



Maintenance of certification-CME review

Treating patients with multiple drug allergies

David A. Khan, MD

University of Texas Southwestern Medical Center, Dallas, Texas

ARTICLE INFO

Article history:

Received for publication August 23, 2012.

Received in revised form November 1, 2012.

Accepted for publication November 5, 2012.

INSTRUCTIONS

Credit can now be obtained, free for a limited time, by reading the review article in this issue and completing all activity components. Please note the instructions listed below:

- Review the target audience, learning objectives and all disclosures.
- Complete the pre-test online at <http://www.annallergy.org> (click on the CME heading).
- Follow the online instructions to read the full version of the article, including the clinical vignette; reflect on all content as to how it may be applicable to your practice.
- Complete the post-test/evaluation and claim credit earned; at this time, you will have earned up to 1.0 AMA PRA Category 1 Credit™. Please note that the minimum passing score on the post-test is 70%.
- Approximately 4–6 weeks later you will receive an online assessment regarding your application of this article to your practice. Once you have completed this assessment, you will be eligible to receive MOC Part II credit from the American Board of Allergy and Immunology.

Release Date: January 1, 2013

Expiration Date: December 31, 2015

Estimated Time to Complete: 60 minutes

Target Audience: Physicians involved in providing patient care in the field of allergy/asthma/immunology

Learning Objectives:

At the conclusion of this activity, participants should be able to:

- Discuss the meaning of the term multiple drug intolerance
- Develop a systematic approach to evaluating patients with multiple antibiotic allergies
- Develop a rational approach to graded dose challenges and induction of drug tolerance procedures

Accreditation: The American College of Allergy, Asthma & Immunology (ACAAI) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Designation: The American College of Allergy, Asthma & Immunology (ACAAI) designates this journal-based CME activity for a maximum of 1 AMA PRA Category 1 Credit™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Planning Committee Members:

David A. Khan, MD (Senior Author)

Michael S. Tankersley, MD (CME Series Editor)

Mitchell H. Grayson, MD (Deputy Editor)

Gailen D. Marshall, Jr, MD, PhD (Editor-in-Chief)

Disclosure of Relevant Financial Relationships:

D.A. Khan, M.S. Tankersley, M.H. Grayson and G.D. Marshall have no relevant financial relationships to disclose. Reviewers and Education/Editorial staff have no relevant financial relationships to disclose. No experimental/investigative use of a product/device is discussed.

Recognition of Commercial Support: This activity has not received external commercial support.

Copyright Statement: © 2012–2014 ACAAI. All rights reserved.

CME Inquiries: Contact the American College of Allergy, Asthma & Immunology at education@acaai.org or 847-427-1200.

Clinical Vignette

A 71-year-old woman presented to the hospital with fever and dysuria and was found to have an *Escherichia coli* urinary tract infection with bacteremia. She was prescribed intravenous ciprofloxacin. Within minutes of the fourth dose she developed itching of her throat, a sense of throat swelling, and dysphonia. She received a single dose of intravenous diphenhydramine, and her symptoms resolved within 30 minutes. Her antibiotic was changed to meropenem, and after the third dose she again had similar symptoms, necessitating discontinuation of use of this drug. An allergy and immunology consultation was obtained. Her medical history was notable for compensated congestive heart failure and recurrent urinary tract infections. She noted a history of “anaphylaxis” to multiple antibiotics. More than 30 years ago she developed respiratory distress after penicillin and was intubated. Since then she reported the development of throat itching, throat tightness, dysphonia, and some tongue swelling to multiple antibiotics, including cephalexin, “sulfa”, tetracycline, and clarithromycin. She could not recall the details of all of these reactions other than that many of them occurred after a few doses of the medicine. Her physical examination findings were notable for the absence of any cutaneous findings, including angioedema.

