

The evaluation of drug provocation tests in pediatric allergy clinic: A single center experience

Emine Vezir, M.D.,¹ Mustafa Erkocoglu, M.D.,¹ Ersoy Civelek, M.D.,¹ Aysenur Kaya, M.D.,¹ Dilek Azkur, M.D.,¹ Aysegül Akan, M.D.,¹ Celal Ozcan, M.D.,¹ Muge Toyran, M.D.,¹ Tayfur Ginis, M.D.,¹ Emine Dibek Misirlioglu, M.D.,¹ and Can Naci Kocabas, M.D.²

ABSTRACT

Drug provocation tests (DPTs) are gold standard to diagnose drug allergy. Our goal was to evaluate the results and safety of diagnostic methods including DPTs during childhood. Between January 2010 and February 2013 DPTs were performed and evaluated, prospectively, in children who attended our pediatric allergy clinic with a suspected drug hypersensitivity reaction. One hundred ninety-eight suspected drug reactions in 175 patients (88 boys and 87 girls) were evaluated. The median age of the subjects at the time of the suspected drug-induced hypersensitivity reaction and at the time of the study was 56 (interquartile range [IQR] = 24–120 months) months and 76 (IQR = 35–149 months) months, respectively. Suspected drugs were beta-lactam antibiotics in 108 cases (54.5%), non-beta-lactam antibiotics in 22 cases (11.1%), and nonsteroid anti-inflammatory drugs in 52 cases (26.3%). The history was compatible with immediate-type reactions in 69 cases (34.8%). Skin-prick tests were not positive in any of the cases. Intradermal tests were positive in three cases (4%). DPTs were positive in 13 (6.8%) of 191 provocation cases, which were performed with culprit drugs. Our results suggest that a positive clinical history is not enough to make a diagnosis of drug allergy, which highlights the significance of undertaking further diagnostic evaluation especially for DPTs.

(Allergy Asthma Proc 35:156–162, 2014; doi: 10.2500/aap.2014.35.3744)

Drug allergies are acute and potentially life-threatening reactions that constitute one-third of all drug-related adverse reactions. Various adverse reactions after drug administration have been described, including nonimmunologic reactions, IgE-mediated allergic reactions (immediate allergic reactions, such as anaphylaxis and generalized urticaria, angioedema), and nonimmediate allergic reactions (maculopapular eruptions, fixed drug eruptions, vasculitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, and drug reaction with eosinophilia and systemic symptoms).^{1–4}

Parents of children who experienced various adverse reactions often report the event as an allergic reaction.⁵ In daily practice, the diagnosis of a drug allergy is often based on history rather than standard diagnostic tests. However, several studies indicated that history-based

diagnosis is not reliable.^{6–8} In a population-based study of children in Turkey, the frequency of proven drug allergies using objective diagnostic methods was reported as 0.11%, and the rate of parent-reported immediate-type drug allergy was 7.87%.⁹

Overdiagnoses of drug allergy based on history can lead to the use of more expensive and less effective treatments.¹⁰ For this reason objective diagnostic methods should be used. Although skin tests and specific IgE measurement can be used, drug provocation tests (DPTs) are considered the gold standard for identifying adverse drug reactions.¹¹

The aim of this study was to evaluate the results and safety of diagnostic methods including DPTs performed for children who attended our outpatient clinic with suspected drug allergy.

MATERIALS AND METHODS

Patients

Between January 2010 and February 2013 patients <18 years old attending (referred by pediatrician) our pediatric allergy clinic with a suspected drug hypersensitivity reaction were evaluated. A detailed history of the reaction was taken and recorded to standard patient files. History of allergic diseases of both the patient and the family including drug reactions were recorded. Patients with a history compatible with drug hypersensitivity reactions were involved in the study. Symptoms were classified according to parents' de-

