Diagnostic procedures & practices in drug allergy/hypersensitivity: a survey of 13 Asian countries

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ABSTRACT

Background: The issues and challenges in the diagnosis of drug allergy/hypersensitivity among children and adults in Asia are likely to be different from non-Asian countries. Objective: To study the diagnostic modalities used in the evaluation and management of drug allergy/drug hypersensitivity reactions (DHRs) among member societies of the Asia Pacific Association of Allergy, Asthma and Clinical Immunology (APAAACI). Methods: A questionnaire comprising 41 questions was circulated electronically to member societies and individual members of APAAACI between January 23, 2020 and March 6, 2020. Results: Twenty-six respondents from 15 member societies and 1 individual member responded. European DHR guidelines were most commonly used. Skin prick and intradermal testing was used by 100%, with only 60% having access to commercial penicillin skin test reagents. In vitro-specific IgE tests were used by 75%, and basophil activation test by 56.3% for immediate DHR. Patch tests were used by 75% in contrast to lymphocyte transformation tests by 25% for nonimmediate DHR. Drug provocation tests were used by 68.8%, the most common indication being to exclude hypersensitivity where history/symptoms were not suggestive of drug hypersensitivity/allergy (93.3%). Human leukocyte antigen (HLA) genotype testing was mandatory among 25% respondents before new carbamazepine prescriptions, and 8.3% for allopurinol prescriptions. Conclusions: There was increased use of skin testing for iodinated contrast media hypersensitivity and patch testing for nonimmediate DHR. HLA genotype testing prior to new carbamazepine, allopurinol and abacavir prescriptions remain variable despite strong associations for severe cutaneous adverse reactions with Asian ethnicity. Results of this survey form a useful framework for developing educational and training needs and for improving access to drug allergy diagnostic and treatment modalities across APAAACI member societies.

Keywords: Anaphylaxis; Contrast media; Penicillins; Pharmacogenetics, Skin tests

INTRODUCTION

Adverse drug reactions account for 1.3% to 6.2% of hospital admissions [1, 2]. The prevalence of physician-reported drug allergies is 7.1% based on population-wide studies in Hong Kong [3]. Up to 14% of hospitalised patients have drug allergy labels [4]. The incidence of drug allergy or drug hypersensitivity reaction (DHR) has been reported to occur in 4.2 per 1,000 hospitalisations, based on a prospective large Asian cohort studies [5]. Drug allergy is an immunologically mediated DHR that should not be confused with intolerance or side effect that is pharmacologically mediated [6]. For example, less than 15% of patients with reported beta-lactam allergies were found to have genuine allergy after evaluation, which is similar to western cohorts [4]. A good understanding of the pathomechanism of an adverse drug reaction is therefore crucial in the correct labelling of a patient’s reaction as this has significant implications in clinical management, from choice of appropriate antibiotics to prevention of a catastrophic outcome due to re-exposure [7].

As clarification of history of a drug reaction alone is sometimes insufficient to confirm a diagnosis, additional in vitro and in vivo testing are often required for further evaluation [8, 9], with the objective of identifying not just the putative active ingredient of the drug, but eventually also define the phenotype and endotype associated with biomarkers of the DHR [10-12]. Comprehensive testing may not be possible in certain locations in the Asia-Pacific
region as specialized immunology/allergy/dermatology centres that provide drug allergy testing services are not always widely available. Furthermore, there is an insufficient critical mass of allergy/immunology specialists or lack of funding in the public health system [13]. Knowledge gaps on drug allergy/hypersensitivity among health care providers [14], infrastructural and access issues in different geographical regions further contribute to heterogeneous practices in drug allergy diagnostics within many geographical regions [15].

In this study, we sought to survey the diagnostic procedures and practices in drug allergy/hypersensitivity among member countries of APAAACI. The specific objectives of this survey were (1) to increase the regional awareness on the requirement of specialized/dedicated allergy clinics/centres for drug allergy testing; (2) to train allergists in performing diagnostic tests; as well as (3) to facilitate exchange of knowledge and research collaborations among society members.