Multiple Drug Intolerance

It is well recognized that some patients report multiple allergies to medications. One of the first descriptions using the term *multiple drug allergy syndrome* was in 1989 in an abstract by Sullivan et al,¹ who reported that 21% of 312 penicillin allergic patients reported allergies to other drugs compared with only 1% of 349 adults with no penicillin allergy history. In contrast, a study by Khoury and Warrington² found the incidence of reactions to non- β -lactam drugs to be similar between patients with penicillin allergy with positive penicillin skin test results, patients with penicillin allergy with negative penicillin skin test results, and patients with vasomotor rhinitis without a history of penicillin allergy. The term *multiple drug allergy* is controversial because a criterion standard for confirming allergy (ie, skin testing or drug challenge) is typically lacking, there is no clear immunologic explanation, and prospective studies are not available.³ Subsequently, another term has been introduced to explain patients with reactions to multiple drugs: *multiple drug intolerance syndrome* (MDIS). This syndrome has been defined to include patients with reactions to 3 or more drugs that are not structurally or pharmacologically related.⁴ A recent study of 23 patients who underwent 350 separate drug challenges revealed that none of the 23 met the criteria for MDIS.⁵ Seventy percent of these patients reported symptoms with challenges (including 26% patients with placebo), but only 7% had objective findings. Recently, Macy et al⁶ reported on data from a large health care electronic medical record involving more than 2 million patients. MDIS cases accounted for 2.1% of health plan members and were more likely to be female, older, and heavier than the average health plan members. Anxiety rather than IgE-mediated allergy was associated with MDIS as has been previously reported.⁷ Nevertheless, these patients present challenges to the patient, treating clinician, and the consulting allergist/immunologist. A logical approach can be used to effectively manage these patients with available tools, including a careful drug allergy history, skin testing, drug challenge, and induction of drug tolerance procedures (Table 1).

Drug Allergy History

Like many other allergic diseases, a detailed history is essential to the management of a drug allergic patient. The history is essential to help (1) confirm whether the reaction is consistent with a drug allergy, (2) classify the nature of the reaction (eg, IgE

Table 1

Approach to patients with multiple drug intolerance syndrome

Step 1 (history)	• Obtain detailed history of listed drug allergies • Determine potential need for future medications
Step 2 (testing)	• Identify medications for drug skin testing • Identify medications requiring drug challenge
Step 3 (guidance)	• Develop list of medications that are safe to use • Develop list of medications to avoid • Develop list of medications that can be considered for future testing or induction of drug tolerance

mediated), (3) choose diagnostic tests, (4) determine the safety of reintroduction of the medication, and (5) determine need for an induction of drug tolerance procedure (eg, drug desensitization). Key elements of the drug allergy history include name of the medication(s), when the reaction occurred, which systems were involved, timing of drug administration and reaction, indication for drug, concomitant medications, underlying medical conditions that can be confused with drug allergy (eg, chronic urticaria, vocal cord dysfunction [VCD]), tolerance to cross-reacting drugs, and similar symptoms in absence of drug.⁸

Drug allergic reactions need to be distinguished from adverse reactions. As defined in the Drug Allergy Practice Parameter, a drug allergy is an immunologically mediated response to a pharmaceutical and/or formulation (excipient) agent in a sensitized person.⁹ Immunologic drug reactions require a period of sensitization and hence should not be first dose reactions unless the patient was previously exposed to the drug or a cross-reacting drug. Clinical features of immunologic drug reactions vary considerably based on the mechanism. The most common form of drug allergic reactions (maculopapular exanthems) are considered type IV delayed-type hypersensitivity reactions and typically evolve after several days of taking the offending drug. Type IV drug reactions may also present with eczematous, pustular, or bullous lesions. Type I immediate reactions to drugs are another common form of drug allergy and are mediated by drug specific IgE antibodies. Clinical manifestations of type I reactions may include urticaria, angioedema, bronchospasm, and anaphylaxis. IgE-mediated drug allergic reactions typically occur rapidly (<1 hour) after exposure to the drug in a sensitized individual. A number of other immunologic drug reactions may present in different fashions but are beyond the scope of this brief review and are discussed in more detail in the Drug Allergy Practice Parameter.⁹

Drug-Specific Diagnostic Testing

Although the history and physical examination are extremely useful in evaluating patients with drug allergic histories, they are usually not adequate to confirm or refute a true drug allergy. Modalities for testing for specific drug allergic reactions include skin tests, in vitro tests, and drug challenge. Drug challenge is the reference standard for confirming a drug allergic reaction because skin tests and in vitro tests may indicate sensitization but have the potential for false-positive and false-negative results.

It is important to recognize that not all drug reactions need to be evaluated. For many patients, particularly those with multiple antibiotic allergies, identifying a few classes of broad-spectrum antimicrobials that they tolerate is typically sufficient. This may depend on the underlying medical condition and anatomical site for which they typically require antibiotics (eg, respiratory, urinary tract, skin). Antibiotics that are most commonly evaluated, particularly for outpatient use, include penicillins, cephalosporins, macrolides and quinolones. Most experts believe that testing for sulfonamide allergy should be approached with caution because

of the well-known propensity for these drugs to cause severe cutaneous adverse reactions.

