, in the visual sight of nurses, and had intravenous access secured prior to the commencement of evaluation. Moderate- and low-risk patients received standard monitoring every 30 minutes during evaluation. In addition, for certain high-risk patients such as those with a reported history of anaphylaxis, the initial starting concentration of skin tests was reduced.

Upon completion of skin testing and/or graded challenge, all patients were observed for one hour before discharge. In patients who had unclear or delayed latency to the original reaction, an additional 5-day course of the index drug was prescribed for home administration. Post-evaluation monitoring was also carried out via a 3-pronged method: (1) nurse-led telephone calls one day after clinical evaluation and an additional call on day 3 for those requiring prolonged 5-day drug challenge; (2) direct access to clinics via telephone hotlines and dedicated emails; and (3) same-day clinic review if required. All patients who reported symptoms were reviewed either in person or via video/phone consult. Non-specific itch in the absence of other clinical signs was not regarded as a positive evaluation.

Baseline information such as patient demographics, comorbidities, number of drug allergies and characteristics of index hypersensitivity reaction was

recorded. Evaluation outcomes including hypersensitivity reactions, treatment administered and disposition were also recorded. Safety of allergy evaluation was measured based on the number of anaphylaxis and systemic episodes as well as resuscitation events, unscheduled emergency department visits and hospital admissions.

Our primary aim was to determine the outcomes and risks of drug allergy testing. The secondary aim was to determine any clinical factors that were predictive of a true drug allergy. Analysis was restricted to drug evaluations performed on the index drug, as the evaluation to alternative drugs is safer and does not carry the same risks or outcomes. Similarly, without allergy testing and direct provocation to the labelled drug, a drug allergy cannot be verified.

Statistical analysis was performed using SPSS version 26. Chi-square tests were performed for qualitative variables, student T-tests were undertaken for quantitative variables, and 1-way analysis of variance tests was used for interval variables. *P* values were double-sided with $P < 0.05$ taken as statistically significant. Ethical approval was obtained from our institution's research board (Singhealth Centralised Institutional Review Board, IRB number 2018/2877).

RESULTS

A total of 482 patients were enrolled in our study from March 2019 to June 2021. Of these, 370 were tested for the index drug while 112 were tested for alternative agents. Of those evaluated for the index drug allergy, 331 completed full drug evaluations that included drug provocation and were included for analysis. The rest with incomplete evaluation or non-definitive results were excluded. The patient allocation is summarised in Fig. 1.

The mean age of the studied cohort who underwent full drug allergy evaluation ($n=331$) was 49 years (standard deviation 17) and 123 (37%) were males. Among the patients, 159 (48%) had 0–2 drug allergy labels, 87 (26%) had 3–4 labels, and 85 (26%) had 5 or more existing drug allergy labels at baseline. Beta-lactam antibiotics were the most common drug class evaluated (170/331, 51%), followed by peri-operative drugs (53/331, 16%) and NSAIDs (38/331, 12%) (Table 1).

Time from index reaction to evaluation was less than 6 months in 40 patients (12%), 6–12 months in 49 (15%), 1–5 years in 76 (23%), 5–10 years in 25 (8%), more than 10 years in 102 (31%), and unknown in 39 (12%). The latency of the reaction was less than 4 hours in 125 patients (38%), more than

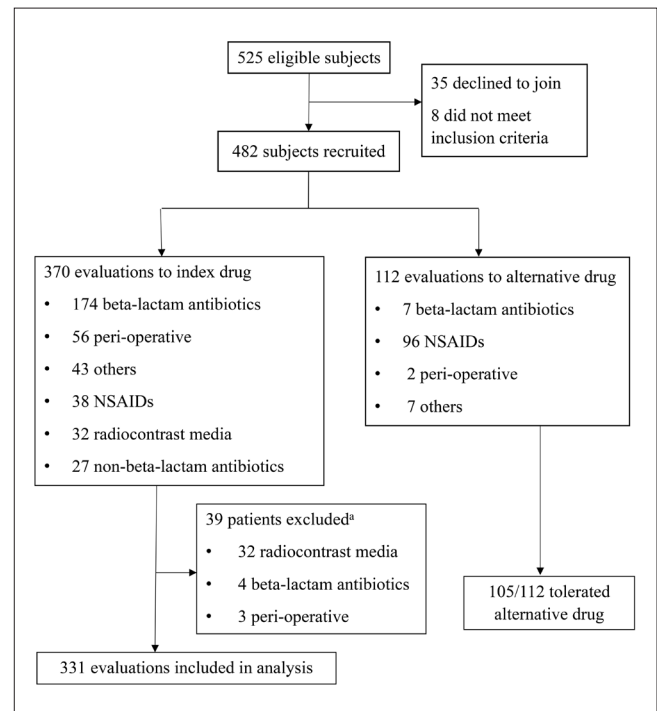


Fig. 1. Study allocation.