From the ¹Department of Pediatric Allergy and Immunology, Ankara Children's Hematology Oncology Education and Research Hospital, Ankara, Turkey, and ²Division of Pediatric Allergy and Immunology, Department of Children's Health and Diseases, Faculty of Medicine, Mugla Sıtkı Kocman University, Mugla, Turkey. Presented in part as a poster presentation at the European Academy of Allergy and Clinical Immunology and World Allergy Organization World Allergy and Asthma Congress, Milan, Italy, June 22–26, 2013, and at the 19th Turkish National Society of Allergy and Clinical Immunology Congress, Antalya, Turkey, November 7–11, 2012. The authors have no conflicts of interest to declare pertaining to this article. Address correspondence to Can Naci Kocabas, M.D., Division of Pediatric Allergy and Immunology, Department of Children's Health and Diseases, Faculty of Medicine, Mugla Sıtkı Kocman University, Mugla 048100, Turkey. E-mail address: cankocabas@yahoo.com. Copyright © 2014, OceanSide Publications, Inc., U.S.A.

scriptions or based on medical records where available. The reactions were classified as immediate when they occurred within the 1st hour of drug administration and nonimmediate (delayed type) when they occurred >1 hour after administration.¹² After a physical examination, patients underwent skin tests and/or drug provocation as needed. Skin-prick tests (SPTs) were performed first and, if negative, intradermal tests (IDTs) were also performed. When skin tests were negative and there was no contraindication, provocation with the suspected drug was performed according to European Network for Drug Allergy guidelines¹³ under strict medical surveillance. Drugs that lead to reaction were grouped as antibiotics, nonsteroid anti-inflammatory drugs (NSAIDs), and others.

In patients who received more than one drug during the hypersensitivity episode or claimed to have hypersensitivity reactions to more than one drug, provocation tests were performed for each drug within a 1-week to 1-month interval.

The study was approved by the Institutional Review Board (2010-02). Before the study, the parents received information about the possible risks of skin and provocation tests, and written informed consent was obtained. If a drug reaction was detected, written instructions to avoid the responsible drug(s) were given.

Exclusion Criteria

The patients who had a history of severe life-threatening drug reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia, and/or acute generalized exanthematous pustulosis) were excluded.

Skin Tests

Skin Tests (Prick–Intradermal). Patients were subjected to prick and intradermal skin testing with β -lactams, macrolides, sulfonamide, paracetamol, and local anesthetics. The β -lactams used for skin testing included penicillin G (10.000 IU/mL), benzylpenicilloyl-octa-L-lysine, minor determinant (sodium benzylpenilloate; Diater Laboratorios S.A., Madrid, Spain), amoxicillin (20 mg/mL), ampicillin (20 mg/mL), and a cephalosporin with the culprit drug. Prick tests with trimethoprim-sulfamethoxazole (0.8 mg/mL) and clarithromycin (0.5 mg/mL) were also performed. Isotonic saline solution was used for dilution of drugs. All drugs were initially tested on volar forearm skin with the prick method, and reactions were considered positive when a wheal diameter of 3 mm greater than the negative control, with surrounding erythema, was present 20 minutes later.

When prick tests yielded negative results, 0.02 mL of the reagent solution was injected intradermally on the volar forearm skin. Readings were made 20 minutes

after injections. Results were considered positive when an increase of >3 mm in the wheal diameter, accompanied by erythema, was present. Positive control assays for SPTs and IDTs were performed with histamine. As a negative control sample for SPTs and IDTs, 0.9% NaCl was used.

Drug Provocation Tests

Drug provocation testing was reserved for participants for whom other investigations were inconclusive and if the provocation test was not contraindicated. European Network for Drug Allergy guidelines for SPTs and DPTs were carefully respected.^{13,14} A provocation test involved administering the suspected drug at divided doses every 30 minutes, until a cumulative dose close to the age/weight-adjusted daily dose of the drug is achieved. The test was discontinued in the event of any adverse drug reaction. In most cases, we used the same route of administration as the patient had used when the allergic reaction had occurred; if oral formulation of an injectable drug was available and identical, we administered the drug orally first and if there was not any reaction we administered the drug with injection thereafter. Administration was open and performed by a physician with full resuscitation backup. Patients had not taken any antihistamines or drugs that could have affected SPTs or DPTs in the previous week.

The DPT result was considered positive if any objective symptoms or signs were documented. The DPT result was considered negative if no sign of drug hypersensitivity occurred after the usual daily dose had been administered. After a reaction without a decrease in blood pressure, loratadine or cetirizine and prednisolone were given. If anaphylaxis occurred, intramuscular epinephrine was injected. After the last dose had been administered without a reaction occurring, the patient was kept under surveillance for at least 2 hours.