Skin Testing

Drug skin testing using epicutaneous followed by intradermal testing may be used for both immediate and some delayed drug allergic reactions. A positive immediate skin test result to a nonirritating concentration in a patient with a history of an immediate-type drug allergic reaction (eg, urticaria within 30 minutes of drug exposure) implies the presence of drug specific IgE and indicates that the patient would be at risk for having an immediate reaction with subsequent drug exposure. In contrast, a negative skin test result does not indicate low risk because of the poor negative predictive value of skin testing to native formulations of the drug. The main exception is with penicillin skin testing.

The negative predictive value for skin testing with commercially available penicillin reagents in the United States (penicilloyl-polylysine [PRE-PEN] and penicillin G) is approximately 97%.^{10,11} Large-scale studies using penicillin skin testing with major and additional minor determinants (eg, penicilloate, penilloate) reported that 10% to 20% of patients with positive penicillin skin test results also tested positive to penicilloate or penilloate.^{12,13} These large studies revealed that only 1% to 3% of patients with negative skin test results developed mild and self-limiting reactions after penicillin challenge, similar to studies without other minor determinants, raising the question of the clinical significance of these isolated penicilloate or penilloate reactions. Because most allergists in the United States do not have access to penicillin minor determinants, testing with PRE-PEN and penicillin G is reasonable. Penicillin G left in solution (aged penicillin) does not degrade spontaneously into other minor determinants and should not be used as a testing reagent.¹⁴ Despite the excellent negative predictive value, a confirmatory penicillin challenge is recommended because of the small risk of reactions in patients who have negative penicillin skin test results, even when testing with other minor determinants. For most patients with MDIS who are being tested in an allergy clinic, a history of penicillin allergy is listed, the history is remote, and the reaction is nonanaphylactic; therefore, the pretest likelihood of penicillin allergy is low. For these patients, after a negative penicillin skin test result, a full dose of amoxicillin may be used with observation for an hour. Amoxicillin may be used because it covers both penicillin and side chains of aminopenicillins. Overall, penicillin skin testing and challenge are useful tools in patients with MDIS because the results are typically negative, and these tests can significantly increase the antimicrobial options for patients. In addition to other penicillins, cephalosporins and carbapenems may be safely taken (if avoidance was due to a history of penicillin allergy).

Although nonirritating concentrations of many nonpenicillin antibiotics and other drugs have been published, their utility is limited because of their unknown negative predictive value.¹⁵ However, in cases of drug-induced anaphylaxis, the frequency of positive reactions is higher, and in this situation, drug-specific skin testing can be a useful tool. Skin testing can be performed to antibiotics other than penicillins; however, the predictive values for these tests are not as robust as with penicillin because the patient populations studied have been much smaller. More information is available for skin testing with cephalosporins, macrolides, and quinolones than other antibiotics.

Several studies have evaluated cephalosporin skin testing in patients with histories of cephalosporin allergy with positive skin test results in more than 75% of cases.^{16,17} Many studies have used concentrations for intradermal testing of 2 mg/mL. The negative predictive value of cephalosporin skin testing has not been established. A recent study from a large drug allergy database

found 3 of 10 cefazolin allergic patients to have had negative skin test results with cefazolin, one of whom had anaphylaxis on challenge.¹⁸ Cephalosporin allergic patients appear to tolerate other β -lactams, such as carbapenems and aztreonam, in more than 95% of cases.¹⁹

A few studies have evaluated macrolide skin tests. One study found that only 8 of 107 patients (7.5%) with a history of macrolide allergy reacted to oral challenge.¹⁷ Only 25 underwent skin testing to erythromycin and spiramycin (0.1, 1, 10 mg/mL), and 7 (28%) were positive only at the highest concentration; therefore, the authors concluded that oral challenge was the preferred diagnostic method. Another study evaluated 64 children with allergic reactions attributed to clarithromycin and found only 6% had positive challenge results. Skin testing was performed to a lyophilized form of clarithromycin (not available in the United States) and was found to have good negative predictive value (98%).²⁰