NSAIDs: non-steroidal anti-inflammatory drugs

^a 39 patients were excluded as the evaluation was incomplete or inconclusive

4 hours in 94 (28%), and unknown in 112 (34%). The most common index reactions were rash (133, 40%), angioedema (85, 26%) and urticaria (57, 17%). Systemic reactions were less common: anaphylaxis (28, 9%), isolated respiratory symptoms, e.g. breathlessness, wheezing, globus sensation, chest tightness (27, 8%) and hypotension (13, 4%). Other baseline demographics and characteristics of index hypersensitivity reactions (Table 1) showed that 57 patients (17%) were stratified as low risk, 222 (67%) as moderate risk, and 52 (16%) as high risk.

Among the allergy evaluations to the index drug, 248 patients (75%) who did not develop reactions during drug provocation were deemed to have negative drug evaluations (false drug allergy labels). Eighty-three (25%) who developed reactions either on skin testing or drug provocation were verified to have positive drug evaluation (true drug allergy label).

Out of the 331 drug evaluations performed, the proportions of positive drug evaluation (true drug allergy label) according to drug class are as follows: 56/170 (33%) beta-lactam antibiotics, 13/38 (34%) NSAIDs, 6/43 (14%) others, 5/53 (9%) peri-operative drugs, and 3/27 (11%) non-beta-lactam antibiotics (Table 2). Within the beta-lactam antibiotic class of 170, 56 patients (33%) had positive drug evaluations (true drug allergy labels), 1 (0.6%) developed reactions

Table 1. Baseline demographics of patients undergoing evaluation to index drug

	Total number of evaluations (n=331) No. (%)	Negative drug evaluation (false drug allergy label) (n=248) No. (%)	Positive drug evaluation (true drug allergy label) (n=83) No. (%)	<i>P</i> value
Age, mean (SD), years	49 (17)	49 (17)	49 (15)	0.87
Sex, male	123 (37)	102 (41)	21 (25)	0.01
Sex, female	208 (63)	146 (59)	62 (75)	
Comorbidities				
Angioedema-urticaria	16 (5)	12 (5)	4 (5)	0.99
Atopic dermatitis	16 (5)	10 (4)	6 (7)	0.24
Cardiac ^a	128 (39)	89 (36)	39 (47)	0.07
Respiratory ^b	42 (13)	33 (13)	9 (11)	0.56
No. of pre-existing drug allergies				0.70
0–2	159 (48)	119 (48)	40 (48)	
3–4	87 (26)	68 (27)	19 (23)	
≥5	85 (26)	61 (25)	24 (29)	
Class of drug evaluated				<0.01
Beta-lactam antibiotics	170 (51)	114 (46)	56 (68)	
Peri-operative drugs	53 (16)	48 (19)	5 (6)	
NSAIDs	38 (12)	25 (10)	13 (16)	
Non-beta-lactam antibiotics ^c	27 (8)	24 (10)	3 (4)	
Others ^d	43 (13)	37 (15)	6 (7)	
Time from reaction to evaluation				0.85
<6 months	40 (12)	32 (13)	8 (10)	
6–12 months	49 (15)	35 (14)	14 (17)	
1–5 years	76 (23)	53 (21)	23 (28)	
5–10 years	25 (8)	20 (8)	5 (6)	
>10 years	102 (31)	80 (32)	22 (27)	
Unknown	39 (12)	28 (11)	11 (13)	
Latency				0.19
<4 hours	125 (38)	89 (36)	35 (43)	
>4 hours	94 (28)	71 (29)	23 (28)	
Unknown	112 (34)	88 (35)	24 (29)	
Type of index reaction				
Rash not otherwise specified	133 (40)	99 (40)	34 (41)	0.87
Angioedema	85 (26)	58 (23)	27 (33)	0.10
Urticaria	57 (17)	42 (17)	15 (18)	0.81
Itch	48 (15)	35 (14)	13 (16)	0.73

