Risk factors for drug allergies in Chinese children

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Abstract

Background: Drug allergy, or drug hypersensitivity, is a potentially fatal disorder, and patients labeled with drug allergies have restricted access to first-line treatments. Full knowledge of the characteristics associated with drug allergies and severe reactions during allergy evaluation is beneficial for appropriate risk stratification.

Objective: We sought to determine whether certain clinical characteristics are associated with drug allergies in Chinese children.

Methods: Charts were reviewed for ethnic Chinese patients less than 18 years old referred to our tertiary allergy center for suspected drug allergies and completed skin and drug provocative testing between 2005 to 2017. Univariate and multivariate analyses were performed on the age of onset of drug allergies, gender, and other atopy versus drug allergies.

Results: Out of 75 children, 18 (24%) had IgE-mediated drug allergies, while 8 (10.7%) had delayed drug hypersensitivities, with a cumulative 26 subjects (34.7%) with any drug hypersensitivity. There were positive independent associations between drug hypersensitivities onset age vs IgE-mediated drug allergies (odds ratio (OR) = 14.9, 95% confidence intervals (CIs) = 1.5-148.3, P = 0.017) and between male gender and IgE-mediated drug allergies (OR = 4.4, CIs = 1.2-16.4, P = 0.019). Age 13 years was the best cut-off for IgE-mediated drug allergies according to the receiver operating characteristic curve (P = 0.026). Older age group (OR = 24.0, CIs = 1.4-417.8, P = 0.024) and atopic dermatitis (OR = 8.2, CIs = 1.4-49.8, P = 0.015) were correlated with delayed drug hypersensitivities.

Conclusions: While several previous studies suggested a higher prevalence of IgE-mediated drug allergies in younger adult females, older boys were more likely to have drug allergies for Chinese children.

Keywords: allergy, anaphylaxis, challenge, drug, epidemiology, IgE, paediatric, pharmacogenomics, pharmacology, provocative, skin testing

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Introduction

Drug allergies, or drug hypersensitivities, are a major public health concern that have a substantial impact on morbidity and inflict a huge economic burden on society.[1] Epidemiological studies from the United States, Europe, Australia, and South America have ranked drug allergies as the most likely etiology for anaphylactic deaths.[2-5] Unfortunately, the prevalence of fatal anaphylactic events has been on the upward trend in many parts of the world.[1,2,4,6,7] Patients who suffer from drug-induced anaphylaxis are also at a greater risk of biphasic reactions than those with food or venom allergies, and they are more likely to experience more severe complications requiring hospitalization.[2,8] Anaphylactic reactions are more likely secondary to foods in the paediatric population, but drug allergy remains as a common culprit.[9,10]

Many patients present to medical practitioners with extensive lists of suspected drug allergies, such as IgE-mediated drug allergies and delayed drug hypersensitivities including maculopapular and fixed drug eruptions, drug-induced

hypersensitivity syndrome (DIHS)/drug reaction with eosinophilia and systemic symptoms (DRESS), Steven-Johnson syndrome/toxic epidermal necrolysis, acute generalised exanthematous pustulosis, and allergic contact dermatitis.[11,12] Often, due to convenience and safety, alternative therapies are chosen for these patients without a comprehensive allergy evaluation to determine whether they are truly allergic and whether induction of temporary tolerance, or desensitization, to first-line medications should be undertaken.[12,13] Indeed, many patients with documented drug allergy spontaneously lose their sensitivity over time.[13] Additionally, some patients were never allergic to begin with, and their symptoms might have been due to infectious exanthem or other underlying diseases, environmental factors, pharmacological side effects not due to immunologic causes, or non-reproducible, idiopathic events.[12,13] Allergy protocols implemented to confirm or induce tolerance to first-line antimicrobials can minimize treatment failures and bacterial resistance.[12,14] As such, it is now recommended that for those who require beta-lactam antimicrobial treatment but had reported a history of penicillin allergy, skin (ST) and drug provocation testing (DPT) should be undertaken if possible before alternative medications are prescribed.[12] This approach has been shown to be cost-saving for individual patients and the entire healthcare system.[12,14]