A few studies have evaluated quinolone skin testing. A retrospective study of 71 patients evaluated patients with mixed histories of immediate and delayed reactions to quinolones. Challenges were conducted in only 44 patients, and 16% had positive challenge results.²¹ Negative predictive value of skin tests was 94%, but positive predictive value was lower, and in fact many controls had positive skin test results. Another study evaluated 101 patients with both immediate and delayed reactions to quinolones using immediate skin testing and patch tests.²² Six of 51 patients (11.8%) with histories of immediate reactions had positive challenge results. The authors were unable to find nonirritating concentrations for intradermal tests and determined that prick testing was not helpful in determining hypersensitivity. These studies suggest that quinolone skin testing may be irritating, and interpretation of positive skin test results is challenging.

Compared with macrolides and quinolones, cephalosporin skin testing is more robust in terms of numbers of studies and numbers of patients studied. Nevertheless, the negative predictive value for any nonpenicillin antibiotic has not been well established, and caution should be used in interpreting results. Because of this dilemma, many experts do not perform skin testing with nonpenicillin antibiotics, with the exception of histories of anaphylaxis, where anecdotally it may be more helpful.

Skin testing using both delayed intradermal and patch tests has been used for certain delayed immunologic drug reactions, including maculopapular exanthems, fixed drug eruptions, and acute generalized exanthematous pustulosis.²³ The negative predictive values for these techniques have not been well established; therefore, a negative test result does not preclude a drug allergy.

In Vitro Tests

Several types of in vitro tests have been found to be useful in various research centers throughout the world. These tests include specific IgE tests, lymphocyte transformation tests, basophil activation tests, and other investigational assays.²⁴ Specific IgE testing for penicillin G has not been found to provide benefit in addition to routine penicillin skin testing.²⁵ Although data from research laboratories using lymphocyte transformation tests and basophil activation tests are promising, it is difficult to apply data on specificity and sensitivity from these research centers to commercially available tests in the United States. Commercial tests do not have the same methods as those used by research centers; thus, additional studies are needed to confirm the specificity, sensitivity, and predictive values for commercially available in vitro drug tests before routinely using these tests in clinical practice.

Drug Challenges

Given the limited negative predictive value of skin testing and in vitro tests to exclude drug allergy, a drug challenge is usually

required to determine tolerance to a drug. Terms to describe drug challenges include *graded dose challenge*, *test dosing*, and *drug provocation*. These are all diagnostic procedures to determine whether a patient will have an adverse reaction to a drug. A patient with a negative drug challenge result can typically be considered not to be allergic to the drug. However, false-negative drug challenges can occur because of such factors as inadequate dose, inadequate duration of drug, or a missing cofactor (eg, no concurrent infection). For β -lactams, false-negative results occur infrequently, with recent studies showing negative predictive values of 94% for drug challenges.²⁶ None of the reported reactions was life-threatening, most were delayed, and all were cutaneous (mostly urticaria or exanthem), and some patients with reported reactions had subsequent negative drug challenge results. It is important to differentiate between a drug challenge and an induction of drug tolerance procedure (eg, desensitization). Drug challenges do not modify an individual's immunologic or non-immunologic response to a given drug and merely answer the question "Can this patient tolerate this drug?"

In clinical practice, drug challenges are intended for patients who, after a full evaluation, are deemed to be at low risk for being allergic to the given drug. Patients with remote histories, vague or subjective symptoms, mild reactions that are self-limited, or histories not consistent with drug allergy (eg, headache) are examples of low-risk characteristics. Typical scenarios for performing drug challenges would be to exclude a drug allergy in a patient with an unconvincing history or to exclude cross-reactivity of structurally related drugs (eg, cephalosporins with different R-group side chains). Furthermore, the benefit of treatment with the drug should outweigh the risk of performing the drug challenge. Drug challenges are contraindicated in several types of drug reactions, such as autoimmune diseases (eg, drug-induced lupus), severe cutaneous adverse reactions (eg, Stevens-Johnson syndrome, drug rash with eosinophilia, and systemic symptoms); vasculitis; organ-specific drug reactions causing cytopenias, hepatitis, nephritis, or pneumonitis; and serum sickness.

