A World Allergy Organization International Survey on Diagnostic Procedures and Therapies in Drug Allergy/Hypersensitivity

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Objective: To study the diagnostic and treatment modalities used in drug allergy/hypersensitivity among members of the World Allergy Organization (WAO).

Methods: A questionnaire comprising 39 questions was circulated electronically to member societies, associate member societies, and regional and affiliate organizations of WAO between June 29, 2009, and August 9, 2009.

Results: Eighty-two responses were received. Skin testing was used by 74.7%, with only 71.4% having access to penicillin skin test reagents. In vitro–specific IgE tests were used by 67.4%, and basophil activation test was used by 54.4%. Lymphocyte transformation tests were used by 36.8% and patch tests by 54.7%. Drug provocation tests were used by 68.4%, the most common indication being to exclude hypersensitivity where history/symptoms were not suggestive of drug hypersensitivity/allergy (76.9%). Rapid desensitization for chemotherapy, antibiotics, or biologic agents was used by 69.6%. Systemic corticosteroid was used in the treatment of Stevens–Johnson syndrome by 72.3%, and high-dose intravenous immunoglobulins in toxic epidermal necrolysis by 50.8%. Human leukocyte antigen screening before prescription of abacavir was used by 92.9% and before prescription of carbamazepine by 21.4%.

Conclusions: 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 WAO member societies.

Key Words: desensitization, drug allergy, hypersensitivity, skin tests

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Drug allergy/hypersensitivity[1] is a common problem seen by general and subspecialty adult and pediatric outpatient clinics,[2] inpatient wards,[3] and emergency department.[4] Among specialists, patients with drug allergy/hypersensitivity may present to an allergologist,[5] dermatologist, or other organ-based specialist depending on the type, extent, and severity[6–9] of clinical manifestations. Although guidelines for the diagnosis, evaluation, and treatment of drug allergy/hypersensitivity have been available for more than a decade, clinical practice is heterogenous across the world and indeed even within districts/regions in the same country. This may be influenced by different origins of undergraduate and postgraduate allergological training (dermatology, pulmonology, or allergy/immunology[10,11]), type of allergological practice (private, government practice, clinical or research-based institution), funding mechanisms, accessibility to various types of diagnostic tests, availability of basic versus tertiary practice infrastructure/laboratory equipment, and many other factors.[12]

OBJECTIVE

The objective of this survey was to study the diagnostic and treatment modalities used in drug allergy/hypersensitivity among members of the World Allergy Organization (WAO), with the results forming the framework for developing the educational and training needs and for improving access to drug allergy diagnostic and treatment modalities across WAO member societies. The specific aims of this survey were

1. To increase the global awareness on the requirement of specialized/dedicated allergy clinics/centers for drug allergy testing and management;

2. To lay foundations toward a globally standardized clinical practice of drug allergy management;
3. To train allergists in performing diagnostic tests;
4. To facilitate exchanges of knowledge and collaborations among allergy centers in different countries.

METHODS

The questionnaire was initiated and circulated to members of the WAO Drug Allergy Special Committee for evaluation in January 2009. The questions covered both diagnostic and therapeutic practices in drug allergy/hypersensitivity. The final questionnaire comprised a total of 39 questions, which was approved by the entire committee (Appendix 1).

The questionnaire was then converted into a Web-based questionnaire by the WAO Secretariat and sent electronically to 77 regional and national member societies of WAO. If representatives of member societies were unable to complete the specific questions on diagnostic tests and therapies available in their own country/region, they were asked to recommend the questionnaire to centers that would be able to respond to the questions. All respondents were given 6 weeks (June 29, 2009 to August 9, 2009) to reply. The responses were then collated by the WAO Secretariat, and the numbers and percentages of respondents for each question were collated.

RESULTS

There were a total of 82 responses comprising respondents from WAO member societies (95%), associate member societies (3.7%), regional organizations (3.7%), and affiliate organizations (1.1%). There were 13 additional responses from individuals who were recommended by the WAO member society representative who was not able to complete the specific questions on diagnostic tests and therapies available in the country/region. The geographical origin of all respondents was Europe (49.1%), Asia Pacific (26.4%), Latin America (15.1%), North America (5.7%), and Africa/Middle East (3.7%).

Among all responders, 95.3% and 55.6% responded that dedicated allergy clinics and dermatology clinics, respectively, in their country conducted evaluations for drug allergy/hypersensitivity. Among responders, 61.8% practiced in countries/regions where there were drug allergy centers/clinics dedicated to adult care, and 64.7% practiced where such centers dedicated to pediatric care were available.

The most widely used clinical practice guideline was the American Academy of Allergy Asthma and Immunology/American College of Allergy, Asthma and Immunology (AAAAI/ACAAI) 2008 Practice Parameter Update: Allergy diagnostic testing[13] (59.7%), followed by the European Academy of Allergy Asthma and Clinical Immunology (EAACI) guidelines on provocation tests for aspirin and other drugs[14,15] (41.6%). The remaining guidelines used[16–26] are summarized in Table 1.

For immediate reactions, skin testing was used by 74.7%, with the majority (67.6%) using this for both clinical care and research. Only 71.4% had access to penicillin skin test reagents, where the commercial Diater product (Diater Laboratories, Madrid, Spain) for penicilloyl polylysine and minor determinant mix was used by 49.1% and in-house reagents by 26.3%. Drugs that were commonly skin tested were penicillins (87.5%), cephalosporins (77.8%), local anesthetic agents (75.0%), general anesthetic agents (61.1%), and non–beta-lactam antibiotics (50.0%) (Table 2). Drugs for skin testing were prepared by the allergist in 65.3%, nurse practitioner/specialist in 34.7%, and pharmacist in 27.8%. Among some respondents, there was more than 1 practitioner who could prepare the drugs for skin testing. Negative skin tests were followed by a drug provocation test (DPT) in only 56.2% of cases.