However, allergy testing involves risks, including life-threatening reactions or death.[12,13,15] Pretest risk stratification is important for identifying candidates who are likely to truly have drug allergies so that the appropriate setting, personnel, and equipment can be prearranged for these higher risk cases.[12,13,15] Currently, risk factors predictive of patients with drug allergies have not been clearly identified. In some studies on adults, young women with multiple antibiotic allergies were more likely to have IgE-mediated drug allergies.[16,17] Interestingly, a cohort of Korean children who had allergies to medications tended to be older.[18] However, another study examining beta-lactam antibiotic drug allergies in a Middle Eastern paediatric population failed to establish these links but found that personal and family histories of drug allergies were most important, whereas human immunodeficiency virus (HIV) status was a strong predictor in Thai children.[19,20] These diverse findings could be due to the fact that different ethnic and genetic backgrounds, environmental surroundings, disease prevalence in different regions, cultural and dietary habits, medication availability, and prescription practices all play a role in modulating the immune system and susceptibility of a patient towards a true and persistent drug allergy.[21]

Our institution is a major public referral center in Hong Kong (HK) that provides tertiary allergy care to children with suspected or confirmed drug allergies.[15] The primary aim of this 13-year retrospective study was to identify whether age, gender, and other atopy such as atopic dermatitis, food allergies, asthma, and allergic rhinitis were associated risk factors for IgE-mediated drug allergies and delayed drug hypersensitivities in paediatric Chinese patients. The secondary aims included characterizing the prevalence of drug allergies for patients in this locality and the types of medications that were involved.

Methods

Study Population

All aspects of this study of human subjects were approved by the HK West Cluster Hospital Authority Research Ethics Committee Institutional Review Board without the need for patient and legal guardian consent due to its retrospective nature. Children suspected of having drug allergies in our locality were referred to our allergy clinic or seen by our inpatient allergy service during their hospital stay at Queen Mary Hospital (QMH) for initial evaluation. Most of these patients were of Chinese descent and residents of Hong Kong. A minority consisted of children from Guangdong Province referred to QMH paediatric subspecialists for their complex cardiac, oncologic, or rheumatologic disorders. Those with a history of non-life-threatening allergic reactions after medication exposures received ST and/or DPT at our Day Center, whereas in-patient DPT was performed for those who previously experienced severe reactions. Since January 2005, their data were recorded in a logbook and our Clinical Management System electronic health record (EHR) system accessible by all public hospitals in the city.[22] Information from a comprehensive chart review between 1 January 2005 to 31 December 2017 which included previous referral information and symptoms, testing results, final diagnoses, onset of drug allergy, age, gender, and other atopic conditions was retrieved and stored in an encrypted file.

Children < 18 years old who received skin prick, intradermal, atopy patch, and/or DPT to all suspected culprit drugs were included, and patients with allergies to multiple medications with known cross-reactivity were coded in the database as a single subject and drug allergy. Our testing modality followed international guidelines.[13,23,24] ST was performed for beta-lactams which had well-established non-irritating concentration (NIC) and patients were deemed allergic if results were positive.[13,25] All patients who were thought be allergic to medications without known NIC or had negative ST underwent DPT. A subject who demonstrated positive allergy testing to ≥1 other non-cross-reactive medication were still considered as a single subject but with multiple drug allergies. To further understand the influence of age groups in drug allergies, 13 years old was used as the cutoff based on a common practice to differentiate paediatric patients as adolescents versus young children. Patients who did not fully complete the aforementioned testing, had ambiguous diagnosis at the time of data extraction, patients ≥ 18 years old, and non-ethnic Chinese were excluded.

Statistical Analysis

Power analyses were performed using G*Power (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany) with 80% power at 5% level of significance in two tails. The effect size estimation was based on the findings from this study to demonstrate the sample sizes needed for different factors to reach the significant level associated with the outcomes of interest. Cohen's d was estimated by using mean differences and standard deviations of continuous outcomes between groups. The Cohen's d values were then used to calculate the sample sizes needed to detect a significant difference for each continuous outcome between two groups. Odds ratios were used

instead of Cohen's *d* if the outcome was a categorical measurement.