Protocols for performing drug challenges vary but typically involve incremental dose escalation (graded challenge). Determining the starting dose is largely dependent on the pretest probability of true drug allergy. Factors such as severity of historical reaction, remoteness of reaction, atypical features, or other explanations for the reaction can all help determine the pretest probability. In other words, the more confident one is that the patient is not truly allergic, the higher the starting dose. Typical starting doses for graded challenges are usually 1/100th or 1/10th of the therapeutic dose but may be lower or higher, depending on the clinical situation. The frequency of dosing is dependent on the type of reaction, immediate or delayed. For immediate reactions, doses are typically administered every 30 to 60 minutes. For delayed reactions, one may choose to administer doses every several days to allow time for a reaction to develop. For patients with purely subjective symptoms or multiple drug allergies, strong consideration should be given to performing a single-blind, placebo-controlled challenge because drug-allergic patients may frequently have symptoms with placebo.^{27,28} For oral challenges, large, colored gelatin capsules can be used to conceal the drug tested, and an inert filler (eg, methylcellulose) can be used for placebo. Equipment to treat reactions from drug challenges are similar to those required to administer allergen immunotherapy. Epinephrine and other treatment for reactions to drug challenges are rarely required.

Induction of Drug Tolerance

In patients who have proven drug allergy (eg, history of urticaria and positive drug specific skin test result) or those with

a high likelihood of an allergic reaction (eg, recent anaphylaxis to the culprit drug) where the culprit drug is required without an alternative therapy, an induction of drug tolerance procedure can be a useful management tool. Induction of drug tolerance procedures results in a temporary state of tolerance to the drug. This temporary state of tolerance is different than the term *immunologic tolerance*, which implies a more permanent state of tolerance. Induction of drug tolerance is a procedure to modify a patient's response to a drug through IgE immune, non-IgE immune, pharmacologic, or other mechanisms to allow them to take the drug temporarily in a safe manner (ie, drug tolerance). The term *drug desensitization* is a term that has typically been used to describe procedures that induce drug tolerance. Strictly speaking, the term *drug desensitization* is one type of induction of drug tolerance procedure for patients with IgE-mediated sensitivity to a drug who afterward typically have diminished or absent skin test reactions and hence are less sensitive or desensitized.²⁹ For other types of induction of drug tolerance procedures where patients are not immunologically sensitized, the term *drug desensitization* can be confusing; hence, the term *induction of drug tolerance* is preferred. All procedures to induce drug tolerance involve administration of incremental doses of the drug but vary considerably over the starting dose and duration of the procedure. IgE immune induction of drug tolerance (eg, desensitization) procedures typically start with 1/10,000th of the therapeutic dose, whereas other induction of drug tolerance procedures may begin at 1/100th of the dose or greater. References for an in-depth discussion of induction of drug tolerance procedures include the Drug Allergy Practice Parameters, which includes 14 separate protocols,⁸ and the recent review from Castells and colleagues,³⁰ which discusses practical tips and safety of rapid drug desensitizations. Similar to drug challenges, a number of reactions are almost always contraindicated for induction of drug tolerance procedures, including autoimmune diseases (eg, drug-induced lupus); severe cutaneous adverse reactions (eg, Stevens-Johnson syndrome, drug rash with eosinophilia, and systemic symptoms); vasculitis; organ-specific drug reactions causing cytopenias, hepatitis, nephritis, or pneumonitis; and serum sickness.

Case Epilogue

The aforementioned case of the elderly woman with a history of "anaphylaxis" to multiple antibiotics, with symptoms of isolated throat itching, swelling, and dysphonia was not believed to represent drug-induced anaphylaxis but rather VCD. Fiberoptic rhinolaryngoscopy was performed and revealed normal vocal cord appearance and function. After informed consent, she underwent an open drug challenge with ciprofloxacin, 500 mg intravenously. Within 15 minutes of the beginning of the infusion, she developed a sensation of throat itching and tightness, which was soon followed by hoarseness without any objective oropharyngeal edema, and her vital signs and oxygen saturation remained normal. On direct questioning, she indicated that these were the same symptoms as her previous antibiotic "anaphylaxis." Repeat fiberoptic rhinolaryngoscopy was performed and revealed paradoxical adduction of the vocal cords during inspiration consistent with VCD. She was instructed on some throat relaxation techniques and within 5 minutes had complete resolution of her symptoms. She was able to complete the rest of her course of ciprofloxacin uneventfully.