**MATERIALS AND METHODS**

The questionnaire was initiated and circulated to members of the APAAACI Drug Allergy Special Committee for evaluation in November 2019 through the software SurveyMonkey® (SurveyMonkey, San Mateo, CA, USA). The questions covered both diagnostic and therapeutic practices in drug allergy/hypersensitivity. The final questionnaire comprised a total of 41 questions, which was approved by the entire committee (Supplementary material 1). The questionnaire was then converted into a web-based questionnaire by the APAAACI Secretariat and sent electronically to 15 member societies and 3 individual members of APAAACI. All respondents were given 6 weeks (January 23, 2020 to March 6, 2020) to reply with a final reminder at the end of 6 weeks. The responses were then collated by the APAAACI Secretariat, and the numbers and percentages of respondents for each question were collated.

**RESULTS**

A total of 16 respondents representing 13 Asian countries participated in the survey as shown in Table 1. Respondents comprised 13 of 15 member societies and 1 of 3 individual members. Member societies submitted from 1 to 4 responses each as some delegated the respondents to key members from paediatrics or adult allergy, or to other subspecialties primarily involved in the evaluation of drug allergy/hypersensitivity in their country e.g., dermatology. The total of 26 responses were then consolidated. Some respondents left questions which they were unable to answer blank, hence the total number of responses (n) were less than the number of respondents (N) for several questions.

There were dedicated allergy clinics in all countries surveyed to perform drug allergy/DHR tests while 68.8% also performed these tests in dermatology clinics. Among the respondents, there were more of such services in adult (87.4%) than paediatric (75.0%) clinics; with the number of adult clinics ranging from 1 to 37 per country, to 1 to 10 paediatric clinics per country. Various published international or regional guidelines were used by the respondents while performing drug hypersensitivity diagnostic procedures as shown in Table 2 [16-52]. Among these, the guidelines from The European Academy of Allergy and Clinical Immunology (EAACI) were the most widely used by as shown in Table 3, as EAACI’s European Network for Drug Allergy (ENDA) had the most number of published drug allergy/hypersensitivity
guidelines pertaining to the evaluation of specific drug classes e.g., beta-lactam antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs).

In the investigation of immediate DHR, measurement of serum tryptase was available among 86.7% of respondents. All clinics performed skin prick and intradermal tests. The drugs most commonly skin-tested were cephalosporins (86.7%), penicillins (80.0%), general anaesthesia (73.3%), and local (66.7%) anaesthetic agents as shown in Table 4. Majority obtained penicilloyl polylysine (PPL) (60.0%) and minor determinant mix (66.7%) commercially. In most instances, the clinicians (allergists/dermatologist) prepared the drugs themselves for skin tests. Commercially available specific IgE in vitro tests such as ImmunoCAP (Phadia AB, Uppsala, Sweden) (92.9%) and Radioallergosorbent test (25.7%) were available in 10 countries. In-house preparation of specific IgE tests was produced in 5 countries. The drugs commonly tested using these in vitro methods included penicilloyl G (61.5%); penicilloyl V, ampicilloyl, amoxicilloyl (55.5% respectively), and cefaclor (46.2% respectively). The basophil activation test was available for 60.0% respondents.

Drug patch testing was available to 75.0% respondents for the investigation of nonimmediate (delayed) DHR. Antibiotics (beta-lactams and non–beta-lactams) (83.3%) and antiepileptics

Table 1. Characteristics of respondents

| Characteristic | No. (%) |
|---------------|---------|
| No. of respondents from the APAAACI Member Society* (n = 26) | |
| Korean Academy of Asthma Allergy and Clinical Immunology (KAAACI) | 4 (15.4) |
| Allergy and Clinical Immunology Society (Singapore) (ACIS) | 3 (11.5) |
| Hong Kong Institute of Allergy (HKIA) | 3 (11.5) |
| Japanese Society of Allergology (JSA) | 3 (11.5) |
| Australasian Society of Clinical Immunology and Allergy (ASCIA) | 2 (7.7) |
| Malaysian Society of Allergy and Immunology (MSAI) | 2 (7.7) |
| Philippines Society of Allergy, Asthma and Immunology (PSAAI) | 2 (7.7) |
| Allergy, Asthma and Immunology Association of Thailand (AAIAT) | 1 (3.8) |
| Bangladesh Society of Allergy and Immunology (BSAI) | 1 (3.8) |
| Chinese Society of Allergology (CSA) | 1 (3.8) |
| Indian College of Allergy, Asthma and Applied Immunology (ICAAI) | 1 (3.8) |
| Indonesian Society of Allergy and Immunology (ISAI) | 1 (3.8) |
| Mongolian Society of Allergology (MSA) | 1 (3.8) |
| Individual members | 1 (3.8) |