Table 1. Baseline demographics of patients undergoing evaluation to index drug (Cont'd)

	Total number of evaluations (n=331) No. (%)	Negative drug evaluation (false drug allergy label) (n=248) No. (%)	Positive drug evaluation (true drug allergy label) (n=83) No. (%)	<i>P</i> value
Anaphylaxis	28 (9)	22 (9)	6 (7)	0.64
Unknown	30 (9)	21 (9)	9 (11)	0.51
Respiratory ^c	27 (8)	21 (9)	6 (7)	0.72
Isolated hypotension	13 (4)	9 (4)	4 (5)	0.63
Others ^f	33 (10)	26 (11)	7 (8)	0.59
Pre-evaluation risk stratification				<0.01
Low	57 (17)	50 (20)	7 (8)	
Moderate	222 (67)	172 (69)	50 (60)	
High	52 (16)	26 (11)	26 (31)	

NSAIDs: non-steroidal anti-inflammatory drugs; SD: standard deviation

^a Cardiac comorbidities including hypertension, hyperlipidaemia, ischaemic heart disease.

^b Respiratory comorbidities including asthma, allergic rhinitis.

^c Non-beta-lactam antibiotics: macrolides = 9, fluoroquinolones = 9, metronidazole = 7, vancomycin = 1, tetracycline = 1.

^d Other drugs evaluated: proton pump inhibitors = 8; opioids = 7; anti-emetics = 5; corticosteroids = 3; anti-hypertensives, anti-platelet, mecobalamin/cyanobalamin, statins, antihistamines = 2 each; anti-tussives, allopurinol, somatotropin, anti-spasmodic, insulin, mesalazine, colchicine, levodopa-benserazide, diuretic, erythropoietin = 1 each.

^e Respiratory reactions including breathlessness, wheezing, globus sensation, chest tightness.

^f Other index reactions: gastrointestinal = 9; fixed drug eruption or blisters = 3; erythema or flushing, rhinorrhoea/lacrimation/chemosis, syncope = 3 each; myoclonic jerks, giddiness, palpitations, fever/chills = 2 each; lethargy, diaphoresis, paraesthesia, pain, family history of allergy = 1 each.

on the skin prick test, 9 (5%) on the intra-dermal test, and 25 (15%) during the in-clinic graded challenge. Prolonged drug challenge was deemed necessary in 102 patients, and 21 of these (21%) developed reactions during the home prolonged challenge. Within the peri-operative drugs, 5/53 patients (9%) had positive drug evaluations (true drug allergy labels), 3/53 (6%) reacted during the intra-dermal test, and 2/53 (4%) reacted during the in-clinic graded challenge. Within the NSAID class, 13/38 patients (34%) had positive drug evaluations (true drug allergy labels), while 12/38 (32%) developed reactions following in-clinic graded challenge, and 1/3 (33%) developed reactions following prolonged drug challenge. For patients who were evaluated to non-beta-lactam antibiotics, 3/27 (11%) had positive drug evaluations (true drug allergy labels), 2/27 (7%) reacted during the in-clinic graded challenge and 1/18 (6%) developed reactions during home prolonged evaluation.

Positive drug evaluations by step of evaluation occurred as follows: 16/237 (7%) skin tests, 44/331 (13%) in-clinic graded challenge, and 23/134 (17%) prolonged home challenge. Among the patients who developed reactions during their 5-day home prolonged

challenge, 2 developed reactions on day 1; 5 each on day 2 and 3; 1 on day 4; 2 on day 5; and 6 on day 6 (Table 2).

The most common elicited reactions during both in-clinic graded challenge and home prolonged evaluations in the 83 patients were 26 unspecified rashes (31%) (13 during the in-clinic graded challenge and 13 during home prolonged evaluation) and 21 urticaria (26%) (18 during the in-clinic graded challenge and 3 during home prolonged evaluation) (Table 3). Two patients developed systemic reactions requiring admission. There were no anaphylactic reactions observed during the evaluation.