Demographic information and results are presented as group medians and 95th interpercentile ranges or confidence intervals. Stepwise multivariate logistic regression with the forward selection method was used to detect independent associations with the outcomes of interest, and *P* < 0.05 was considered significant. Statistical comparisons were completed using SPSS (IBM, Armonk, NY, USA) and JMP (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

This study had adequate power to detect associations between age of onset vs IgE-mediated drug allergies, delayed drug hypersensitivities, and any drug hypersensitivity (**Table 1**). Of the 75 patients, there was a predominance of children < 13 years old (89.3%), with a median age of 3.0 years old (**Table 2**). Forty-one (54.7%) of all subjects were males. Eighteen were confirmed to have IgE-mediated drug allergies, 8 had delayed drug hypersensitivities, equating to 26 (34.7%) with any drug hypersensitivity. Drug allergy was ruled out for the remaining 49 patients (65.3%). Atopic conditions were similar amongst the different diagnostic groups, with a slightly higher prevalence in patients with drug allergies. Half of the patients with IgE-mediated drug allergies had ST or DPT positive to other medications (confirmed multiple drug hypersensitivities). Eleven out of 21 (52.4%) of those who had suspected multiple drug allergies were found to have no drug allergy at all after several sessions of ST and DPT, whereas 7 (33.3%) had a single drug allergy. Interestingly, no individual with delayed drug hypersensitivities

Table 1. Power analyses for drug allergy outcomes of interest.

IgE-mediated Drug Allergies		
	Effect Sizes	**Sample Size Needed**
Age of onset (continuous)	*d* = 0.692	68
Age of onset (adolescent)	OR = 25	66
Gender	OR = 3.5	92
Total numbers of atopic disease	*d* = 0.295	362
Any atopy	OR = 1.92	312
Delayed Drug Hypersensitivities		
	Effect Sizes	**Sample Size Needed**
Age onset (continuous)	*d* = 0.34	272
Age of onset (adolescent)	OR = 14.2	32
Gender	OR = 0.56	785
Total numbers of atopic disease	*d* = 0.1	3020
Any atopy	OR = 3.36	218
Any Drug Hypersensitivity		
	Effect Sizes	**Sample Size Needed**
Age onset (continuous)	*d* = 0.59	92
Age of onset (adolescent)	OR = 21.4	73
Gender	OR = 1.94	296
Total numbers of atopic disease	*d* = 0.39	210
Any atopy	OR = 2.2	218

All power analyses performed with 1-β = 0.80 and two-tailed level of significance at 0.05.
d, Cohen's *d*; OR, odds ratio; adolescent, grouped by < 13 vs ≥ 13 years old.

Table 2. Clinical characteristics of all 75 subjects in the study.