In vitro–specific IgE tests were used by 67.4% of respondents. The tests commercially available were the immunoCAP-fluorescent enzyme immunoassay (CAP-FEIA) (previously Pharmacia now called Phadia, Uppsala, Sweden) in 80.6%, radioallergosorbent test (RAST) in 56.5%, flow cytometric cellular allergen stimulation test (Buhlmann Labs, Switzerland) in 25.8%, cellular allergen stimulation test enzyme-linked immunosorbent assay (CAST-ELISA) (Buhlmann Labs) in 24.2%, and flow cytometry-2-cellular allergen stimulation test (Flow-2-CAST) (Buhlmann Labs) in 14.5% (Table 3). In-house assays most commonly used were radioallergosorbent test (48.6%) and radioimmunoassays (22.9%). The most commonly tested drugs were penicillins (93.7%), cephalosporins (61.9%), general anesthetic agents (36.5%), and nonsteroidal anti-inflammatory drugs (NSAID) (27.0%). Other tests available to respondents included serum total tryptase in 75.0% and basophil activation test in 54.4%.

For nonimmediate reactions, lymphocyte transformation tests (LTTs) were used by 36.8% of respondents, the majority for both clinical care and research (48.6%) but more for research (37.1%) than for clinical care (14.3%) alone. Where available, in-house LTT was used by 52.9%, sent to another facility in the same region/country by 32.4%, and sent out of the region/country by 14.7%. The drugs most commonly tested using LTT were beta-lactam antibiotics (77.8%), non–beta-lactam antibiotics (58.3%), and NSAID/selective cyclooxygenase inhibitors (36.1%). The other drugs commonly tested are listed in Table 4. The types of nonimmediate reactions most commonly tested using LTT were drug-induced hypersensitivity syndrome (DIHS) (65.6%), Stevens–Johnson syndrome (SJS) (65.6%), maculopapular exanthema (46.9%), acute generalized exanthematous pustulosis (AGEP) (46.9%), and toxic epidermal necrolysis (TEN) (46.9%). The other types of nonimmediate reactions commonly tested using LTT are shown in Table 5.

Patch tests were used for both clinical care and research (59.6%) but more for clinical care (30.8%) than for research (9.6%) alone. Commercialized form of the drug was used by 55.3%, the pure substance by 21.3%, and both by the remaining 23.4%. The most common dilutions were 1% (34.2%) and 5% (31.6%), with majority using petrolatum (90.0%). Drugs used for patch testing were obtained commercially by 55.3%, prepared in-house by 34.0%, and obtained

TABLE 1. Commonly Used Clinical Guidelines

	Europe, n (%)	Asia Pacific, n (%)	North America, n (%)	Latin America, n (%)	Africa Middle East, n (%)	Total (n = 77)
AAAAI/ACAAI 2008 Practice Parameter Update: Allergy diagnostic testing[13]	14 (18.2)	16 (19.5)	6 (7.8)	7 (9.1)	3 (3.9)	46 (59.7)
EAACI/GA2LEN 2007: Aspirin provocation tests for aspirin hypersensitivity[14]	20 (26.0)	3 (3.9)	2 (2.6)	5 (6.5)	2 (2.6)	32 (41.6)
ENDA 2003 Guidelines: DPTs[15]	21 (27.3)	6 (7.8)	1 (1.3)	3 (3.9)	1 (1.3)	32 (41.6)
ENDA 2006: Statement on penicillin skin testing[17]	17 (22.1)	4 (5.2)	1 (1.3)	4 (5.2)	2 (2.6)	28 (36.4)
ENDA 2004 Guidelines: Non-immediate allergic reactions to beta-lactam antibiotics[18]	19 (24.7)	4 (5.2)	1 (1.3)	3 (3.9)	1 (1.3)	28 (36.4)
ENDA 2003 Guidelines: Immediate allergic reactions to beta-lactam antibiotics[19]	18 (23.4)	4 (5.2)	1 (1.3)	3 (3.9)	1 (1.3)	27 (35.1)
BSACI 2009 Guidelines: Management of drug allergy[16]	12 (15.6)	11 (14.3)	0 (0.0)	2 (2.6)	1 (1.3)	26 (33.8)
ENDA 2005 Guidelines: Management of hypersensitivity to iodinated contrast media[20]	18 (23.4)	2 (2.6)	1 (1.3)	3 (3.9)	1 (1.3)	25 (32.5)
AAAAI/ACAAI 1999 Practice Parameter: Drug hypersensitivity[21]	6 (7.8)	9 (11.7)	3 (3.9)	4 (5.2)	3(3.9)	25 (32.5)
AAAAI/ACAAI 2006 Practice Parameter: Contact dermatitis[22]	10 (13.0)	3 (3.9)	4 (5.2)	4 (5.2)	1 (1.3)	22 (28.6)
SFAR/ENDA 2005 Guidelines: Reducing the risk of anaphylaxis during anaesthesia[23]	13 (16.9)	4 (5.2)	1 (1.3)	2 (2.6)	1 (1.3)	21 (27.3)
European Society of Contact Dermatitis 2001 Guidelines for the study of skin testing in investigating CADR[24]	13 (16.9)	3 (3.9)	2 (2.6)	1 (1.3)	1 (1.3)	20 (26.0)
International Contact Dermatitis Research Group (ICDRG) 1970: Criteria for patch test reading[25]	5 (6.5)	5 (6.5)	3 (3.9)	3 (3.9)	1 (1.3)	17 (22.1)
BSACI 2003 Guidelines: Suspected anaphylactic reactions associated with anaesthesia[26]	4 (5.2)	5 (6.5)	0 (0.0)	1 (1.3)	0 (0.0)	10 (13.0)