For those who developed reactions on testing, 40/83 patients (48%) (27 during the in-clinic graded challenge and 13 during home prolonged evaluation) required antihistamines for their hypersensitivity reactions; 39/83 (47%) (29 during the in-clinic graded challenge and 10 during the home prolonged challenge) did not require any treatment. Nine out of 83 patients (11%) (7 during in-clinic graded challenge and 2 during home prolonged evaluation) required intravenous or oral corticosteroids (Table 3). Nine (11%) who developed reactions during home prolonged evaluation required

early clinic reviews. Two (2%) required inpatient admission after in-clinic graded challenge for closer monitoring. The first patient developed angioedema, breathlessness and globus sensation after ibuprofen evaluation. He received oral and systemic anti-histamines, and oral corticosteroids in the clinic, and was admitted for airway monitoring as he had morbid obesity. He remained well inpatient. The second patient developed acute generalised exanthematous pustulosis after systemic penicillin evaluation for an unknown childhood reaction. She was admitted for monitoring and systemic corticosteroids, and improved inpatient with treatment. There were no cases of unscheduled emergency department attendances for post-challenge reactions. Seven out of 57 (12%) low-risk patients, 50/222 (23%) moderate-risk patients, and 26/52 (50%) high-risk patients were proven to have true allergy labels ($P<0.01$) (Fig. 2).

Secondary analysis showed that sex ($P=0.01$), class of drug evaluated ($P<0.01$), and pre-evaluation risk prognostication ($P<0.01$) were significant for the outcome of evaluation ($P<0.01$).

All other baseline demographics, atopic comorbidity, clinical characteristics of index reaction, and time to evaluation were not predictive of true drug allergy (Table 1).

DISCUSSION

Our study has shown that the majority of drug allergy labels are inaccurate. With formal allergological evaluations, more than 75% of drug allergy labels can be safely removed. In addition, we have demonstrated the utility of prolonged drug challenges in allergy evaluation, particularly in individuals with non-immediate reactions or reactions with unknown latency. Protocolised, supervised drug allergy testing is safe with rare systemic reactions (2/331, 0.6%) and no anaphylaxis is reported in our test cohort of 482 patients.

In our cohort, 83/331 (25%) were verified to have true drug hypersensitivity following systematic drug allergy evaluation. Positive results (true drug allergy) were seen in 16/237 (7%) skin tests, 44/331 (13%) in-clinic graded challenges, and 23/134 (17%) home prolonged challenges. These findings validated the utility of a stepwise protocolised approach to drug allergy validation. Firstly, such an approach allowed the removal of allergy labels in most patients. Secondly, 7% of skin testing (consisting of skin prick tests and intra-dermal testing) was positive and patients avoided the need and risks associated with direct oral provocation. Although direct drug provocation has been recommended as an alternative approach, particularly in low-risk patients and in settings where