	All Subjects (*n* = 75)	IgE-mediated Drug Allergies (*n* = 18)	Delayed Drug Hypersensitivities (*n* = 8)	Any Drug Hypersensitivity (*n* = 26)	No Drug Allergy (*n* = 49)
Age of drug hypersensitivities onset (yrs)	3.0 (0.2-16.2)	5.5 (0.2-17.5)	4.5 (0.8-16.0)	5.5 (0.2-17.5)	3.0 (0.1-12.5)
Age group at drug hypersensitivies onset (0-5 years old)	47 (62.7%)	9 (50.0%)	4 (50%)	13 (50%)	34 (69.4%)
Age group at drug hypersensitivies onset (6-12 years old)	20 (26.7%)	4 (22.2%)	2 (25.0%)	6 (23.3%)	14 (28.6%)
Age group at drug hypersensitivies onset (≥ 13 years old)	8 (10.7%)	5 (27.8%)	2 (25.0%)	7 (26.9%)	1 (2.0%)
Age at testing (yrs)	6.2 (0.6-17.8)	11.2 (0.8-17.8)	5.9 (1.4-18.0)	8.4 (0.8-18.0)	6.1 (0.5-16.7)
Age group on testing date (0-5 years old)	35 (46.7%)	7 (38.9%)	4 (50%)	11 (42.3%)	24 (50.0%)
Age group on testing date (6-12 years old)	24 (32.0%)	2 (11.1%)	2 (25.0%)	4 (15.4%)	20 (40.8%)
Age group on testing date (≥ 13 years old)	16 (21.3%)	9 (52.3%)	2 (25.0%)	11 (42.3%)	5 (10.2%)
Male gender	41 (54.7%)	14 (77.8%)	3 (37.5%)	17 (65.4%)	24 (50.0%)
History of atopic dermatitis	18 (24.0%)	3 (16.7%)	5 (62.5%)	8 (30.8%)	10 (20.4%)
History of suspected IgE-mediated food allergies	12 (16.0%)	3 (16.7%)	3 (37.5%)	6 (23.3%)	6 (12.2%)
History of allergic rhinitis	24 (32.0%)	9 (50.0%)	2 (25.0%)	11 (42.3%)	13 (26.5%)
History of asthma	19 (25.3%)	5 (27.8%)	3 (25.0%)	7 (26.9%)	12 (24.5%)
History of any of the above allergic diseases	43 (57.3%)	12 (66.7%)	7 (75.0%)	18 (69.2%)	25 (51.0%)
Suspected multiple drug hypersensitivities	21 (28.0%)	7 (38.9%)	3 (37.5%)	10 (38.5%)	11 (22.4%)
Confirmed multiple drug hypersensitivities	10 (13.0%)	9 (50.0%)	1 (12.5%)	10 (38.5%)	0 (0%)
Reported immediate onset (< 2 hrs) of symptoms	26 (34.7%)	14 (77.8%)	0 (0%)	14 (53.8%)	12 (24.5%)

Data are medians (and 95% interpercentile ranges) or counts (and percentages).

reported immediate onset (< 2 hrs) of symptoms during their initial allergic presentation, while 4/18 (22.2%) with IgE-mediated drug allergies reported delayed onset (≥ 2 hrs) of symptoms.

Univariate logistic regression between patient characteristics and drug allergies

Older age was significantly associated with higher odds of IgE-mediated drug allergies and any drug hypersensitivity (*P* < 0.05) (**Table 3**). This correlation was more pronounced when patients were dichotomized into two groups: young children

(< 13 years old) versus adolescents (≥ 13 years old) (*P* < 0.01). Males were more likely to have IgE-mediated drug allergies than females (*P* = 0.030). Patients ≥ 13 years old or with a history of atopic dermatitis had significantly higher odds of delayed drug hypersensitivities (*P* < 0.05).

Use of age ≥ 13 years as cutoff to compare age-group differences

To further investigate the possibility of a better age cutoff than 13 years old, we performed the receiver operating characteristic (ROC) analyses. Interestingly, the ROCs confirmed that 13 years was the cutoff age with the highest sensitivities and

Table 3. Univariate logistic regression with odds ratios between patient characteristics and drug hypersensitivities.