Percentage represents percentage of all 77 respondents who answered this question.

from both sources in the remaining 10.7%. In addition to the parent drug, 53.3% also tested components other than the parent drug including preservative (44.4%), coloring (37.8%), and excipient (28.9%). Patch test reading was done, and read at 20 minutes by 4.2%, 48 hours by 47.9%, 96 hours by 10.4%, and on day 7 (if days 2 and 4 are negative) by 37.5%. Photopatch tests were done by only 46.5% of respondents. Drugs most commonly used for patch testing were beta-lactam antibiotics (83.3%), non–beta-lactam antibiotics (64.6%), and corticosteroids (60.4). The drugs commonly patch tested are shown in Table 6. Patch tests were most commonly used in the diagnosis of maculopapular exanthema (66.0%), DIHS (63.8%), fixed drug eruption (61.7%), and AGEP (55.3%). The other types of nonimmediate reactions for which patch tests were commonly used are shown in Table 7.

DPTs were used by 68.4% with the most common indication being to exclude hypersensitivity where the history was not suggestive or the symptoms not specific for drug hypersensitivity/allergy (76.9%). It was used for definitive diagnosis where history was suggestive but allergological tests were negative, nonconclusive or not available by 67.7%; to exclude cross-reactivity of related drugs in proven hypersensitivity (eg, cephalosporin in a penicillin allergic individual) by 63.1%; and to provide safe pharmacologically/structurally nonrelated drugs in proven hypersensitivity (e.g. beta-lactams) by 60.0%. This is summarized in Table 8.

TABLE 2. Drugs Commonly Skin Tested

	Europe, n (%)	Asia Pacific, n (%)	North America, n (%)	Latin America, n (%)	Africa Middle East, n (%)	Region Not Specified, n (%)	Total (n = 72), n (%)
Penicillins	26 (36.1)	15 (20.8)	6 (8.3)	8 (11.1)	6 (8.3)	2 (2.6)	63 (87.5)
Cephalosporins	25 (34.7)	14 (19.4)	6 (8.3)	7 (9.7)	2 (2.6)	2 (2.6)	56 (77.8)
Local anesthetic agents	28 (38.9)	8 (11.1)	7 (9.7)	7 (9.7)	2 (2.6)	2 (2.6)	54 (75.0)
General anesthetic agents	25 (34.7)	4 (5.6)	4 (5.6)	7 (9.7)	2 (2.6)	2 (2.6)	44 (61.1)
Non-beta lactam antibiotics	21 (29.2)	6 (8.3)	3 (4.2)	4 (5.6)	1 (1.4)	1 (1.4)	36 (50.0)
Non-steroidal anti-inflammatory drugs	15 (20.8)	6 (8.3)	2 (2.6)	4 (5.6)	1 (1.4)	1 (1.4)	29 (40.3)

Percentage represents percentage of all 72 respondents who answered this question.

TABLE 3. Commercially Available In Vitro–Specific IgE Tests

	Europe, n (%)	Asia Pacific, n (%)	North America, n (%)	Latin America, n (%)	Africa Middle East, n (%)	Region Not Specified, n (%)	Total (n = 62), n (%)
CAP-FEIA	25 (40.3)	9 (14.5)	6 (9.7)	3 (4.8)	4 (6.5)	3 (4.8)	50 (80.6)
RAST	18 (29.0)	3 (4.8)	4 (6.5)	3 (4.8)	4 (6.5)	3 (4.8)	35 (56.5)
CAST-ELISA	10 (16.1)	1 (1.6)	0 (0.0)	2 (3.2)	2 (3.2)	1 (1.6)	16 (25.8)
FLOW-CAST	11 (17.7)	1 (1.6)	1 (1.6)	0 (0.0)	0 (0.0)	2 (3.2)	15 (24.2)
FLOW-2-CAST	8 (11.1)	0 (0.0)	1 (1.6)	0 (0.0)	2 (3.2)	2 (3.2)	9 (14.5)

Percentage represents percentage of all 72 respondents who answered this question.

CAP-FEIA, immunoCAP fluorescent enzyme immunoassay; CAST-ELISA, cellular allergen stimulation test enzyme-linked immunosorbent assay; FLOW-CAST, flow cytometry cellular allergen stimulation test; FLOW-2-CAST: flow cytometry-2-cellular allergen stimulation test; RAST, radio allergosorbent test.

Preparation of drugs for challenges was performed by the doctor (62.1%), pharmacist (39.4%), and nurse practitioner (25.8%), respectively. Challenges used were most commonly open challenges (75.4%), followed by single-blind placebo-controlled (44.6%), or double-blind placebo-controlled (24.6%). Oral challenges were more commonly used compared with parenteral challenges. Among oral challenges, the most commonly used formulations were tablet (80%), capsule (73.8%), or syrup (61.5%). Among parenteral challenges, subcutaneous challenges (49.2%) were more commonly done compared with intravenous (27.7%) and intramuscular (21.5%) routes.