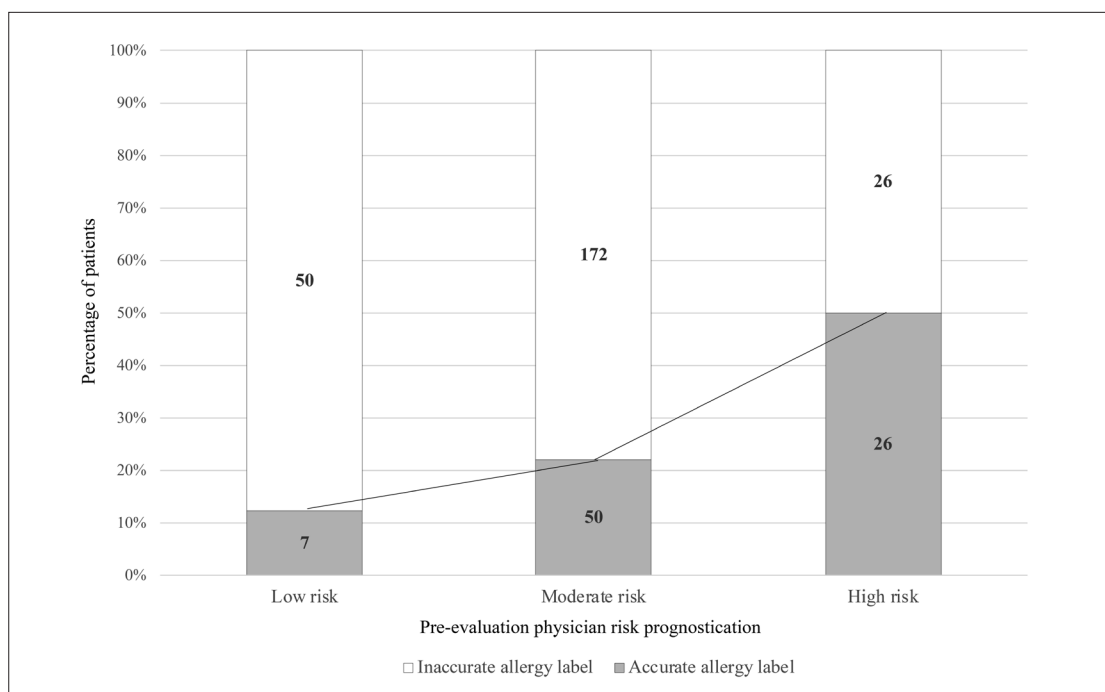


Fig. 2. Pre-evaluation physician risk prognostication and accuracy of allergy labels. A stepwise relationship was found between pre-test risk and the accuracy of drug allergy labels. 7/57 (12%) low-risk, 50/222 (23%) moderate-risk, and 26/52 (50%) high-risk patients were proven to have true allergy labels ($P<0.01$).

Table 2. Outcomes of drug allergy evaluation

Drug class (n=331) No. (%)	Negative drug evaluation (false drug allergy label) (n=248) No. (%)	Positive drug evaluation (true drug allergy label) (n=83) No. (%)	Number of positive evaluations ^a			
			Skin testing		In-clinic graded challenge (n=331) No. (%) ^b	Home prolonged evaluation (n=134) No. (%) ^b
			Skin prick test (n=237) No. (%) ^b	Intra- dermal test (n=237) No. (%) ^b		
Beta-lactam antibiotics 170 (51)	114 (46)	56 (68)	1/170 (0.4)	9/170 (4)	25/170 (8)	21/102 (16) ^c
Peri-operative drugs 53 (16)	48 (19)	5 (6)	0/53 (0)	3/53 (1)	2/53 (0.6)	0
NSAIDs 38 (12)	25 (10)	13 (16)	0	0	12/38 (4)	1/3 (0.7) ^d
Non-beta-lactam antibiotics 27 (8)	24 (10)	3 (4)	0/3 (0)	0/3 (0)	2/27 (0.6)	1/18 (0.7) ^e
Others 43 (13)	37 (15)	6 (7)	0/11 (0)	3/11 (1)	3/43 (0.9)	0/11 (0)
Total	248 (100)	83 (100)	1 (0.4)	15 (6)	44 (13)	23 (17)

NSAIDs: non-steroidal anti-inflammatory drugs

^a Number of positive evaluations out of total number of evaluations done per drug class.

^b Percentage calculated using denominator of total number of evaluations performed across all drug classes (column percentage).

^c Among the 21 reactions that occurred in beta-lactam antibiotics prolonged evaluations, 2 occurred on day 1, 5 on day 2, 5 on day 3, 1 on day 4, 2 on day 5, and 6 on day 6.

^d Delayed reaction occurred on day 2.

^e Delayed reaction occurred on day 3.

allergology service is not readily available,^{19,20} such an approach, obviating prior skin testing, may be risky. Thirdly, prolonged drug challenges increased the sensitivity of drug allergy evaluation.

Although prolonged drug provocation has been advocated to increase the sensitivity of drug allergy evaluation, particularly in non-immediate reactions²¹ occurring in adults, it is not uniformly adopted. If the prolonged challenge were omitted, up to 23/83 (28%) of patients with true drug allergies would have been missed and their drug allergy labels erroneously removed based on our findings. Similar findings have also been reported by Hjortlund et al.—10 out of 291 patients had positive single-dose challenges, but a further 23 patients went on to develop positive evaluations on 7-day challenges.¹⁶ Fransson et al. found that in direct drug allergy provocation of patients without prior skin testing, 11% of the study population (n=1,913) had positive challenges: 20% of these positive provocations were positive on the first dose, whereas 45% were positive more than 3 days later, reinforcing the need for prolonged challenges. The rationale behind prolonged drug challenge lies in the fact that drug hypersensitivity reactions consist of both immediate and non-immediate reactions (such as

drug exanthems), with the latter requiring prolonged exposure to a drug before the allergic reaction occurs. Similarly, a longer exposure to the culprit drug may be required to elicit the allergic response in drug allergy evaluation.