| Composition of APAAACI respondents (n = 26) | |
|------------------------------------------|---------|
| Member society | 25 (96.2) |
| Individual member | 1 (3.8) |

| Types of clinic that perform evaluation of drug hypersensitivity (n = 16) | |
|-----------------------------|---------|
| Allergy clinic | 16 (100) |
| Dermatology clinic | 11 (68.8) |

| Category of clinics (n = 16) | |
|-----------------------------|---------|
| Adult | 14 (87.5) |
| Paediatric | 12 (75.0) |

| Tests available (n = 16) | |
|--------------------------|---------|
| Skin prick test and intradermal test | 16 (100) |
| Serum tryptase | 13 (86.7) |
| Specific IgE in vitro tests | 12 (75.0) |
| Drug patch test | 12 (75.0) |
| Pharmacogenomic tests | 12 (75.0) |
| Drug provocation tests | 11 (68.8) |
| Basophil activation test | 9 (56.3) |
| Lymphocyte transformation test | 8 (50.0) |

*Nonresponders: Allergy and Immunology Society of Sri Lanka (AISS) and Taiwan Academy of Allergy Asthma and Clinical Immunology (TAAACI).
Table 2. Guidelines used for references (n = 16)

| Guideline                                                                 | No. |
|---------------------------------------------------------------------------|-----|
| **Drug allergy**                                                          |     |
| EAAIC position paper on how to classify cutaneous manifestations of drug hypersensitivity 2019 | 13  |
| Drug allergy: an updated practice parameter 2010                          | 7   |
| Drug allergy passport and other documentation for patients with drug hypersensitivity – an ENDA/EAAIC Drug Allergy Interest Group Position Paper 2016 | 3   |
| In vitro tests for drug hypersensitivity reactions: an ENDA/EAAIC Drug Allergy Interest Group position paper 2016 | 2   |
| BSACI guidelines for the management of drug allergy 2009                   | 1   |
| EAAIC task force report: recognising the potential of the primary care physician in the diagnosis and management of drug hypersensitivity 2018 | 1   |
| **Antibiotic allergy**                                                    |     |
| Towards a more precise diagnosis of hypersensitivity to beta-lactams — an EAAIC position paper | 11  |
| Hypersensitivity reactions to non–beta-lactam antimicrobial agents, a statement of the WAO special committee on drug allergy 2013 | 4   |
| Update on the evaluation of hypersensitivity reactions to beta-lactams. Allergy 2009 | 3   |
| Diagnosis of Immediate Allergic Reactions to Beta-Lactam Antibiotics 2003 | 3   |
| **NSAIDs hypersensitivity**                                               |     |
| Hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs) – classification, diagnosis and management: review of the EAAIC/ENDA and GA2LEN/HANNA | 9   |
| Statement of the Spanish Society of Allergology and Clinical Immunology on provocation tests with aspirin/nonsteroidal anti-inflammatory drugs 2020 | 2   |
| **Intraoperative anaphylaxis/anaesthetic agents**                         |     |
| EAAIC position paper on the investigation of perioperative immediate hypersensitivity reactions 2019 | 9   |
| BSACI guidelines for the investigation of suspected anaphylaxis during general anaesthesia 2010 | 2   |
| **Radiocontrast media**                                                   |     |
| Management of hypersensitivity reactions to iodinated contrast media 2005 | 5   |
| Clinical practice guidelines for diagnosis and management of hypersensitivity reactions to contrast media 2016 | 3   |
| **Vaccine adverse reactions**                                             |     |
| Administration of influenza vaccines to egg allergic recipients: a practice parameter update 2017 | 7   |
| Adverse reactions to vaccines practice parameter 2012 update              | 3   |
| **Skin tests**                                                            |     |
| In vivo diagnosis of allergic diseases -- allergen provocation tests 2015  | 7   |
| Skin test concentrations for systemically administered drugs -- an ENDA/EAAIC Drug Allergy Interest Group position paper 2013 | 5   |
| ASCIA skin prick test manual 2016                                         | 5   |
| Patch testing in nonimmediate drug eruptions 2008                          | 1   |
| Allergy diagnostic testing: an updated practice parameter 2008             | 4   |
| **In vitro tests**                                                        |     |
| In vitro tests for drug hypersensitivity reactions: an ENDA/EAAIC Drug Allergy Interest Group position paper 2016 | 4   |
| The clinical utility of basophil activation testing in diagnosis and monitoring of allergic disease 2015 | 2   |
| **Drug provocation test**                                                 |     |
| Risk and safety requirements for diagnostic and therapeutic procedures in allergology: World Allergy Organization Statement 2016 | 6   |
| EAAIC/GA2LEN guideline: aspirin provocation tests for diagnosis of aspirin hypersensitivity 2007 | 4   |
| Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations 2003 | 4   |
| **Desensitization**                                                       |     |
| Desensitization in delayed drug hypersensitivity reactions -- an EAAIC position paper of the Drug Allergy Interest Group 2013 | 8   |
| General considerations on rapid desensitization for drug hypersensitivity - a consensus statement 2010 | 3   |
| **Pharmacogenomic testing**                                               |     |
| Clinical pharmacogenetics implementation consortium of the pharmacogenomics | 3   |
| **Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis**                   |     |
| UK guidelines for the management of Stevens-Johnson syndrome/toxic epidermal necrolysis in adults 2016 | 4   |
| **Mastocytosis and mast cell activation syndromes**                       |     |
| Drug hypersensitivity in clonal mast cell disorders: ENDA/EAAIC position paper 2015 | 3   |
| Mastocytosis and allergic diseases 2014                                   | 1   |
| **Paediatric drug allergy**                                               |     |
| Diagnosis and management of drug-induced anaphylaxis in children: an EAAIC position paper 2019 | 7   |
| Drug allergy: diagnosis and management of drug allergy in adults, children and young people 2014 | 4   |
| EAAIC/ENDA position paper: diagnosis and management of hypersensitivity reactions to NSAIDs in children and adolescents 2018 | 3   |
| The RCPCH care pathway for children with drug allergies: an evidence and consensus based national approach 2011 | 1   |