In the survey on therapies for drug allergy, rapid desensitizations for the treatment of IgE-mediated and non–IgE-mediated anaphylactic reactions to chemotherapy, antibiotics, or biologic agents, such as monoclonal antibodies, were used by 69.6% of respondents. Systemic corticosteroids were used by 72.3% for the treatment of SJS and/or systemic manifestations of TEN, high-dose intravenous immunoglobulins for TEN by 50.8%, and other immunosuppressive drugs by 9.2% (most commonly cyclosporine). Comanagement with an intensive care/high-dependency/burns unit was commonly practiced by 67.7% of respondents, whereas comanagement with an ophthalmologist (49.2%), daily pain assessment and management (36.9%), and the use of the Severity of Illness Score for TEN for prognostication during the first 24 hours (29.2%) were less frequently practiced.

Human leukocyte antigen (HLA) testing for specific drugs associated with severe cutaneous adverse reactions (SCAR) before prescription was reported by 14 respondents (17.1%). Of these, 92.9% of respondents from the American, Australasian, Austrian, Azerbaijan, Chilean, Columbian, Dutch, French, and Swiss societies screened for HLA-B*5701 in white ancestry before the prescription of abacavir. There were 21.4% of respondents from the Australasian, Chinese, and Dutch societies who screened for HLA-B*1502 in Han Chinese or people with Asian ancestry before the prescription of carbamazepine. None of the respondents screened for HLA-B*5801 before the prescription of allopurinol in Han Chinese.

DISCUSSION

There was a good response rate for this survey, reflecting significant interest in the diagnosis and management of drug allergy/hypersensitivity among WAO member organizations. Most regions used existing guidelines and practice parameters from their own (where available) and those from other international allergy/immunology member groups and regional organizations.

There were more respondents who did not have dedicated pediatric drug allergy services in their region compared with adult drug allergy clinics. First, this could be due to children with drug allergy/hypersensitivity being usually seen within general pediatric or general pediatric allergy clinics, in contrast to adult internal medicine/specialty services, which tend to be more subspecialized. Second, most clinical and research groups in pediatric allergology tend to focus more on pediatric asthma, eczema, rhinitis, food allergy, and anaphylaxis rather than drug allergy/hypersensitivity[27–31].

TABLE 4. Drugs Commonly Tested Using LTT

	Europe, n (%)	Asia Pacific, n (%)	North America, n (%)	Latin America, n (%)	Africa Middle East, n (%)	Region Not Specified, n (%)	Total (n = 36), n (%)
Antibiotics (beta-lactams)	19 (52.8)	3 (8.3)	3 (8.3)	1 (2.8)	1 (2.8)	1 (2.8)	28 (77.8)
Antibiotics (Non beta-lactams)	14 (38.9)	2 (5.6)	3 (8.3)	1 (2.8)	1 (2.8)	0 (0.0)	21 (58.3)
NSAIDs and Selective Cox-2 inhibitors	11 (30.6)	1 (2.8)	1 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	13 (36.1)
Anti-epileptics	11 (30.6)	0 (0.0)	1 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	12 (33.3)
Anti-tuberculous drugs	8 (22.2)	1 (2.8)	0 (0.0)	1 (2.8)	1 (2.8)	0 (0.0)	11 (30.6)
Pyrazolones	8 (22.2)	1 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	2 (5.6)	11 (30.6)
Local anesthetic agents	8 (22.2)	1 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.8)	10 (27.8)
Neuromuscular blockers	6 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (5.6)	8 (22.2)

Percentage represents percentage of all 36 respondents who answered this question.

TABLE 5. Types of Nonimmediate Reactions Commonly Tested Using LTT

	Europe, n (%)	Asia Pacific, n (%)	North America, n (%)	Latin America, n (%)	Africa Middle East, n (%)	Region Not Specified, n (%)	Total (n = 32), n (%)
DIHS	16 (50.0)	1 (3.1)	1 (3.1)	2 (6.3)	1 (3.1)	0 (0.0)	21 (65.6)
SJS	14 (43.8)	1 (3.1)	2 (6.3)	0 (0.0)	0 (0.0)	4 (12.5)	21 (65.6)
Maculopapular exanthema	11 (34.3)	1 (3.1)	2 (6.3)	0 (0.0)	0 (0.0)	1 (3.1)	15 (46.9)
AGEP	14 (43.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.1)	15 (46.9)
TEN	11 (34.3)	1 (3.1)	1 (3.1)	0 (0.0)	0 (0.0)	2 (6.3)	15 (46.9)
Fixed drug eruption	7 (21.9)	2 (6.3)	1 (3.1)	1 (3.1)	1 (3.1)	1 (3.1)	13 (40.6)
Immunbullous eruptions	9 (28.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.1)	10 (31.3)
Vasculitis	6 (18.8)	1 (3.1)	0 (0.0)	1 (3.1)	1 (3.1)	0 (0.0)	9 (28.1)
Hepatitis	4 (12.5)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (15.6)
Blood dyscracias	2 (6.3)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (9.4)
Interstitial nephritis	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.1)

Percentage represents percentage of all 32 respondents who answered this question.