Statistical Analysis

Statistical analyses were performed using the SPSS-15 statistical software package (SPSS, Inc., Chicago, IL) for Windows. Kolmogorov-Smirnov test was used to determine whether or not the variables were normally distributed. Descriptive analyses were presented using means and SDs for normally distributed variables and using median and interquartile ranges (IQRs) for not normally distributed variables. The chi-square test or Fisher's exact test where appropriate, was used to compare groups. Mann-Whitney *U* test was used to compare two groups for not normally distributed variables and one-way ANOVA was used to compare more than two groups. A value of $p \leq 0.05$ was considered statistically significant.

Table 1 Characteristics of patients with immediate and nonimmediate reactions

	Immediate Reactions (<i>n</i> = 69)	Nonimmediate Reactions (<i>n</i> = 129)	<i>p</i> Value
Age, median (IQR; mo)	141 (66.5–162.5)	56 (26.5–99.5)	<0.001
Girls, <i>n</i> (%)	36 (52.2)	62 (48.1)	0.581
Time since last drug reaction, median (IQR), mo	8 (2–30)	5 (2–12)	0.01
Proven drug allergy, <i>n</i> (%)	8 (11.9)	8 (6.2)	0.164

IQR = interquartile range; mo = month.

RESULTS

Demographic Data

One hundred ninety-eight suspected reactions in 175 patients (88 boys and 87 girls) were evaluated. Three patients with Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis and 1 patient with Drug Reaction with Eosinophilia and Systemic Symptoms were not included in the study. The median age of the subjects at the time of the suspected drug-induced hypersensitivity reaction and at the time of the study was 56 (IQR = 24–120 months) months and 76 (IQR = 35–149 months) months, respectively. Forty-two (24%) patients have a personal history of allergic diseases and 53 (30.3%) patients have family history of allergic diseases. Median time since last drug reaction was 6 months (range, 1–154 months).

Historical Drug Reaction

Twenty-two patients were suspected to have more than one drug allergy. The most frequent suspected drugs were β -lactam antibiotics in 108 cases (54.5%; penicillin, 19; amoxicillin, 4; amoxicillin-clavulanic acid, 61; cephalosporin, 21; and ampicillin-sulbactam, 3) followed by NSAIDs in 52 cases (26.3%; ibuprofen, 21; flurbiprofen, 1; naproxen, 1; paracetamol, 23; acetyl salicylic acid, 4; and methimazole, 2), non- β -lactam antibiotics in 22 cases (11.1%; macrolide, 18, and trimethoprim, 4), and other drugs in 16 cases (8.1%; local anesthetics, 3; ferric ammonium citrate, 2; vitamin B12, 2; methylprednisolone, 1; octreotide, 1; lactulose, 1; fentanyl, 1; and pseudoephedrine, 5). In 173 cases (87.4%) the incriminated drug had been administered orally, by intramuscular route in 19 cases (9.6%), by intravenous route in 3 cases (1.5%), and by subcutaneous route in 3 cases (1.5%).

The history was compatible with immediate-type reactions in 69 cases (34.8%), and with nonimmediate-type in 129 (65.2%) of the reactions. Characteristics of patients with immediate and nonimmediate reactions are given in Table 1. Both the age at the time of evaluation and the time since last drug reaction were lower among children with nonimmediate reactions (Table 1).

The clinical presentations were cutaneous in 192 (97%), respiratory in 10 (5.1%), cardiovascular in 13 (6.6%), gastrointestinal in 8 (4%), and anaphylaxis in 23 (11.6%) of the cases. Cutaneous reactions were macular/maculopapular exanthema in 87 (43.9%), urticaria in 58 (29.3%), and angioedema in 47 (23.7%) of the cases. In 6 (3%) cases there were no cutaneous reactions. Demographic and reaction characteristics of patients grouped according to the suspected drug are given in Table 2. Nonimmediate reactions were higher in the antibiotics group ($p = 0.002$) and median age of patients in the group of antibiotics was lower than other groups ($p < 0.001$). Clinical findings that were reported by parents were not different between groups.