EAACI, European Academy of Allergy and Clinical Immunology; ENDA, European Network for Drug Allergy; BSACI, British Society of Allergy and Clinical Immunology; WAO, World Allergy Organization; ASCIA, Australasian Society of Clinical Immunology and Allergy; GA2LEN, Global Allergy and Asthma European Network; RCPCH, Royal College of Paediatrics and Child Health.
(58.3%) were the most frequently patch-tested drugs as shown in Table 5. Stevens-Johnson syndrome (SJS) (75.0%), drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms (DRESS) (66.7%), acute generalized exanthematous pustulosis (AGEP), and maculopapular eruptions (58.3% respectively) were the common indications for drug patch testing. Most (75.0%) used the commercialized form of drugs prepared in-house, in both 10% and 30% dilution using petrolatum (or aqueous) to perform the patch test. Less than half of the respondents tested the colouring (41.7%), and preservative (33.0%). All performed the first patch test reading after 48 hours of occlusion. Only 69.2% performed the second reading at 96 hours, and 15.4% performed a day-7 reading.

Lymphocyte transformation test (LTT) was only used in research settings among 75% of respondents, while only 12.5% used LTT for research and clinical care. The drugs tested by LTT were mainly NSAIDs and selective cyclooxygenase (COX)-2 inhibitors (42.9% respectively); beta-lactam antibiotics and antituberculous drugs (28.6% respectively).

Drug provocation test (DPT) was performed by 93.8% respondents mainly to exclude the diagnosis of drug hypersensitivity for nonsuggestive history or nonspecific symptoms (93.3%) as shown in Table 6. Preparation of drugs for drug provocation was done mainly by doctors (80.0%). Almost all performed open DPT (93.3%) with only 33.3% doing single-blind placebo control DPT. None routinely performed double blind placebo control drug provocation. The most common route of administration of the challenge drug was oral using tablet, syrup, or capsule. For the diagnosis of aspirin hypersensitivity, aspirin provocation was performed in all countries with oral provocation (100.0%) as the most common route used.