Third, children present, in general, with less complex drug-related allergies than adults because they do not tend to take many drugs at the same time. Although the principles of when and how to evaluate children with suspected drug allergy is no different from adults,[32,33] pragmatically, testing in children is mainly recommended if no alternative drug is available and there is an absolute requirement for that specific drug to be administered. There are logistic constraints as intradermal testing and DPTs may be difficult to perform on children, especially the very young. Even if drug allergy is documented in childhood, full retesting is often necessary once the adult age is reached. This pragmatic approach has not, however, reached unanimous consensus among allergists.

Skin tests (74.7%) and in vitro blood tests (67.4%) were commonly used in the diagnosis of immediate reaction, with beta-lactam antibiotics and anesthetic agents being the most commonly tested. However, only 70% of respondents had access to penicillin skin test reagents. Benzylpenicilloyl-polylysine, a major penicillin skin test reagent commercially known in the United States as, was not commercially available after September 2003. Hollister-Stier, the sole producer of PrePen in the United States, was directed by the Food and Drug Administration to cease its production in 2003 because of the lack of a dedicated penicillin manufacturing facility and hence quality concerns. A product containing major and minor determinants (Allergopen) was available on the European market until 2004, then it was also withdrawn by Merck worldwide.[17] Thus, major and minor penicillin determinants produced commercially by Diater S.A. (Madrid, Spain) were used in several European and Asian countries with comparable performance characteristics compared with PrePen and Allergopharma kit.[34–37] In September 2009, ALK-Abelló and AllerQuest, LLC announced the return of PrePen to the United States and the international market. With this, penicillin skin testing is likely to become more widely available among WAO member societies again.

Although intradermal tests (IDTs) are used in the diagnosis of immediate reactions,[13] the delayed IDT reading usually at 24 hours and 72 hours is useful in the diagnosis of nonimmediate reactions[38] and has been recommended in guidelines on the evaluation of drug allergy,[16] for instance, for nonimmediate reactions to beta-lactam antibiotics.[18] However, this survey did not look specifically at the number of sites that carried out delayed IDT readings.

For nonimmediate reactions, patch tests were used more commonly (54.7%) compared with LTT (36.8%). The use of patch tests and LTT is more common in Europe compared with other regions of the world. A positive patch test or LTT is useful, but a negative test cannot exclude drug allergy/hypersensitivity. Patch tests preparations are not well

TABLE 6. Drugs Commonly Tested Using Patch Tests

	Europe, n (%)	Asia Pacific, n (%)	North America, n (%)	Latin America, n (%)	Africa Middle East, n (%)	Region Not Specified, n (%)	Total (n = 48), n (%)
Antibiotics (beta-lactams)	22 (45.8)	6 (12.5)	4 (8.3)	6 (12.5)	3 (6.3)	1 (2.1)	40 (83.3)
Antibiotics (non–beta-lactams)	19 (39.6)	1 (2.1)	4 (8.3)	5 (10.4)	2 (4.2)	0 (0.0)	31 (64.6)
Corticosteroids	20 (41.7)	3 (6.3)	2 (4.2)	3 (6.3)	1 (2.1)	0 (0.0)	29 (60.4)
Anti-epileptics	19 (39.6)	1 (2.1)	2 (4.2)	5 (10.4)	0 (0.0)	1 (2.1)	28 (58.3)
Cotrimoxazole	16 (33.3)	1 (2.1)	2 (4.2)	3 (6.3)	0 (0.0)	0 (0.0)	22 (45.8)
NSAIDs and Selective Cox-2 inhibitors	13 (27.1)	3 (6.3)	2 (4.2)	3 (6.3)	1 (2.1)	1 (2.1)	21 (43.8)
Anti-tuberculous drugs	12 (25.0)	1 (2.1)	1 (2.1)	2 (4.2)	0 (0.0)	1 (2.1)	17 (35.4)
Radiocontrast media	13 (27.1)	1 (2.1)	1 (2.1)	1 (2.1)	0 (0.0)	0 (0.0)	16 (33.3)
Acyclovir	11 (22.9)	0 (0.0)	1 (2.1)	2 (4.2)	0 (0.0)	0 (0.0)	14 (29.2)

Percentage represents percentage of all 48 respondents who answered this question.

TABLE 7. Types of Nonimmediate Reactions Commonly Tested Using Patch Tests

	Europe, n (%)	Asia Pacific, n (%)	North America, n (%)	Latin America, n (%)	Africa Middle East, n (%)	Region Not Specified, n (%)	Total (n = 47), n (%)
Maculopapular exanthema	18 (38.3)	2 (4.3)	4 (8.5)	5 (10.6)	1 (2.1)	1 (2.1)	31 (66.0)
Drug induced hypersensitivity syndrome (DIHS)	14 (29.8)	6 (12.8)	3 (6.4)	4 (8.5)	2 (4.3)	1 (2.1)	30 (63.8)
Fixed drug eruption	14 (29.8)	3 (6.4)	2 (4.3)	4 (8.5)	4 (8.5)	2 (4.3)	29 (61.7)
AGEP	15 (31.9)	3 (6.4)	4 (8.5)	3 (6.4)	0 (0.0)	1 (2.1)	26 (55.3)
Stevens–Johnson syndrome	13 (27.7)	2 (4.3)	0 (0.0)	4 (8.5)	2 (4.3)	1 (2.1)	22 (46.8)
TEN	8 (17.0)	1 (2.1)	0 (0.0)	3 (6.4)	1 (2.1)	1 (2.1)	14 (29.8)
Immunobullous eruptions	8 (17.0)	1 (2.1)	0 (0.0)	2 (4.3)	0 (0.0)	1 (2.1)	12 (25.5)
Vasculitis	7 (14.9)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (17.0)
Blood dyscracias	1 (2.1)	1 (2.1)	0 (0.0)	1 (2.1)	0 (0.0)	0 (0.0)	3 (6.4)