Diagnostic Workup

In two cases diagnostic tests (including SPTs) were not performed because of a history of severe anaphylaxis. All other patients were skin-prick tested and the test was not positive in any case. SPTs were not positive in any cases. IDTs were positive in three cases (4%): one to amoxicillin, one to clarithromycin, and the other one to octreotide (Table 3). In seven of the cases provocation tests were not performed (three patients had positive IDTs, two patients had history of severe anaphylaxis, and two patients refused challenges with suspected drugs). Drug challenge tests were positive in 13 (6.8%) of 191 provocation cases, which were performed with a culprit drug. Characteristics of patients with positive provocation tests are given in Table 4.

Proven drug allergy among children who had maculopapular eruption (3.4%; 3/87) was less frequent than patients presenting with urticaria and/or angioedema (12.6%; 13/103; $p = 0.034$).

Ratio of suspected and proven reactions according to groups of drug are shown in Fig. 1. The rate of negative provocation was higher in the β -lactam group ($p = 0.021$).

In addition to 198 provocations performed with the culprit drug, 6 provocation tests were performed to advice an alternative drug (cefuroxime, 2; meloxicam,

Table 2 Clinic and demographic characteristics of drug groups

	Antibiotic 130 Cases 120 Patients	NSAID 52 Cases 49 Patients	Other 16 Cases 16 Patients	<i>p</i> Value
Boy, <i>n</i> (%)	72 (55.4)	19 (36.5)	9 (56.3)	0.087
Age (yr; median; IQR)	3.5;1.5–6.4	7.2;4.6–11.3	7.3;2.4–12.3	<0.001
Cutaneous reaction, <i>n</i> (%)	125 (96.2)	51 (98.1)	16 (100)	0.6
GIS reaction, <i>n</i> (%)	4 (3.1)	2 (3.8)	2 (12.5)	0.195
CVS reaction, <i>n</i> (%)	9 (6.9)	3 (5.8)	1 (6.3)	0.952
Respiratory system reaction, <i>n</i> (%)	5 (3.8)	3 (5.8)	2 (12.5)	0.321
Anaphylaxis, <i>n</i> (%)	13 (10)	7 (13.5)	3 (18.8)	0.537
Immediate, <i>n</i> (%)	34 (26.2)	26 (50)	9 (56.3)	0.001

NSAIDs = nonsteroidal anti-inflammatory drugs; IQR = interquartile range; GIS = gastrointestinal system; CVS = cardiovascular system.

Table 3 Results of the diagnostic workup

	Prick <i>n</i> =167 <i>n</i> Performed/ <i>n</i> Positive	Intradermal <i>n</i> =75 <i>n</i> Performed/ <i>n</i> Positive	Provocation <i>n</i> =191 <i>n</i> Performed/ <i>n</i> Positive
β-lactam	108/0	41/1	106/3
Non-β-lactam	22/0	6/1	20/3
NSAIDs	23/0	20/0	51/5
Others	14/0	8/1	14/2

NSAIDs = nonsteroidal anti-inflammatory drugs.

2; paracetamol, 1; and methimazole, 1). None of the provocation tests for alternative drugs were positive.

DISCUSSION

During the study period 175 patients admitted with 198 suspected drug allergy reactions were evaluated with skin and/or provocation tests. Two hundred two provocation tests were performed in these patients and six of them were performed to advise an alternative drug. Two patients had a history obviously suggestive of anaphylaxis so these patients did not undergo any diagnostic testing. In 3 cases IDTs were positive and in 13 cases provocation tests were positive. Thus, 16 (8.16% in 196 drug evaluation) reactions were confirmed as drug hypersensitivity after complete evaluation. The frequency of positive DPTs in our study is comparable with previous studies, which were performed in children^{5,8} but is much lower than some other reports.^{15,16} In studies reporting higher frequencies,^{15,16} study groups included adults and subjective symptoms were recorded during provocations and this may have caused the difference because proven drug allergy is shown to be more frequent among adults.⁸

Parental or patient reports of drug hypersensitivity overestimated the true frequency^{8,9,17} of drug allergy. Therefore, a complete allergic evaluation is required: a

detailed clinical history and physical examination, followed by skin tests and DPTs.¹³ The DPT is considered the gold standard to verify or rule out drug hypersensitivity. A positive DPT result prevents the occurrence of allergic reactions, whereas a negative one prevents the unnecessary avoidance of a needed drug.⁴ This is of utmost importance because alternative drugs are often less effective, have more side effects, increase treatment costs, and, in the case of antibiotics, may lead to development of bacterial resistance.^{1,18,19} In our study, using objective diagnostic methods including DPTs, drug hypersensitivity could be definitely excluded in 182 of 198 suspected reactions.

