Antibiotic Allergies in Children and Adults: From Clinical Symptoms to Skin Testing Diagnosis

Antonino Romano, MD[a,b], and Jean-Christoph Caubet, MD[c] *Rome and Troina, Italy; and Geneva, Switzerland*

Hypersensitivity reactions to β-lactam and non-β-lactam antibiotics are commonly reported. They can be classified as immediate or nonimmediate according to the time interval between the last drug administration and their onset. Immediate reactions occur within 1 hour after the last drug administration and are manifested clinically by urticaria and/or angioedema, rhinitis, bronchospasm, and anaphylactic shock; they may be mediated by specific IgE-antibodies. Nonimmediate reactions occur more than 1 hour after the last drug administration. The most common manifestations are maculopapular exanthems; specific T lymphocytes may be involved in this type of manifestation. The diagnostic evaluation of hypersensitivity reactions to antibiotics is usually complex. The patient's history is fundamental; the allergic examination is based mainly on *in vivo* tests selected on the basis of the clinical features and the type of reaction, immediate or nonimmediate. Immediate reactions can be assessed by immediate-reading skin tests and, in selected cases, drug provocation tests. Nonimmediate reactions can be assessed by delayed-reading skin tests, patch tests, and drug provocation tests. However, skin tests have been well validated mainly for β-lactams but less for other classes of antibiotics. © **2014 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2014;2:3-12)**

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Antibiotics can be classified as β-lactam and non-β-lactam. The former consists of 2 major classes (penicillins and cephalosporins) and 4 minor ones (carbapenems, monobactams, oxacephems, and clavams), all of which contain a 4-membered β-lactam ring. Non-β-lactam antibiotics (eg, quinolones, sulfonamides, macrolides, aminoglycosides, rifamycins, glycopeptides, and clindamycin) have very different chemical structures, antimicrobial spectra, and immunogenic properties. Hypersensitivity reactions to antibiotics are commonly reported both in adults and children, with a prevalence of approximately 10%.[1-3] They are adverse effects of antibiotics that clinically resemble allergy[4] and belong to the type B of adverse drug reactions, which have been defined by Rawlins and Thompson[5] as dose independent and unpredictable noxious, and unintended responses to drugs taken at a dose normally used in humans. Only when a definite immunologic mechanism is demonstrated should these reactions be classified as allergic. The latter reactions can be further classified according to the Coombs and Gell classification system into 4 types: I (mediated by drug-specific IgE antibodies), II (cytotoxic), III (mediated by drug-specific IgG or IgM antibodies), and IV (mediated by drug-specific T lymphocytes).

Clinically, hypersensitivity reactions to antibiotics are commonly classified as immediate or nonimmediate according to the time interval between the last drug administration and their onset.[6] Immediate reactions occur within the first hour after drug administration and are possibly induced by an IgE-mediated mechanism. They usually are manifested as urticaria, angioedema, conjunctivitis, rhinitis, bronchospasm, gastrointestinal symptoms, and anaphylactic shock. Nonimmediate reactions are those that occur more than 1 hour after drug administration and are often associated with a delayed T-cell-dependent type of allergic mechanism. The most common nonimmediate reactions are maculopapular exanthemas and delayed-appearing urticaria and/or angioedema; more rarely, fixed drug eruption, exfoliative dermatitis, acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) can be elicited.[7,8] Furthermore, certain antibiotics can even cause interstitial nephritis, pneumonitis, hepatitis, and/or vasculitis with or without signs of serum sickness as well as drug reactions (or rash) with eosinophilia and systemic symptoms (DRESS), also called drug-induced hypersensitivity syndrome.[7]

Assessment of hypersensitivity reactions to antibiotics is clinically complex. A detailed clinical history of the patient's reaction is required, including the symptoms, the time elapsed between administration of the drug and the appearance of symptoms, and that elapsed between the clinical reaction and the allergic evaluation. Confirmation of the diagnosis should be based on skin tests,[8-13] *in vitro* tests,[6,7] and drug provocation tests (DPT).[12,14,15] The allergy tests are selected on the basis of the clinical features and the type of reaction, immediate or nonimmediate. Immediate reactions can be assessed *in vitro* by serum-specific IgE assays and flow cytometric basophil activation tests (BAT), and *in vivo* by immediate-reading skin tests and, in selected cases, DPTs. Nonimmediate reactions can be evaluated *in vitro* with lymphocyte transformation tests (LTT), lymphocyte activation tests (LAT), and enzyme-linked immunospot (ELISpot; Millipore, Bedford, Mass) assays for analysis of