Percentage represents percentage of all 47 respondents who answered this question.

standardized across all drugs, seem to be useful only in certain types of drug eruptions (eg, exanthema, eczema, and AGEP) but not others (eg, TEN), and are useful only with certain drugs.[38,39] The same is true for LTT, which has been found to be useful in exanthema, AGEP, bullous exanthema, drug rash with eosinophilia and systemic symptoms, and only for certain drugs. Many of the respondents, mainly from Europe, used patch tests and LTT in diagnosing the putative drug for severe reactions (SJS, TEN, DIHS). The many disadvantages for LTT including the requirement for sterile cell cultures, long time required to run the test, use of radioactivity, and expensive equipment limit its use to specialized tertiary clinical and research centers.[40]

DPTs were used by 68.4% of respondents with the most common indication being to exclude hypersensitivity where the history was not suggestive or the symptoms not specific for drug hypersensitivity/allergy (76.9%). DPT is generally safe when properly carried out under supervision and with constant, careful patient assessment[41] both in adults[42] and in children.[43] It is most commonly used in the definitive diagnosis of beta-lactam (penicillin or cephalosporin) allergy,[44–46] or demonstration of tolerance to alternative NSAIDs—weak COX-1 inhibitors (paracetamol) and/or preferential (meloxicam) or highly selective COX-2 inhibitors (etoricoxib, parecoxib)—in patients with NSAID/aspirin exacerbated respiratory disease, urticaria/angioedema, or NSAID intolerance.[47–51]

Definitive treatment of drug allergy includes avoidance of the drug in question, patient education on prevention, knowledge of potentially cross-reacting drugs, and giving patients some form of medic alert identification or notification. The survey looked at 2 specific treatment modalities: drug desensitization and management of SCAR (SJS/TEN/DIHS).

Rapid desensitizations, carried out by 69.6% of respondents, has been described for the treatment of IgE-mediated and non–IgE-mediated anaphylactic reactions to chemotherapy, antibiotics, or biologic agents, such as monoclonal antibodies,[52–54] and to high-dose aspirin in aspirin exacerbated respiratory disease[55] and low-dose aspirin (desensitization rechallenge) in patients with coronary artery disease requiring percutaneous coronary intervention.[56–58]

The management of SJS/TEN[59] was variable across different respondents, among whom 72.3% used systemic corticosteroids in SJS and/or systemic manifestations of TEN, 50.8% used high-dose intravenous immunoglobulin

TABLE 8. Indications for DPTs

	Europe, n (%)	Asia Pacific, n (%)	North America, n (%)	Latin America, n (%)	Africa Middle East, n (%)	Region Not Specified, n (%)	Total (n = 65), n (%)
Exclude hypersensitivity (non-suggestive history/non-specific symptoms)	25 (38.5)	10 (15.4)	4 (6.2)	4 (6.2)	2 (3.1)	5 (7.7)	50 (76.9)
Definitive diagnosis in suggestive history with negative, non-conclusive or non- available allergological tests	22 (33.8)	9 (13.8)	4 (6.2)	5 (7.7)	4 (6.2)	0 (0.0)	44 (67.7)
Exclude cross-reactivity of related drugs in proven hypersensitivity (e.g. cephalosporin in a penicillin allergic individual)	22 (33.8)	8 (12.3)	4 (6.2)	3 (4.6)	2 (3.1)	2 (3.1)	41 (63.1)
Provide safe pharmacologically/ structurally non-related drugs in proven hypersensitivity (e.g. beta-lactams)	21 (32.3)	5 (7.7)	5 (7.7)	3 (4.6)	2 (3.1)	3 (4.6)	39 (60.0)

Percentage represents percentage of all 65 respondents who answered this question.

for TEN and 9.2% used other immunosuppressive drugs including cyclosporine. More than two thirds would consider comanaging TEN patients with an intensivist/ burns unit[60,61]; this may have been limited by the availability of such tertiary specialty care in certain regions. Only 49.2% considered comanagement with an ophthalmologist, suggesting that a greater awareness of the ocular complications of SCAR and the need for aggressive ocular immunomodulatory therapy may be needed.[62]

HLA screening[63] has been shown to be useful in preventing SCAR before the prescription of abacavir in whites,[64] carbamazepine in Han Chinese or individuals of Asian ancestry,[65] and allopurinol in Han Chinese.[66] Only 17.1% of respondents had access to HLA screening for drugs at high risk of causing SCAR, with the majority (92.9%) screening for HLA B*5701 before prescribing abacavir, and 21.4% screening for HLA B*1502 before prescribing carbamazepine in Asians. This may have been due to lack of availability of rapid HLA screening kits in certain parts of Asia, or differences in local pharmacovigilance requirements.[67]

There were several limitations to this survey, which was highlighted by respondents. First, within large countries/ regions, the president/chair of the WAO affiliated society may not have had ample opportunity to run the survey through all members from different states/districts within the 6-week consultation period, especially where practices may be heterogenous and in large countries/regions. Second, interest and expertise in dealing with drug allergies also varied within different countries/regions, as certain types of drug allergies were looked after by organ-based specialists rather than allergologists, for example, patients with SJS were looked after by dermatologists in certain regions. In this context, the survey may have inevitably been slightly skewed toward obtaining/ receiving the results from the most dedicated centers with specific research interests. For example, the use of basophil activation test or LTT as diagnostic tools may not be as common in clinical practice as it appears from the audit's results. Third, there were clinical practices in certain regions, which were not covered by the questions used in the survey (eg, delayed IDT readings for nonimmediate reactions).