	Odds Ratios and 95% CIs for IgE-mediated Drug Allergies	*P* value	Odds Ratios and 95% CIs for Delayed Drug Hypersensitivities	*P* value	Odds Ratios and 95% CIs for Any Drug Hypersensitivity	*P* value
Age of drug hypersensitivities onset (yrs)	11.0 (1.2-95.6)	0.026*	7.0 (0.5-105.2)	0.163	8.8 (1.3-57.9)	0.020*
Age group at drug hypersensitivities onset (adolescent)	18.5 (2.0-172.2)	0.002*	16.0 (1.3-204.1)	0.029*	17.7 (2.0-153.6)	0.001*
Age at testing (yrs)	13.4 (1.8-99.1)	0.008*	2.5 (0.2-41.4)	0.522	7.1 (1.3-38.7)	0.020*
Age group on testing date (adolescent)	8.8 (2.4-32.5)	< 0.001*	2.9 (0.5-18.6)	0.279	6.5 (1.9-21.6)	0.002*
Male gender	3.6 (1.1-12.7)	0.030*	0.6 (0.1-2.9)	0.544	2.0 (0.7-5.3)	0.172
History of atopic dermatitis	0.78 (0.2-3.2)	0.728	6.5 (1.3-31.9)	0.019*	1.7 (0.6-5.1)	0.323
History of suspected IgE-mediated food allergies	0.70 (0.2-3.1)	0.644	0.23 (0-1.2)	0.100	0.46 (0.1-1.6)	0.233
History of allergic rhinitis	0.36 (0.1-1.1)	0.075	1.1 (0.2-6.1)	0.927	0.49 (0.2-1.3)	0.167
History of asthma	0.84 (0.2-2.9)	0.785	0.97 (0.2-5.3)	0.975	0.88 (0.3-2.6)	0.818
History of any of the above allergic diseases	0.52 (0.2-1.6)	0.249	0.35 (0.1-1.9)	0.196	0.46 (0.2-1.3)	0.125

Data are odds ratios (and 95% confidence intervals). *, *P* < 0.05.
Adolescent, grouped by < 13 vs ≥ 13 years old.
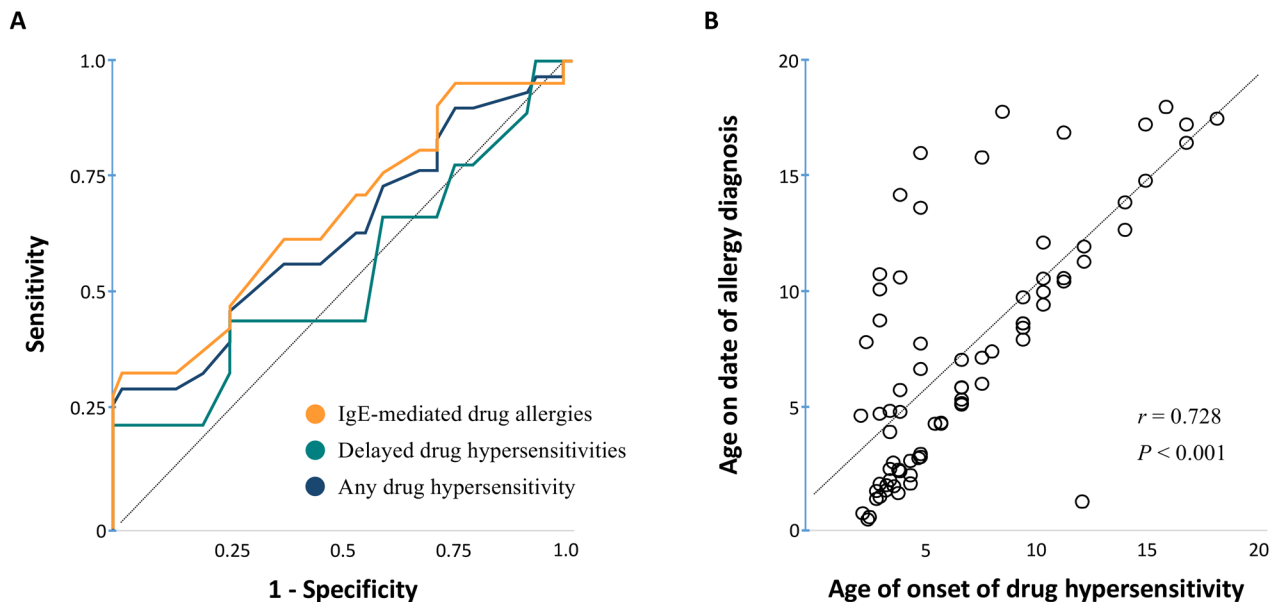
Figure 1. (Figure 1A) Receiver operating characteristics (ROCs) analyses indicated that the onset age of drug allergies had significant associations with IgE-mediated drug allergies (orange; area under the curve (AUC) = 0.648, *P* < 0.01) and any drug hypersensitivity (blue; AUC = 0.631, *P* < 0.05), with the highest levels of sensitivity and specificity at 13 years old. A cutoff of 15 years of onset age was suggested to have the highest sensitivity and specificity although there was no significant association between the age of onset and delayed drug hypersensitivities (turquoise; AUC = 0.594, *P* = 0.16). (Figure 1B) There was a high level of correlation (*r* = 0.728, *P* < 0.001) between the age of onset of drug hypersensitivities and the age on the date of allergy diagnosis (by skin or drug provocative testing).