Comparable with previous studies, the most frequent clinical manifestations were dermatologic symptoms in our study.^{9,17,20,21} Proven drug allergy among children who had maculopapular eruption was less frequent than patients presenting with urticaria in accordance with previous studies.⁸ This may be related to the presence of frequent viral infections in childhood.

Antibiotics are the most frequently prescribed pediatric drugs, causing the majority of adverse reactions in children.^{22–24} However, true frequency of antibiotic allergy is much lower than parental or patient reports.^{8,18,25} Therefore, accurate diagnosis of antibiotic allergy is

Table 4 Patients with positive provocation tests

Patient	Provocation Age (yr)	Sex	Drug	Time of Reaction	Clinical Manifestation	Skin Test Results	Rxn Dose (mg)	Cumulative dose (mg)	Delay between DPT and Reaction (min)	DPT Results	Time Elapsed after Reaction (mo)
1	12.8	Male	Ibuprofen	Immediate	Angioedema	Not done	300	556	30	Angioedema	94
2	13.4	Male	Ibuprofen	Immediate	Angioedema	Not done	300	556	30	Angioedema	12
3	17	Female	Clarithromycin	Nonimmediate	Urticaria	Negative	500	680	30	Urticaria	2
4	1.8	Male	Ibuprofen	Nonimmediate	Angioedema	Not done	80	115	55	Angioedema	3
5	12.5	Female	Ferrous glycine sulfate	Immediate	Anaphylaxis	Negative	100	186	30	Urticaria	24
6	4.5	Female	Clarithromycin	Nonimmediate	Maculopapular exanthema	Negative	200	326	1440	Maculopapular exanthema	10
7	7.4	Female	Ibuprofen	Nonimmediate	Angioedema	Not done	10	10	10	Anaphylaxis	6
8	16.1	Male	Paracetamol	Immediate	Anaphylaxis	Negative	50	60	10	Urticaria	17
9	13.5	Female	Amoxicillin/clavulanic	Immediate	Anaphylaxis	Negative	5	6	5	Anaphylaxis	12
10	7	Male	Amoxicillin/clavulanic	Immediate	Urticaria	Negative	8	10	15	Urticaria	12
11	17	Female	Apikobal	Nonimmediate	Anaphylaxis	Negative	700	1000	80	Urticaria	1
12	7.1	Female	Amoxicillin/clavulanic	Nonimmediate	Maculopapular exanthema	Negative	500	810	300	Maculopapular exanthema	2
13	2.6	Female	Clarithromycin	Nonimmediate	Urticaria	Negative	1	1	15	Urticaria	2

DPT = drug provocation test.

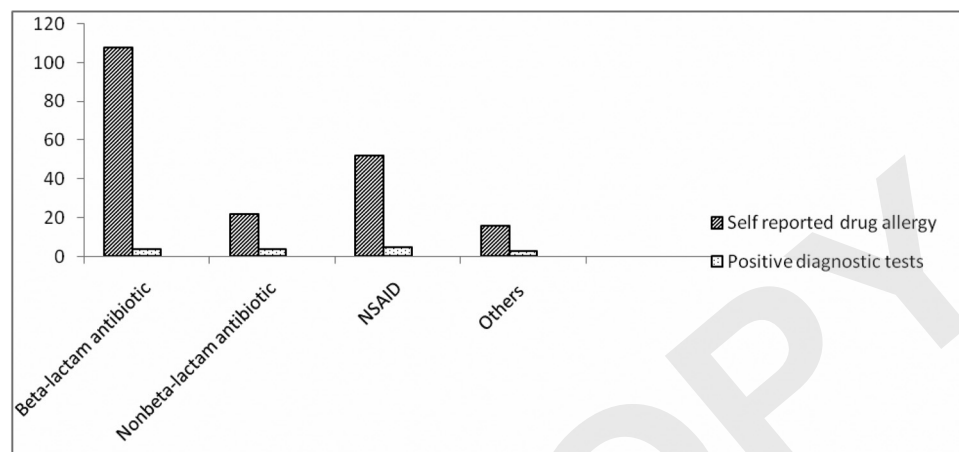


Figure 1. Ratio of suspected and proven reactions according to drug groups.

important not only to prevent serious or even life-threatening reactions, but also to avoid unnecessary drug restrictions associated with increased resistance and health costs.^{1,19,26–28} In our study only 8 of 130 suspected antibiotic allergy cases were proven. Patients with suspected antibiotic allergy were younger than other drug groups and nonimmediate reactions were more frequent in this group. This may be related to frequent antibiotic use because of infections and more frequent maculopapular eruptions in the younger age group.