Although this survey has shown the types of tests available and practiced in various parts of the world, this need not necessarily mean that the tests are uniformly useful. For instance, patch tests, although carried out in many European centers for nonimmediate reactions, are drug-specific and reaction-specific and thus are more useful where certain types of nonimmediate reactions predominate. The use of standardized nomenclature, patient profiles, harmonization of test procedures, measurements, and outcome measures are crucial in improving the diagnostic modalities presently used in evaluating drug hypersensitivity/ allergy, findings similarly reflected in the Drug Ambassador Project carried out by the European Network for Drug Allergy.[68]

CONCLUSIONS

This survey shows that even though well-established international guidelines are available for the diagnosis and management of drug allergy, practices vary across the different regions of the world due to differences in allergology training, practice setups, funding mechanisms, and resource limitations. Nonetheless, the results of this survey will help facilitate multicenter networking in education, practice, and resource development in drug allergy/hypersensitivity. It is our hope that the results of this survey will, through WAO, facilitate clinical, educational, and research collaboration among the different allergy centers with an interest in drug allergy/hypersensitivity.

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Annex A

WORLD ALLERGY ORGANIZATION
SURVEY ON DRUG ALLERGY DISGNOSTIC PROCEDURES 2009

Thank you for spending some time to fill in this questionnaire. The objective of this is to survey the types of allergological tests available worldwide for the diagnosis of drug allergy/hypersensitivity. It is our hope that the results of this survey will through WAO facilitate collaboration and education among the different allergy centres with an interest in managing patients and undertaking research in drug allergy/hypersensitivity. Please check all answers that apply.

Questions 1-7 are applicable to all member societies of WAO.
Questions 8-42 are specific questions. If member societies are unable to complete this part of the questionnaire, please fill in the name, centre, e-mail of the centres in your country (Question 8).

Name of Society:

1	WAO Member Status	Member Society	☐
		Associate Member Society	☐
		Regional Organization	☐
		Affiliate Organization	☐
2	Do the Allergy Clinics in your country carry out evaluation for drug hypersensitivity/allergy?	Yes	☐
		No	☐
3	Do the Dermatology Clinics in your country carry out evaluation for drug hypersensitivity/allergy?	Yes	☐
		No	☐
4	If they do, which of the following guidelines are used?		
	International Contact Dermatitis Research Group (ICDRG) 1970: Criteria for patch test reading		☐
	AAAAI/ACAAI 1999 Practice Parameter: Drug hypersensitivity		☐
	European Society of Contact Dermatitis 2001 Guidelines for the study of skin testing in investigating CADR		☐
	BSACI 2003 Guidelines: Suspected anaphylactic reactions associated with anaesthesia		☐
	ENDA 2003 Guidelines: Immediate allergic reactions to beta-lactam antibiotics		☐
	ENDA 2003 Guidelines: Drug provocation tests		☐
	ENDA 2004 Guidelines: Non-iImmediate allergic reactions to beta-lactam antibiotics		☐
	ENDA 2005 Guidelines: Management of hypersensitivity to iodinated contrast media		☐
	SFAR/ENDA 2005 Guidelines: Reducing the risk of anaphylaxis during anaesthesia		☐
	ENDA 2006: Statement on penicillin skin testing		☐
	AAAAI/ACAAI 2006 Practice Parameter: Contact dermatitis		☐
	EAACI/GA2LEN 2007: Aspirin provocation tests for aspirin hypersensitivity		☐
	AAAAI/ACAAI 2008 Practice Parameter Update: Allergy diagnostic testing		☐
	BSACI 2009 Guidelines: Management of drug allergy		☐
5	Are there adult drug allergy centres/clinics in your country?	Yes: please specify the number:	☐
		No	☐
6	Are there paediatric drug allergy centres/clinics in your country?	Yes: please specify the number:	☐
		No	☐
7	Which of the following tests for drug allergy/hypersensitivity are available in your country?	Skin prick and intradermal test → go to section (A)	☐
		Specific IgE in-vitro tests → go to section (B)	☐
		Other tests for immediate reactions → go to section (C)	☐
		Lymphocyte transformation test → go to section (D)	☐
		Patch testing → go to section (E)	☐
		Drug provocation tests → go to section (F)	☐

(A) SKIN TESTING

8	Is skin testing used in the clinical or research setting?	Clinical Research Both clinical and research	☐ ☐ ☐
9	Do you have access to penicillin skin test reagents?	Yes No	☐ ☐
10	From where do you obtain your skin test reagent for penicilloyl polylysine (PPL)?	In-house Diater ® Others – specify:	☐ ☐ ☐
11	From where do you obtain your skin test reagent for minor determinant mix (MDM)?	In-house Diater ® Others – specify:	☐ ☐ ☐
12	Which drugs are commonly skin tested in your country?	Penicillins Cephalosporins Non-beta lactam antibiotics General anaesthetic agents Local anaesthetic agents NSAIDs Others – specify:	☐ ☐ ☐ ☐ ☐ ☐ ☐
13	Who prepares the drugs for skin testing?	Allergist Pharmacist Nurse clinician/specialist Others – specify:	☐ ☐ ☐ ☐
14	Are negative skin tests followed by a drug provocation test in all instances?	Yes No	☐ ☐