Drug-Associated Vocal Cord Dysfunction

VCD is a well-known entity to the allergist/immunologist and has been the subject of a recent review in this journal.³¹ VCD is most commonly considered in the differential diagnosis of asthma; however, it can also be mistaken for anaphylaxis and, depending on the presentation, should be considered in the differential diagnosis

of anaphylaxis.³² Although laryngeal edema from anaphylaxis and VCD can both result in dyspnea, throat tightness, and stridor, certain clues are suggestive of VCD. Most patients with laryngeal edema from anaphylaxis will have readily visible oropharyngeal edema and often other signs of anaphylaxis (eg, urticaria). Regarding drug-induced laryngeal edema, it would be extremely rare for someone to have this type of immunologic response to numerous non-cross-reactive medications of differing chemical structure. In our experience, VCD is a relatively common presentation in patients with multiple antibiotic allergies, particularly those with histories of multiple episodes of “anaphylaxis.” Nevertheless, there are only rare reports of drug-associated VCD mimicking anaphylaxis in the literature.³³ Hence, in a patient with a history of isolated throat “swelling” without objective confirmation to multiple medications, a diagnosis of drug-induced VCD should be considered. Drug challenge with confirmation via direct laryngoscopy is extremely helpful in properly diagnosing this condition.

Conclusion

Although specific diagnostic tools are limited, even patients with multiple medication allergy can typically be effectively managed. As allergist/immunologists we are commonly asked to help manage patients with multiple antibiotic allergies. Although often viewed as a daunting challenge, such patients can typically be managed through a combination of a detailed history, penicillin skin testing (when appropriate or other antibiotic skin tests), and 1 to 2 graded challenges of different antibiotic classes. All of this can be performed in an allergist's office without special laboratory equipment. Patients are extremely grateful for this service that is unique to our specialty but unfortunately underused.