Of the 130 cases with suspected antibiotic allergy, 108 was with β -lactam and 22 with non- β -lactam antibiotics and 4 of the β -lactam cases (3.7%) and 4 of non- β -lactam cases (18.1%) had proven hypersensitivity. In studies including adult patients, the frequency of β -lactam allergy is higher.^{26,29} In a study based on the data from a large cohort, 9.6% of β -lactam and 7.8% of non- β -lactam pediatric cases were proven to have hypersensitivity.⁸ The age group of children in this study was older than our group and this may have caused the difference. Also, prescription attitudes and differences in the perception of allergy among people living in the country can affect the results.

NSAIDs are the second-most frequently suspected agents causing drug hypersensitivity. Although predictivity is considerably low for most NSAIDs, skin tests can be used for some and can be useful as a step before provocation tests.³⁰ In a study based on the data from a large cohort, NSAID hypersensitivity was proven in 18.5% of suspected reactions. In the study by Zamborino *et al.*, 61.3% of children had drug hypersensitivity confirmed by DPTs.³¹ In our study only 9.6% of cases were proven to have NSAID hypersensitivity. The ratio of ibuprofen hypersensitivity among positive reactions was 53.4% in the aforementioned study whereas it was only 17% in our study group. Angioedema was the most frequent clinical symptom of ibuprofen hypersensitivity in that study as was the case in our data. Although paracetamol is frequently sus-

pected to cause allergic reactions, the ratio of positive provocation is low in our study in accordance with previous reports.^{8,31}

The study results showed that a positive clinical history is not enough to make a diagnosis of drug allergy. The true diagnosis of drug allergy to prevent unnecessary treatment with less effective agents is very important. Therefore, patients with suspicion of a drug allergy should always be subjected to further diagnostic evaluation, especially DPTs, for confirmation.

REFERENCES

- Demoly P, and Bousquet J. Epidemiology of drug allergy. *Curr Opin Allergy Clin Immunol* 1:305–310, 2001.
- Johansson SG, Hourihane JO, Bousquet J, et al. A revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force. *Allergy* 56:813–824, 2001.
- Gruchalla RS. Clinical assessment of drug-induced disease. *Lancet* 356:1505–1511, 2000.
- Mirakian R, Ewan PW, Durham SR, et al. BSACI guidelines for the management of drug allergy. *Clin Exp Allergy* 39:43–61, 2009.
- Seitz CS, Bröcker EB, and Trautmann A. Diagnosis of drug hypersensitivity in children and adolescents: Discrepancy between physician-based assessment and results of testing. *Pediatr Allergy Immunol* 22:405–410, 2011.
- Martín-Muñoz F, Moreno-Ancillo A, Domínguez-Noche C, et al. Evaluation of drug-related hypersensitivity reactions in children. *J Invest Allergol Clin Immunol* 9:172–177, 1999.
- Borch JE, Andersen KE, and Bindslev-Jensen C. The prevalence of suspected and challenge-verified penicillin allergy in a university hospital population. *Basic Clin Pharmacol Toxicol* 98: 357–362, 2006.
- Rubio M, Bousquet PJ, Gomes E, et al. Results of drug hypersensitivity evaluations in a large group of children and adults. *Clin Exp Allergy* 42:123–130, 2012.
- Erkoçoğlu M, Kaya A, Civelek E, et al. Prevalence of confirmed immediate type drug hypersensitivity reactions among school children. *Pediatr Allergy Immunol* 24:160–167, 2013.
- Demoly P, Pichler W, Pirmohamed M, and Romano A. Important questions in allergy: 1–Drug allergy/hypersensitivity. *Allergy* 63:616–619, 2008.
- Aberer W, and Kränke B. Provocation tests in drug hypersensitivity. *Immunol Allergy Clin North Am* 29:567–584, 2009.