Pharmacogenetics testing for HLA-B*15:02 prior to prescribing carbamazepine, HLA-B*58:01 for allopurinol, and HLA-B*57:01 for abacavir, was not mandatory or recommended by local pharmacoregulatory agencies in the majority of countries in the region as shown in Table 7.
### Table 4. Investigations for immediate drug hypersensitivity

| Characteristic                                | No. (%) |
|-----------------------------------------------|---------|
| **Skin prick test and intradermal test**     |         |
| Drugs commonly tested (n = 15)               |         |
| Cephalosporins                               | 13 (86.7) |
| Penicillin                                    | 12 (80.0) |
| General anaesthetic agents                    | 11 (73.3) |
| Local Anaesthetic agents                      | 10 (66.7) |
| Radiocontrast media                           | 9 (60.0) |
| NSAIDs                                        | 6 (40.0) |
| Carbapenems                                   | 4 (26.7) |
| Non–beta-lactam antibiotics                   | 4 (26.7) |
| Source of penicilloy polylysine (n = 10)      |         |
| Diater®                                       | 6 (60.0) |
| In-house                                      | 3 (30.0) |
| Source of minor determinant mix (n = 9)       |         |
| Diater®                                       | 6 (66.7) |
| In-house                                      | 3 (33.3) |
| Persons who prepare the drugs for skin testing (n = 15) |         |
| Allergist                                     | 15 (100) |
| Nurse/clinicians/specialist                   | 4 (26.7) |
| Pharmacist                                    | 3 (20.0) |
| Dermatologist                                 | 1 (6.7) |
| **Specific IgE in vitro tests**               |         |
| Types of available assay (n = 15)             |         |
| Commercial                                    | 8 (53.3) |
| In-house preparation                          | 3 (20.0) |
| Both                                          | 2 (13.3) |
| Neither                                       | 2 (13.3) |
| Types of commercial assay used (n = 14)       |         |
| CAP-FEIA (Phadia ImmunoCAP®)                   | 13 (92.9) |
| RAST (Radioallergosorbent test®)              | 5 (35.7) |
| Drugs commonly tested using these in vitro methods (n = 13) |         |
| Penicilloy G                                  | 8 (61.5) |
| Penicilloy V                                  | 7 (53.8) |
| Ampicilloy                                    | 7 (53.8) |
| Amoxicilloy                                   | 7 (53.8) |
| Alfa-gal                                      | 6 (46.2) |
| Cefaclor                                      | 6 (46.2) |
| Chlorhexidine                                 | 2 (15.4) |
| Gelatin                                       | 2 (15.4) |
| General anaesthetic agents                    | 2 (15.4) |
| NSAIDs                                        | 2 (15.4) |
| Suxamethonium                                 | 2 (15.4) |
| Cephalosporins                                | 1 (7.7) |
| Morphine                                      | 1 (7.7) |
| Pholcodine                                    | 1 (7.7) |
| No. with serum tryptase available for test (n = 15) | 13 (86.7) |
| No. with basophil activation test available for drug hypersensitivity (n = 15) | 9 (60.0) |

NSAIDs, nonsteroidal anti-inflammatory drugs.

### Table 5. Investigations for nonimmediate (delayed) drug hypersensitivity

| Characteristic                                | No. (%) |
|-----------------------------------------------|---------|
| **Drug patch test**                           |         |
| Drugs commonly tested (n = 12)                |         |
| Antibiotics (beta-lactam)                     | 10 (83.3) |
| Antibiotic (non–beta-lactams)                 | 10 (83.3) |
| Antiepileptics                                | 7 (58.3) |
| Antituberculous drugs                         | 5 (41.7) |
| NSAIDs and Selective COX-2 inhibitor          | 5 (41.7) |
| Cotrimoxazole                                 | 5 (41.7) |

(continued to the next page)
Table 5. (Continued) Investigations for nonimmediate (delayed) drug hypersensitivity