[a]Allergy Unit, Complesso Integrato Columbus, Rome, Italy
[b]Istituto di Ricovero e Cura a Carattere Scientifico Oasi Maria S.S., Troina, Italy
[c]Department of Child and Adolescent, University Hospitals of Geneva and Medical School of The University of Geneva, Geneva, Switzerland
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Corresponding author: Jean-Christoph Caubet, MD, Département de Pédiatrie, Hôpitaux Universitaires de Genève, 6 rue Willy-Donzé, CH-1211 Genève 14, Switzerland. E-mail: Jean-Christoph.Caubet@hcuge.ch.
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Abbreviations used
AGEP- Acute generalized exanthematous pustulosis
AM- Ampicillin
AX- Amoxicillin
BAT- Basophil activation tests
BP- Benzylpenicillin
CLV- Clavulanic acid
DPT- Drug provocation tests
DRESS- Drug reaction (or rash) with eosinophilia and systemic symptom
LTT- Lymphocyte transformation test
SJS- Stevens-Johnson syndrome
TEN- Toxic epidermal necrolysis

antigen-specific, cytokine-producing cells, and *in vivo* by delayed-reading skin prick tests, patch tests, and DPTs. In severe reactions (eg, SJS, TEN, AGEP, and DRESS), the European guidelines[10] advise not to perform intradermal tests with the highest concentrations before performing patch tests. In effect, patch tests are useful and safe for identifying agents, including β-lactams, quinolones, vancomycines, and amikacin, responsible for severe cutaneous reactions, as demonstrated by a recent multicenter study by Barbaud et al.[16]

However, skin tests have been well validated mainly for β-lactams but less well validated for other classes of antibiotics. Moreover, they are not indicated for evaluating types II and III reactions. Therefore, these reactions will not be discussed in this article. With regard to *in vitro* tests, there are some concerns about the usefulness of serum-specific IgE assays, especially in subjects with a remote history of penicillin allergy.[17] The other tests (BAT, LTT, lymphocyte activation test, and ELISpot assays) have not been fully validated in large samples of subjects. Moreover, the LTT and its variants are still complex procedures, which require skilled personnel and specific experience.[18]

β-LACTAM ANTIBIOTICS

Together with cephalosporins, penicillins are the antibiotics that most frequently provoke hypersensitivity reactions mediated by immunologic mechanisms. Specifically, penicillin allergy is the most commonly reported drug allergy, with a prevalence rate of 5% to 10% in adults and children.[1,19-21] With regard to the responsible penicillins, benzylpenicillin (BP) has progressively been replaced by amoxicillin (AX) and to a lesser extent by other penicillins. There is increasing evidence that supports the role of side chains as the relevant part of the structure of the allergenic determinants.[9] Two distinct diagnostic algorithms for evaluating either immediate or nonimmediate reactions to β-lactams can be applied.

Immediate reactions

Immediate reactions can be evaluated by using an algorithm, which combines skin tests with a common panel of reagents, including the classic penicillin reagents (penicilloyl-polylysine [PPL], minor determinant mixture [MDM], and BP) and AX as well as any other suspect β-lactam, and DPTs (Figure 1). In both the European guidelines[9] and the American practice parameters,[12] skin testing represents the first-line method for diagnosing immediate hypersensitivity reactions to β-lactams (Figure 1). The highest concentrations accepted nowadays in both prick and intradermal testing are the following: 5×10^{-5} mmol/L for PPL (ie, undiluted), 2×10^{-2} mmol/L for MDM (ie, undiluted), 10,000 IU/mL for BP, 20 mg/mL for AX, and any other suspect penicillin, as well as for cephalosporins, excluding cefepime, which should be tested at 2 mg/mL.[13] In Europe, both PPL and MDM are available (DAP; Diater, Madrid, Spain), whereas, in the United States only PPL is (PRE-PEN, AllerQuest LLC, West Hartford, Conn). Skin testing only with PPL and BP (without penicilloate or penilloate) may miss up to 20% of patients with penicillin allergy, but these data are controversial, and several studies, including DPTs, have shown a similar rate of reactions in patients who display negative skin prick tests to PPL and BP compared with patients with negative skin prick tests to the full set of major and minor penicillin determinants.[22-24] In Europe, AX and ampicillin (AM) for parenteral administration are used for skin testing. The final concentration of these penicillins, which are sodium salts, ranges from 100 to 200 mg/mL; thus, it is easy to obtain a solution of 20 mg/mL. In the United States, instead, some clinicians[25] use a trihydrate compound of AX that cannot be dissolved beyond 4 mg/mL unless the pH is raised to 8.5, which converts it into a sodium salt. For noninjectable cephalosporins, the powder contained in capsules or obtained by removing the external layer of tablets with a scalpel can be used. After weighing the powder, solutions are prepared under a laminar flow and are sterilized by filtration through single-use devices, as previously described.[26] It is advisable to perform skin tests with the classic penicillin determinants as well as with AX and any other suspect β-lactam. The guidelines devised by the European Network for Drug Allergy, the European Academy of Allergy and Clinical Immunology interest group on drug hypersensitivity, to which both of us belong, also include serum-specific IgE assays, because cases of patients with clear-cut histories of immediate hypersensitivity reactions to β-lactams that display negative results in skin tests and positive ones in such assays have been reported.[9] Moreover, these guidelines suggest to perform *in vitro* tests before skin testing in subjects with a history of severe anaphylaxis to reduce the risk of systemic reactions to skin prick tests. Another option for increased safety (instead of *in vitro* testing) is starting skin testing with diluted reagents.