12. Demoly P, Kropf R, Bircher A, and Pichler WJ. Drug hypersensitivity: Questionnaire. EAACI interest group on drug hypersensitivity. *Allergy* 54:999–1003, 1999.
13. Aberer W, Bircher A, Romano A, et al. Drug provocation testing in the diagnosis of drug hypersensitivity reactions: General considerations. *Allergy* 58:854–863, 2003.
14. Brockow K, Romano A, Blanca M, et al. General considerations for skin test procedures in the diagnosis of drug hypersensitivity. *Allergy* 57:45–51, 2002.
15. Messaad D, Sahla H, Benahmed S, et al. Drug provocation tests in patients with a history suggesting an immediate drug hypersensitivity reaction. *Ann Intern Med* 140:1001–1006, 2004.
16. Kao L, Rajan J, Roy L, et al. Adverse reactions during drug challenges: A single US institution's experience. *Ann Allergy Asthma Immunol* 110:86–91.e1, 2013.
17. Rebelo Gomes E, Fonseca J, Araujo L, et al. Drug allergy claims in children: From self-reporting to confirmed diagnosis. *Clin Exp Allergy* 38:191–198, 2008.
18. Kamboj S, Yousef E, McGeady S, and Hossain J. The prevalence of antibiotic skin test reactivity in a pediatric population. *Allergy Asthma Proc* 32:99–105, 2011.
19. Lee CE, Zembower TR, Fotis MA, et al. The incidence of antimicrobial allergies in hospitalized patients: Implications regarding prescribing patterns and emerging bacterial resistance. *Arch Intern Med* 160:2819–2822, 2000.
20. Aun MV, Bisaccioni C, Garro LS, et al. Outcomes and safety of drug provocation tests. *Allergy Asthma Proc* 32:301–306, 2011.
21. Chalabianloo F, Berstad A, Schjøtt J, et al. Clinical characteristics of patients with drug hypersensitivity in Norway: A single-centre study. *Pharmacoepidemiol Drug Saf* 20:506–513, 2011.
22. Clavenna A, and Bonati M. Drug prescriptions to outpatient children: A review of the literature. *Eur J Clin Pharmacol* 65: 749–755, 2009.
23. Amadeo B, Zarb P, Muller A, et al. European surveillance of antibiotic consumption (ESAC) point prevalence survey 2008: Paediatric antimicrobial prescribing in 32 hospitals of 21 European countries. *J Antimicrob Chemother* 65:2247–2252, 2010.
24. Thong BY, and Tan TC. Epidemiology and risk factors for drug allergy. *Br J Clin Pharmacol* 71:684–700, 2011.
25. Miller LE, Knoderer CA, Cox EG, and Kleiman MB. Assessment of the validity of reported antibiotic allergic reactions in pediatric patients. *Pharmacotherapy* 31:736–741, 2011.
26. Bousquet PJ, Pipet A, Bousquet-Rouanet L, et al. Oral challenges are needed in the diagnosis of beta-lactam hypersensitivity. *Clin Exp Allergy* 38:185–190, 2008.
27. Picard M, Paradis L, Nguyen M, et al. Outpatient penicillin use after negative skin testing and drug challenge in a pediatric population. *Allergy Asthma Proc* 33:160–164, 2012.
28. Prematta T, Shah S, and Ishmael FT. Physician approaches to beta-lactam use in patients with penicillin hypersensitivity. *Allergy Asthma Proc* 33:145–151, 2012.
29. Silva R, Cruz L, Botelho C, et al. Work up of patients with history of beta-lactam hypersensitivity. *Allergol Immunopathol (Madr)* 37:193–197, 2009.
30. Palma-Carlos AG, Medina M, and Palma-Carlos ML. Skin tests in NSAIDS hypersensitivity. *Eur Ann Allergy Clin Immunol* 38:182–185, 2006.
31. Zambonino MA, Torres MJ, Muñoz C, et al. Drug provocation tests in the diagnosis of hypersensitivity reactions to non-steroidal anti-inflammatory drugs in children. *Pediatr Allergy Immunol* 24:151–159, 2013. □

Copyright of Allergy & Asthma Proceedings is the property of OceanSide Publications Inc. and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.