A secondary analysis was performed to determine any underlying demographics, clinical history or other factors that could predict true drug allergy labels. Subjects who were female ($P=0.01$) or who had beta-lactam evaluation ($P<0.01$) were more likely to have true drug allergy labels. Factors such as age, comorbidities, number of drug allergies, clinical presentation, latency and time to evaluation were not found to be significant ($P>0.05$). Similar conclusions were reached in a French study, which was unable to derive a predictive model based on allergist-collected history.²³ These findings reinforce the inaccuracy of drug allergy history and behave the need for a formal drug allergy evaluation.

In our centre, a multidisciplinary meeting between physicians, pharmacists and nurses is convened prior to actual drug allergy evaluation sessions. This allows for discussions on the suitability for evaluation based on patients' comorbidities, assigning the appropriate challenge protocol as well as risk prognostication. Risk

Table 3. Breakdown of reactions encountered following in-clinic graded challenge or prolonged home challenge

	In-clinic graded challenge (n=60) No. (%)	Home prolonged evaluation (n=23) No. (%)
Type of reaction ^a		
Rash	13 (30)	13 (57)
Urticaria	18 (41)	3 (13)
Angioedema	11 (25)	7 (30)
Respiratory ^b	9 (20)	4 (17)
Anaphylaxis	0	0
Others ^c	12 (27)	6 (26)
Treatment administered ^d		
Antihistamine	27 (61)	13 (57)
Nil treatment	29 (66)	10 (43)
Intravenous/oral corticosteroid	7 (16)	2 (9)
Adrenaline	0	0
Others ^d	5 (11)	6 (26)

^a Patients may experience more than one sign and symptom; hence total number of reactions and treatments administered is more than the number of patients in each group.

^b Respiratory reactions including breathlessness, wheezing, globus sensation, chest tightness, changes in voice.

^c Other types of reactions encountered in both in-clinic graded challenge and prolonged home challenge: lacrimation, blurring of vision, conjunctiva injection = 5, gastrointestinal = 4, dysaesthesia, numbness = 3, central nervous system = 2, chills and rigours, lower limb oedema, desquamation, discomfort = 1 each.

^d Other treatment administered in both in-clinic graded challenge and prolonged home challenge: topical creams (anti-pruritic, corticosteroid, emollients) = 6, intravenous hydration = 2, anti-emetic, paracetamol, albuterol and ipratropium combination inhaler = 1 each.

prognostication is essential for patient counselling, appropriate monitoring as well as allocation of manpower and resources. In addition, there was also a stepwise relationship between the pre-test risk and the likelihood of true drug allergy. Seven (12%) low-risk patients, 50 (23%) moderate-risk patients, and 26 (50%) high-risk patients were proven to have true allergy labels ($P < 0.01$). In a risk-stratified, protocolised setting, drug allergy evaluation is safe.^{24,25} There were no cases of anaphylaxis, and common hypersensitivity reactions were unspecified rash (26/83, 31%) and urticaria (21/83, 26%). Most patients (40/83, 48%) required only antihistamines or no rescue treatment at all (39/83, 47%). Nine patients (11%) required early clinic review and only 2 (2%) patients were admitted for closer monitoring. The 2 patients who required admission were each deemed to be moderate risk and high risk, and both were discharged uneventfully after the resolution of their hypersensitivity reactions.

The limitations of our study include referral bias, as the patients seen in our tertiary centre often have multiple comorbidities and are subject to polypharmacy.

However cardiac, respiratory, and atopic comorbidities and the number of drug allergy labels pre-evaluation were not found to be significant in predicting the outcomes of allergy evaluation. Pre-evaluation risk stratification by our multidisciplinary team was based on consensus after discussing patient factors and characteristics of index reaction. In our study, some patients with skin tests only did not undergo further confirmatory drug provocation, thus the possibility of false positives cannot be excluded. However, such a practice is consistent with current best practices.¹⁰ Lastly, patients who underwent allergy evaluation in relation to peri-operative drugs did not receive graded intravenous provocative challenge due to lack of anaesthesia provocation, and were excluded from statistical analysis.

CONCLUSION

Many drug allergy labels are untrue and drug allergy evaluation is essential in verifying them. In a risk-stratified, protocolised setting, drug allergy evaluation is safe and the hypersensitivity reactions observed were mostly cutaneous in nature. Prolonged

drug provocation testing, where indicated, increases the sensitivity of drug allergy evaluation and is important in the verification of allergy labels.

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