specificities for IgE-mediated drug allergies (area under the curve (AUC) = 0.648, $P < 0.01$; sensitivity = 27.8%, specificity = 98.0%) and any drug hypersensitivity (AUC = 0.631, $P < 0.05$; sensitivity = 26.9%, specificity = 98.0%), respectively (**Figure 1A**). In contrast, for delayed drug hypersensitivities, the optimal age was 15 years, although this finding was not statistically significant (AUC = 0.594, $P = 0.16$; sensitivity = 25.0%, specificity = 100%).

A potential confounding issue with using the age of onset is the possibility of recall bias, as patients and parents might not remember precisely the actual date of drug allergy onset. The advantage of using age on the date of diagnosis provides a more accurate time-point of the confirmed hypersensitivity. However, some patients may have been tested many years later, when they might have developed natural immune tolerance. In this study, there was a high level of correlation ($r = 0.728$, $P < 0.001$) between patient/parental reporting of the age of onset of drug hypersensitivities and age on date of allergy diagnosis by ST or DPT (**Figure 1B**). As the onset of drug allergies would be more indicative of the actual age of drug allergies, the onset age was used for multivariate logistic regression, although the age of diagnosis yielded similar significant results.

Multivariate logistic regression between age and gender versus drug allergies

The age of onset was independently associated with IgE-mediated drug allergies and any drug hypersensitivity ($P < 0.05$) (**Table 4**). Additionally, males were more likely to have IgE-mediated drug allergies ($P < 0.05$). Older age groups and a history of atopic dermatitis remained to be significant independently associated with delayed drug hypersensitivities ($P < 0.05$).

Table 4. Multivariate logistic regression with odds ratios between patient characteristics and drug hypersensivities.

	Odds Ratios and 95% CIs for IgE-mediated Drug Allergy	P value
Age of drug hypersensitivities onset (yrs)	14.9 (1.5-148.3)	0.017*
Male gender	4.4 (1.2-16.4)	0.019*
	Odds Ratios and 95% CIs for Delayed Drug Hypersensitivities	P value
Age group at drug hypersensitivities onset (adolescent)	24.0 (1.4-417.8)	0.024*
History of atopic dermatitis	8.2 (1.4-49.8)	0.015*

Data are odds ratios (and 95% confidence intervals). *, $P < 0.05$.