| Characteristic                                                                 | No. (%) |
|-------------------------------------------------------------------------------|---------|
| **Radiocontrast media**                                                       | 2 (16.7)|
| **Hydroxyzine**                                                               | 1 (8.3) |
| **Corticosteroids**                                                           | 1 (8.3) |
| **Indications (n = 12)**                                                      |         |
| Stevens-Johnson syndrome                                                      | 9 (75)  |
| Drug-induced hypersensitivity syndrome                                          | 8 (66.7)|
| Acute generalized exanthematous pustulosis                                     | 7 (58.3)|
| Maculopapular eruption                                                         | 7 (58.3)|
| Toxic epidermal necrolysis                                                     | 6 (50.0)|
| Fixed drug eruption                                                            | 6 (50.0)|
| Drug-induced immune-bullous eruptions                                          | 3 (25.0)|
| Drug-induced lupus erythematosus                                               | 3 (25.0)|
| Symmetrical drug-related intertriginous and flexural exanthema                 | 3 (25.0)|
| Drug-induced vasculitis                                                        | 3 (25.0)|
| **Used in clinical or research setting (n = 13)**                              |         |
| Clinical                                                                      | 9 (69.2)|
| Research                                                                      | 2 (15.4)|
| Both                                                                         | 2 (15.4)|
| **Formulation of drugs (n = 12)**                                             |         |
| Commercialized form of drugs                                                  | 9 (75.0)|
| Pure substance                                                                | 5 (41.7)|
| **Dilution of drugs (n = 13)**                                                |         |
| 10% and 30%                                                                   | 8 (61.5)|
| 1%                                                                           | 6 (46.2)|
| 5%                                                                           | 3 (23.1)|
| 0.1%                                                                         | 3 (23.1)|
| **Vehicle used (n = 13)**                                                     |         |
| Petrolatum                                                                    | 11 (84.6)|
| Water                                                                         | 5 (38.5)|
| Alcohol                                                                       | 1 (7.7)|
| **Source of drugs for patch test (n = 13)**                                   |         |
| In-house                                                                       | 9 (69.2)|
| Chemotechnique®                                                                | 3 (23.1)|
| Commercial                                                                    | 2 (15.4)|
| **Other agent tested (n = 12)**                                               |         |
| Photoallergen                                                                  | 7 (58.3)|
| Colouring                                                                      | 5 (41.7)|
| Preservative                                                                   | 4 (33.3)|
| Excipient                                                                      | 3 (25.0)|
| **Reading of patch test (n = 13)**                                            |         |
| 48 Hours                                                                       | 13 (100)|
| 96 Hours                                                                       | 9 (69.2)|
| 20 Minutes                                                                     | 2 (15.4)|
| Day 7                                                                         | 2 (15.4)|
| **Lymphocyte transformation test (LTT)**                                       |         |
| Type of LTT service (n = 8)                                                    |         |
| Research                                                                       | 6 (75.0)|
| Clinical                                                                       | 1 (12.5)|
| Clinical and research                                                          | 1 (12.5)|
| Facility that provide LTT (n = 8)                                             |         |
| In-house                                                                       | 4 (50.0)|
| Another facility within the country                                            | 4 (50.0)|
| **Drugs tested using LTT (n = 7)**                                            |         |
| NSAIDs and Selective COX-2 inhibitor                                           | 3 (42.9)|
| Contact allergens                                                              | 3 (42.9)|
| Antibiotics (beta-lactam)                                                      | 2 (28.6)|
| Antituberculous drugs                                                         | 2 (28.6)|
| Antibiotic (non–beta-lactams)                                                  | 1 (14.3)|
| Antiepileptics                                                                | 1 (14.3)|

NSAIDs, nonsteroidal anti-inflammatory drugs.
Table 6. Drug provocation tests

| Characteristic                                                                 | No. (%)   |
|-------------------------------------------------------------------------------|-----------|
| Indications (n = 15)                                                          |           |
| To exclude hypersensitivity (for nonsuggestive history/nonspecific symptoms)  | 14 (93.3) |
| To exclude cross-reactivity of related drugs in proven hypersensitivity (e.g., cephalosporin in a penicillin allergic) | 12 (80.0) |
| To provide safe pharmacologically/structurally nonrelated drugs in proven hypersensitivity (e.g., beta-lactam) | 11 (73.3) |
| Definitive diagnosis in suggestive history with negative, nonconclusive or nonavailable allergological tests | 11 (73.3) |
| Preparation of drugs (n = 15)                                                 |           |
| Doctor                                                                        | 12 (80.0) |
| Pharmacist                                                                    | 6 (40.0)  |
| Nurse                                                                         | 5 (33.3)  |
| Types of provocation (n = 15)                                                 |           |
| Open challenge                                                                | 14 (93.3) |
| Single blind placebo control                                                   | 5 (33.3)  |
| Routes of administration (n = 15)                                             |           |
| Oral                                                                          |           |
| Tablet                                                                        | 14 (93.3) |
| Syrup                                                                         | 11 (73.3) |
| Capsule                                                                       | 8 (53.3)  |
| Intravenous                                                                   | 9 (60.0)  |
| Subcutaneous                                                                  | 6 (40.0)  |
| Intramuscular                                                                 | 1 (6.7)   |
| The common routes of aspirin provocation (n = 15)                             |           |
| Oral                                                                          | 15 (100)  |
| Bronchial (inhalation) L-lysine-aspirin challenge                             | 1 (6.7)   |