(B) SPECIFIC IgE IN-VITRO TESTS

15	Are these used in the clinical or research setting?	Clinical Research Both clinical and research	☐ ☐ ☐
16	Are in-house or commercial assays available for these tests?	In-house Commercial Both Neither	☐ ☐ ☐ ☐
17	Which commercial tests are available in your country?	CAP-FEIA (Pharmacia®) RAST (Radioallergosorbent test®) FLOW-CAST (Buhlmann Labs®) FLOW-2-CAST (Buhlmann Labs®) CAST-ELISA (Buhlmann Labs®) Others – specify:	☐ ☐ ☐ ☐ ☐ ☐
18	Which in-house methods are used in your country?	RAST (Radioallergosorbent tests) RIA (Radioimmunoassay) Others – specify:	☐ ☐ ☐
19	Which drugs are commonly tested using these in-vitro methods?	Penicillins Cephalosporins General anaesthetic agents NSAIDs Others – specify:	☐ ☐ ☐ ☐ ☐

(C) OTHER TESTS FOR IMMEDIATE REACTIONS

20	Is serum total tryptase available in your country?	Yes No	☐ ☐
21	Is the basophil activation test (BAT) available in your country?	Yes No	☐ ☐

(D) LYMPHOCYTE TRANSFORMATION TESTS (LTT)

22	Is LTT used in the clinical or research setting?	Clinical Research Both clinical and research	☐ ☐ ☐
23	Where are these tests done?	In-house Sent to another facility in the same region/country Sent to another facility out of the region/country	☐ ☐ ☐
24	What drugs are commonly tested using LTT in your country?	Antibiotics (betalactams) Antibiotics (non-beta lactams) Anti-epileptics ACE inhibitors Anti-tuberculous drugs Diuretics NSAIDs & selective COX-2 inhibitors Pyrazolones Local anaesthetic agents HMG-CoA reductase inhibitors Opioids Neuromuscular blockers Contact allergens Others - specify:	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
25	For what types of delayed reactions are LTT commonly used for diagnosis?	Acute generalized exanthematous pustolosis (AGEP) Blood dyscracias (cytopaenias) Drug induced hypersensitivity syndrome (DIHS) Fixed drug eruption (FDE) Hepatitis Immunobullous eruptions Interstitial nephritis Maculopapular exanthems (MPE) Stevens Johnson syndrome Toxic epidermal necrolysis Vasculitis Others – specify:	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

(E) PATCH TESTS

26	Is this used in the clinical or research setting?	Clinical Research Both clinical and research	☐ ☐ ☐
27	What formulation of the drug is used for testing?	Pure substance Commercialized form of the drug Others – specify:	☐ ☐ ☐

28	What dilutions of the drug are used	0.1% 1% 5% 10%	☐ ☐ ☐ ☐
29	What vehicle is used?	Petrolatum Water Alcohol	☐ ☐ ☐
30	How do you obtain the drugs for patch testing?	In-house Commercial - specify: Others - specify:	☐ ☐ ☐
31	Which of the following are also tested?	Preservative Colouring Excipient None of the above	☐ ☐ ☐ ☐
32	When is the patch test reading done?	20 minutes 48 h (Day 2) 96 h (Day 4) Day 7 if Day 2,4 negative	☐ ☐ ☐ ☐
33	Is photo patch testing done?	Yes No	☐ ☐
34	What drugs have you used for patch testing?	Antibiotics (betalactams) Antibiotics (non-beta lactams) Anti-epileptics Anti-tuberculous drugs Aciclovir, valaciclovir Corticosteroids NSAIDs & selective COX-2 inhibitors Cotrimoxazole Diltiazem Hydroxyzine Heparin derivatives Pseudoephedrine Radiocontrast media Tetrazepam Others - specify:	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
35	For what types of delayed reactions have you used patch testing to help in diagnosis?	Acute generalized exanthematous pustolosis (AGEP) Blood dyscracias (cytopaenias) Drug induced hypersensitivity syndrome (DIHS) Fixed drug eruption (FDE) Hepatitis Immunobullous eruptions Interstitial nephritis Maculopapular exanthems (MPE) Stevens Johnson syndrome Toxic epidermal necrolysis Vasculitis Others – specify:	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

(F) DRUG PROVOCATION TESTS

36	What are the main indications for drug provocation tests in your centre/country ?		
		Exclude hypersensitivity (non-suggestive history/non-specific symptoms)	☐
		Provide safe pharmacologically/structurally non-related drugs in proven hypersensitivity (e.g. betalactams)	☐
		Exclude cross-reactivity of related drugs in proven hypersensitivity (e.g. cephalosporin in a penicillin allergic)	☐
		Definitive diagnosis in suggestive history with negative, non-conclusive or non- available allergological tests	☐
		Others - specify:	☐
37	Who prepares the drug used for challenge?	Pharmacist	☐
		Nurse clinician	☐
		Doctor	☐
		Others – specify:	☐
38	What are the types of challenges used?	Open challenge	☐
		Single blind placebo control	☐
		Double blind placebo control	☐
		Others - specify	☐
39	What are the common routes of administration used?	Oral (tablet)	☐
		Oral (capsule)	☐
		Oral (syrup)	☐
		Intramuscular	☐
		Subcutaneous	☐
		Intravenous	☐

(G) OTHER COMMENTS