Distribution of medications involved in drug allergies

Of the 26 patients diagnosed with any drug hypersensitivity, 8 (30.8%) were found to have cross reactivity to other similar medications. In contrast, 1 (3.8%) had co-allergies to other unrelated medications. In the total of 28 independent drug allergies, antimicrobials ($n = 23$, 82.1%) were the most common, followed by anaesthetics ($n = 2$, 7.1%, to lignocaine and tetracaine) (**Figure 2A**). One had an allergy to paracetamol (3.8%), one to mefenamic acid (3.8%), and another to hydrocortisone sodium succinate (3.8%). Of the antimicrobials, this cohort was most likely allergic to cephalosporins ($n = 12$, 52.2%) and penicillins ($n = 9$, 39.1%) (**Figure 2B**).
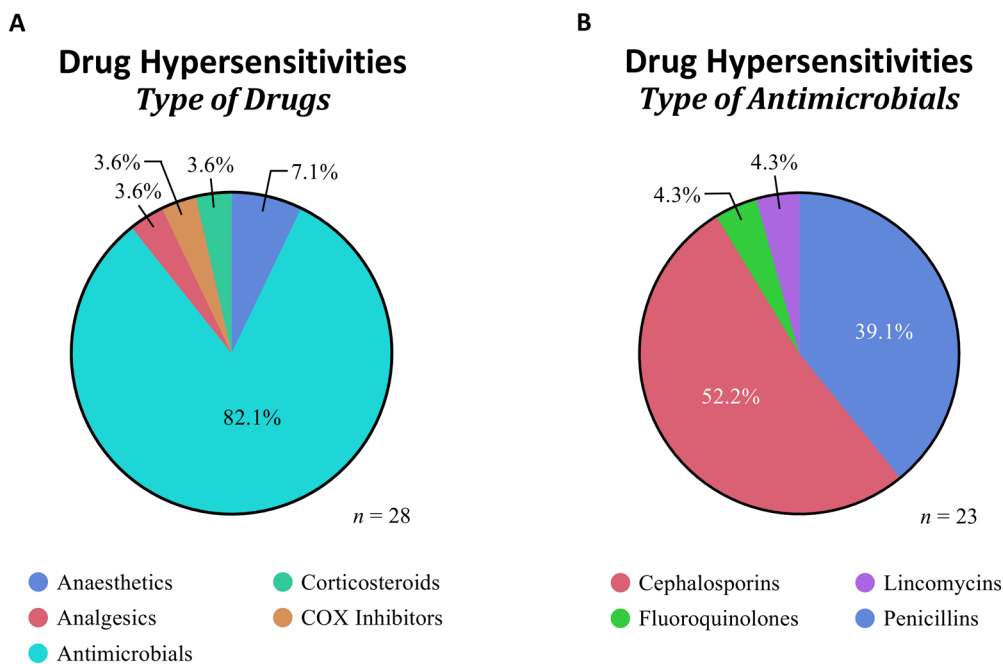
Figure 2. Distributions of (Figure 2A) any drug hypersensitivity (n total = 28), with antimicrobials = 23 (82.1%), anaesthetics = 2 (7.1%), analgesics = 1 (3.6%), corticosteroids = 1 (3.6%), cyclooxygenase (COX) inhibitors = 1 (3.6%), and of (Figure 2B) antimicrobials (n total = 23), with cephalosporins = 12 (52.2%), penicillins = 9 (39.1%), fluoroquinolones = 1 (4.3%), and lincomycins = 1 (4.3%).

Discussion

In our cohort of 75 Chinese children, older age and male gender were associated with IgE-mediated drug allergies. On the other hand, previous studies examining risk factors for drug allergies had reported mixed results. There is some evidence supporting the notion that Caucasian adult females were more likely to have IgE-mediated drug allergies.[16,17] The reasons for this observation are unclear but may be related to a differential genetic expression of sex chromosomes, influences of estrogens, or medication use for diseases that are more prevalent in young adult women.[26,27] Information regarding clinical characteristics that pose risks for children and Asian adults having drug allergies are scarce. Choi and colleagues observed their group of drug allergic children in Korea were older, but this finding was not substantiated in studies that consisted mostly of Middle Eastern and Thai children.[18,20] Our data are more analogous to the study of Korean children and suggest that East Asian geographical or ethnic factors may contribute to a higher likelihood of development and persistence of drug allergies in adolescent boys.[18]

The exact mechanisms underlying the pathogenesis of drug allergies in humans are still unclear. Based on *in vitro* experiments and animal models, it is hypothesized that most medications and their metabolites are small molecules that lack the ability to elicit antibody-mediated immunogenic responses and therefore these occur via hapten-carrier conjugate effects or interactions with peptides and T-cell receptors rather than direct IgE binding.[28] Indeed, patients with certain human leukocyte antigen (HLA) haplotypes, such as HLA-B*15:02 predominantly found in Southeast Asians, are at a high risk of potentially life-threatening reactions due to Steven-Johnson syndrome after taking certain medications, including carbamazepine.[28] Therefore, immunogenetics is a key aspect that underlies the diversity of susceptibilities of patients towards developing drug allergies since specific HLA alleles can be found in higher frequencies in certain ethnic groups, which may explain the differences observed in our Chinese cohort compared to other ethnic groups.[28] According to our data, teens had higher odds of true immediate drug allergies. It is possible that during this pubertal period, hormonal fluctuations and psychologic stress lead to immunomodulatory changes and these adolescent boys become more prone to drug hypersensitivities.[26] Additionally, older children are also more likely to have experienced more medication exposure and hence chance of sensitization, although during our chart review, detailed information on past drug use was unavailable.[13]