Table 7. Pharmacogenetics testing

| Characteristic                                                                 | No. (%)   |
|-------------------------------------------------------------------------------|-----------|
| Mandatory testing before prescribing (n = 12)                                 |           |
| None of the drugs below                                                       | 7 (58.3)  |
| HLA-B*1502 (carbamazepine)                                                    | 3 (25.0)  |
| HLA-B*5701 (abacavir)                                                         | 2 (16.7)  |
| HLA-B*5801 (allopurinol)                                                      | 1 (8.3)   |
| Recommended testing before prescribing (n = 11)                               |           |
| None of the drugs below                                                       | 5 (45.5)  |
| HLA-B*5801 (allopurinol)                                                      | 4 (36.4)  |
| HLA-B*1502 (carbamazepine)                                                    | 3 (27.3)  |
| HLA-B*5701 (abacavir)                                                         | 0 (0)     |

HLA, human leukocyte antigen.

DISCUSSION

Since the World Allergy Organization (WAO) International Survey on Diagnostic Procedures and Therapies in Drug Allergy/Hypersensitivity was carried out and published almost a decade ago [53], there have been several other physician surveys on the diagnosis and management of drug allergy/hypersensitivity to date. By far the area with the highest priority has been on penicillin [54] and beta-lactam allergy [55], with surveys led by EAACI’s ENDA group and the British Society of Allergy and Clinical Immunology [56]. There have also been other surveys done specifically by specialists involved in the management of specific DHRs, e.g., aspirin desensitization for coronary artery disease among interventional cardiologists [57], and SJS/toxic epidermal necrolysis among directors managing Burns Units in the United States [58].

In the WAO 2009 survey, APAAACI member countries comprised 26.4% of the 82 responses from the then 77 regional and national member societies of WAO. Since then, there have
been several significant changes in the practice of drug allergy/DHR in our region. Firstly, we have had new member societies join APAAACI since the 2009 survey: Bangladesh Society of Allergy and Immunology, Mongolian Society of Allergology and Allergy and Clinical Immunology Society of Sri Lanka. In addition, we also have 2 individual members from Pakistan and 1 from Myanmar, representing countries with emerging interests in allergy and clinical immunology. As such this is likely to contribute to an increase in the number of new allergy/immunology practices within our region.

Secondly, there are now also many more published international and regional guidelines on important areas in drug allergy/hypersensitivity, including risk and safety requirements for diagnostic and therapeutic procedures [23], desensitization [44,45], pharmacogenetic testing [46], and paediatric drug allergy [50-52]. In contrast to 2009 where the American Academy of Allergy Asthma and Immunology/American College of Allergy Asthma and Immunology Practice Parameters were the most commonly accessed, this has since been overtaken by the EAACI/ENDA guidelines.

In terms of diagnostic tests, the use of skin prick and intradermal tests for immediate DHR appears to be similar to 2009, with similar types of drugs being the most commonly tested (beta-lactam antibiotics, general and local anaesthetic agents). However, in our current survey, there are 2 interesting trends. Firstly, there were marginally more respondents who answered to do skin testing for cephalosporins than penicillins. This may be a reflection of the increasing use of cephalosporins in Asia and hence increase in DHR [59]; intermittent difficulties in accessing commercial PPL and minor determinants, and emerging safety data of direct amoxicillin oral provocation tests in low-risk patients without the need for prior skin testing [60]. Secondly, iodinated contrast media (ICM) has now emerged as one of the “new” drugs for which skin testing has become increasingly used, likely for several reasons. These include the increasing incidence of solid organ cancers in the region, in particular with our ageing population; the increasing need for repeated computed tomography scans/magnetic resonance imaging for follow-up and surveillance increasing the risk of developing DHR, and because of the extensive work done by our colleagues in Korea on ICM hypersensitivity [61].