References

- [1] Sullivan TJ, Ong RC, Gilliam LK. Studies of the multiple drug allergy syndrome [abstract]. *J Allergy Clin Immunol*. 1989;83:270.
- [2] Khoury L, Warrington R. The multiple drug allergy syndrome: a matched-control retrospective study in patients allergic to penicillin. *J Allergy Clin Immunol*. 1996;98:462–464.
- [3] Warrington R. Multiple drug allergy syndrome. *Can J Clin Pharmacol*. 2000;7:18–19.
- [4] Schiavino D, Nucera E, Roncallo C, et al. Multiple-drug intolerance syndrome: clinical findings and usefulness of challenge tests. *Ann Allergy Asthma Immunol*. 2007;99:136–142.
- [5] Ramam M, Bhat R, Jindal S, et al. Patient-reported multiple drug reactions: clinical profile and results of challenge testing. *Indian J Dermatol Venereol Leprol*. 2010;76:382–386.
- [6] Macy E, Ho NJ. Multiple drug intolerance syndrome: prevalence, clinical characteristics, and management. *Ann Allergy Asthma Immunol*. 2012;108:88–93.
- [7] De Pasquale T, Nucera E, Boccascino R, et al. Allergy and psychologic evaluations of patients with multiple drug intolerance syndrome. *Intern Emerg Med*. 2012;7:41–47.
- [8] Solensky R, Gruchalla RS. Nonanaphylactic drug disorders. *Clin Allergy Immunol*. 2002;16:411–433.
- [9] Drug allergy: an updated practice parameter. *Ann Allergy Asthma Immunol*. 2010;105:259–273.
- [10] Green GR, Rosenblum AH, Sweet LC. Evaluation of penicillin hypersensitivity: value of clinical history and skin testing with penicilloyl-polylysine and penicillin G. A cooperative prospective study of the penicillin study group of the American Academy of Allergy. *J Allergy Clin Immunol*. 1977;60:339–345.
- [11] del Real GA, Rose ME, Ramirez-Atamoros MT, et al. Penicillin skin testing in patients with a history of beta-lactam allergy. *Ann Allergy Asthma Immunol*. 2007;98:355–359.
- [12] Gadde J, Spence M, Wheeler B, Adkinson NF Jr. Clinical experience with penicillin skin testing in a large inner-city STD clinic. *JAMA*. 1993;270:2456–2463.
- [13] Sogn DD, Evans R III, Shepherd GM, et al. Results of the National Institute of Allergy and Infectious Diseases Collaborative Clinical Trial to test the predictive value of skin testing with major and minor penicillin derivatives in hospitalized adults. *Arch Intern Med*. 1992;152:1025–1032.
- [14] Ressler C, Neag PM, Mendelson LM. A liquid chromatographic study of stability of the minor determinants of penicillin allergy: a stable minor determinant mixture skin test preparation. *J Pharm Sci*. 1985;74:448–454.
- [15] Empedrad R, Darter AL, Earl HS, Gruchalla RS. Nonirritating intradermal skin test concentrations for commonly prescribed antibiotics. *J Allergy Clin Immunol*. 2003;112:629–630.
- [16] Antunez C, Blanca-Lopez N, Torres MJ, et al. Immediate allergic reactions to cephalosporins: evaluation of cross-reactivity with a panel of penicillins and cephalosporins. *J Allergy Clin Immunol*. 2006;117:404–410.
- [17] Romano A, Gueant-Rodriguez RM, Viola M, et al. Diagnosing immediate reactions to cephalosporins. *Clin Exp Allergy*. 2005;35:1234–1242.
- [18] Pipet A, Veyrac G, Wessel F, et al. A statement on cefazolin immediate hypersensitivity: data from a large database, and focus on the cross-reactivities. *Clin Exp Allergy*. 2011;41:1602–1608.
- [19] Romano A, Gaeta F, Valluzzi RL, Caruso C, Rumi G, Bousquet PJ. IgE-mediated hypersensitivity to cephalosporins: cross-reactivity and tolerability of penicillins, monobactams, and carbapenems. *J Allergy Clin Immunol*. 2010;126:994–999.
- [20] Mori F, Barni S, Pucci N, et al. Sensitivity and specificity of skin tests in the diagnosis of clarithromycin allergy. *Ann Allergy Asthma Immunol*. 2010;104:417–419.
- [21] Venturini Diaz M, Lobera Labairu T, del Pozo Gil MD, Blasco Sarrañan A, Gonzalez Mahave I. In vivo diagnostic tests in adverse reactions to quinolones. *J Invest Allergol Clin Immunol*. 2007;17:393–398.
- [22] Seitz CS, Brocker EB, Trautmann A. Diagnostic testing in suspected fluoroquinolone hypersensitivity. *Clin Exp Allergy*. 2009;39:1738–1745.
- [23] Barbaud A. Skin testing in delayed reactions to drugs. *Immunol Allergy Clin North Am*. 2009;29:517–535.
- [24] Lochmatter P, Zawodniak A, Pichler WJ. In vitro tests in drug hypersensitivity diagnosis. *Immunol Allergy Clin North Am*. 2009;29:537–554.
- [25] Macy E, Goldberg B, Poon KY. Use of commercial anti-penicillin IgE fluorometric enzyme immunoassays to diagnose penicillin allergy. *Ann Allergy Asthma Immunol*. 2010;105:136–141.
- [26] Demoly P, Romano A, Botelho C, et al. Determining the negative predictive value of provocation tests with beta-lactams. *Allergy*. 2010;65:327–332.
- [27] Hein UR, Chantraine-Hess S, Worm M, Zuberbier T, Henz BM. Evaluation of systemic provocation tests in patients with suspected allergic and pseudoallergic drug reactions. *Acta Derm Venereol*. 1999;79:139–142.
- [28] Llicardi G, Senna G, Russo M, et al. Evaluation of the nocebo effect during oral challenge in patients with adverse drug reactions. *J Invest Allergol Clin Immunol*. 2004;14:104–107.
- [29] Stark BJ, Earl HS, Gross GN, Lumry WR, Goodman EL, Sullivan TJ. Acute and chronic desensitization of penicillin-allergic patients using oral penicillin. *J Allergy Clin Immunol*. 1987;79:523–532.
- [30] Liu A, Fanning L, Chong H, et al. Desensitization regimens for drug allergy: state of the art in the 21st century. *Clin Exp Allergy*. 2011;41:1679–1689.
- [31] Gimenez LM, Zafra H. Vocal cord dysfunction: an update. *Ann Allergy Asthma Immunol*. 2011;106:267–274.
- [32] Lieberman P, Nicklas RA, Oppenheimer J, et al. The diagnosis and management of anaphylaxis practice parameter: 2010 update. *J Allergy Clin Immunol*. 2010;126:477–480.
- [33] Nugent JS, Nugent AL, Whisman BA, White K, Hagan LL. Levothyroxine anaphylaxis? vocal cord dysfunction mimicking an anaphylactic drug reaction. *Ann Allergy Asthma Immunol*. 2003;91:337–341.