Our retrospective study was limited by the fact that not all data were recorded into our EHR system. Fortunately, the most relevant and essential information was documented by our allergists and retrieved. Despite that, some of these data, for example, the specific onset ages of drug allergies, might have been subjected to recall bias. There was a lack of recorded information on family history as well. The relatively small sample size did not allow sub-categorical analyses on risk factors for allergies to specific types of medications, such as antibiotics, anaesthetics, or anti-inflammatories.[29] True paediatric drug allergies are uncommon, and recruitment of a large number of subjects for completion of allergy testing by repeated skin prick and intradermal injections in the apprehensive children can be challenging. These are likely reasons that risk factors for paediatric drug allergies are not yet fully studied. In our cohort, 34.7% was confirmed to have drug allergies, seemingly higher than previous reports which were reported at 10-20%.[20] The relatively high percentage of confirmed cases of drug allergies in this study was possibly due to selection bias. The scope of our patients consisted of those who were deemed worthwhile by the referring physician for testing at our tertiary allergy center and who were motivated to attend our consultations to complete all steps of allergy testing comprehensively. As a result, these cases may not represent all Chinese children. It is important to note that the ROCs in our sample, although significant based on statistical calculations, did not result in levels of AUC that may translate to the use of 13 years of age as a highly reliable cutoff for predicting drug allergies within the clinical context. As such, these risk factors are more for general predictive rather than diagnostic purposes. Due to the retrospective nature of this study following international guidelines, skin but not blood testing was performed.[13,23,24] More research, which may include more comprehensive allergy testing (including blood eosinophil count and other allergy testing), basic science laboratory testing of mechanisms, and larger sample size will further enhance our understanding of paediatric drug allergies.

Conclusion

From these 75 subjects, we were able to identify an overall, consistent association between older age and male gender versus IgE-mediate drug allergies. Therefore, in the clinical setting, a higher level of caution should be considered when performing drug provocation testing in older or male Chinese paediatric patients as they carry a significantly higher risk of genuine drug allergy.

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Statement of Contribution

- Jaime S Rosa Duque was involved in the clinical care, study design, statistical analyses, interpretation of results, and drafting of the manuscript.
- Daniel KL Cheuk was involved in the clinical care, study design, statistical analyses, interpretation of results, and drafting of the manuscript.
- Patrick CY Chong was involved in the clinical care, study design, and drafting of the manuscript.
- Patrick Ip was involved in the clinical care, study design, statistical analyses, interpretation of results, and drafting of the manuscript.
- Wilfred HS Wong was involved in the study design, power analyses, statistical analyses, interpretation of results, and drafting of the manuscript.

- Pamela PW Lee was involved in the clinical care and drafting of the manuscript.
- Ian CK Wong was involved in the interpretation of results and drafting of the manuscript.
- Godfrey CF Chan was involved in the clinical care, interpretation of results, and drafting of the manuscript.
- Yu-Lung Lau was involved in the clinical care, study design, interpretation of results, and drafting of the manuscript.
- Marco HK Ho was involved in the clinical care, study design, statistical analyses, interpretation of results, and drafting of the manuscript.

Abbreviations

- AUC: area under the curve
- CI: 95% confidence interval
- COX inhibitor: cyclooxygenase inhibitor
- EHR: electronic health record
- DIHS: drug-induced hypersensitivity syndrome
- DRESS: drug reaction with eosinophilia and systemic symptoms
- HIV: human immunodeficiency virus
- HK: Hong Kong
- HLA: human leukocyte antigen
- OR: odds ratio
- QMH: Queen Mary Hospital
- ROC: receiver operating characteristic

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