For nonimmediate DHR, in contrast to 2009, there is now increased use of drug patch tests in particular for beta-lactam and non–beta-lactam antibiotics, antiepileptic drugs and antituberculous drugs; and for selected patients with more severe reactions like SJS, DRESS, and AGEP [62]. These are much easier to carry out and interpret when performed by physicians trained in doing and interpreting these tests e.g., dermatologists, than setting up in vitro assays like LTT and enzyme-linked immunosorbent spot (Elispot) assays [63]. Many of the in vitro tests for nonimmediate reactions remain limited in their use to academic medical centres with links to research laboratories which carry out these tests. With the recognition of phenotypes and endotypes in various DHR, measurement of different cytokines, such as gamma-interferon, interleukin (IL)-5, IL-6, and IL-40 may in future be increasingly useful for the diagnosis of nonimmediate reactions [9, 11].

In the area of pharmacogenomic testing, even though there has been increasing interest in the risk of severe cutaneous adverse reactions (SCAR) in Asians with the use of carbamazepine and allopurinol, it may appear unusual that to date less than half the countries in the APAACI region mandate HLA genotype testing prior to prescription. This is likely to be due to heterogeneous ethnicities even within the same geographical region limiting the positive predictive value of testing, different health care financing systems,
relatively high costs of HLA testing which may not be government subsidized, and limited availability to alternative lower-cost drugs that make mandatory testing not cost-effective, especially in countries where healthcare financing is based on a copayment system rather than universal health care [64-68]. Nonetheless, nongenetic risk factors (e.g., chronic kidney disease) [69] and other HLA-genetic risk factors [70] need to be considered in the risk stratification for high-risk drugs like allopurinol.

There are several limitations in this survey. Firstly, the difficulties with validation, equity, and interpretation of responses. For instance, one centre in a large country with a large population that performs all the possible investigations available may seem to suggest that all types of tests are widely available. However, this is not the case as a vast majority of the population will not be able to access the service due to limited availability or difficulties accessing specialist centres e.g., rural practices. Likewise, for economies of scale, there may only be 1 or 2 centres in each country that performs ICM skin tests versus multiple centres in one country that performs ICM skin tests but none in others. Thus, the overall results of this survey will need to be geographically contextualized.

Secondly, we did not look at the discrepancies among responses within a member society, nor ask that each society consolidate responses on behalf of the member society. The survey was administered unfortunately when Asia was just at the start of the COVID-19 outbreak, so it was not feasible to coordinate responses. Discrepancies may or may not be present depending on whether the respondents consolidated responses on behalf of his/her geographical region or forwarded to members actively involved in managing drug allergy patients, and if so whether adult or paediatrics or both.

Thirdly, the types and frequency of tests used may be a result of differences in the type of practice of the respondents, and composition of the base-specialties in the allergy/immunology community managing drug allergy/hypersensitivity in the region. Between adult and paediatric allergists, the scope of procedures used (e.g., direct amoxicillin challenges being safe in low-risk children without a need for skin tests [71]); and the scope of drugs tested may differ (e.g., anaphylaxis to general anaesthetic agents being more common among adults than children). Some practices may also manage both children and adults. Likewise, allergists with dermatology as a base-specialty may also perform patch tests more frequently than nondermatologists.

Fourthly, there are other areas in which this survey has merely provided preliminary information for which further details are lacking. Examples include differences between adult and paediatric drug allergy/hypersensitivity clinical practices, the use of intradermal testing with delayed readings for nonimmediate reactions, and variations in DPT protocols e.g., the use a single dose versus multidose DPT, in particular beta-lactam allergy. As this survey was already considerably lengthy, follow-up surveys on these specific areas of interest will be considered.

In conclusion, notable changes in the past decade in drug allergy/hypersensitivity diagnostics within our region include increased use of European guidelines from EAACI/ENDA, use of skin testing for ICM hypersensitivity and drug patch testing for nonimmediate drug hypersensitivity. The use of HLA genotype testing prior to new carbamazepine, allopurinol and abacavir prescriptions remain variable throughout the region despite strong associations of SCAR with Asian ethnicity for a variety of reasons. The results of this survey form a useful
framework for developing educational and training needs and for improving access to drug allergy diagnostic and treatment modalities across APAAACI member societies.

SUPPLEMENTARY MATERIAL

Supplementary material 1 can be found via https://apallergy.org/src/sm/apallergy-10-e36-s001.pdf

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