In selected cases, DPTs (or graded challenges)[27] with the suspect β-lactam may be performed according to the recommendations of the international guidelines.[9,11,12,14] The authors of the US Practice Parameters[12] consider that the DPT is intended for patients who, after a thorough evaluation, are unlikely to be allergic to the given drug. According to this indication, negative skin tests with β-lactam reagents can be followed by a full-dose DPT to verify that a patient will not experience an immediate adverse reaction to a given β-lactam. The European Academy of Allergy and Clinical Immunology—European Network for Drug Allergy guidelines[9,11,14] address the role of the DPT as a gold standard to establish a firm diagnosis in subjects with clear-cut histories and negative allergy tests. In this case, DPTs can be performed by administering an initial dose of one hundredth of the therapeutic one. In patients with negative results, a one-tenth dose is administered 1 hour later, and, if the result is again negative, then a full dose is administered after another hour.

In the case of IgE-mediated hypersensitivity to β-lactams, skin-test sensitivity may decrease with time.[11] For this reason, the European guidelines[9] advise to retest patients who experienced immediate reactions to β-lactams and display negative

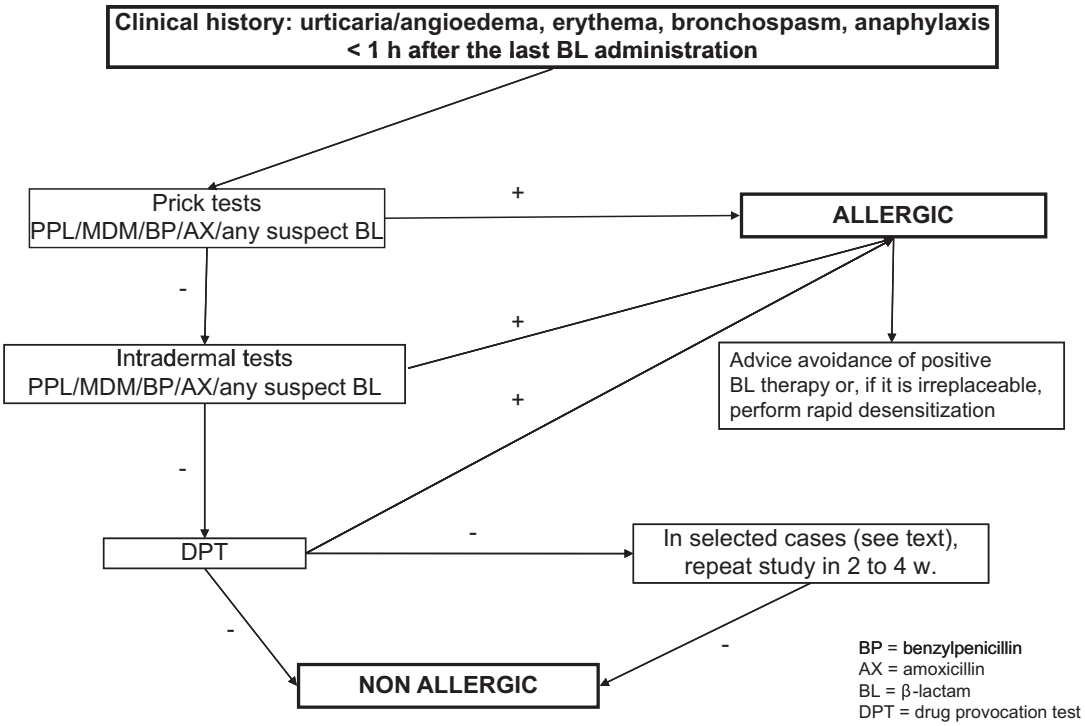

FIGURE 1. Algorithm for the diagnosis of immediate allergic reactions to β-lactams.

results in the first allergic evaluation, including DPTs, as shown in Figure 1. However, the US practice parameters[12] state that resensitization after treatment with oral penicillin is rare, and, therefore, penicillin skin testing does not routinely need to be repeated in patients with a history of penicillin allergy who have tolerated one or more courses of oral penicillin, whereas resensitization after treatment with parenteral penicillin appears to be higher than for oral treatment and, therefore, repeated penicillin skin testing may be considered in patients with a history of penicillin allergy who have tolerated a course of parenteral penicillin.

Torres et al[27] evaluated 330 patients with histories of immediate hypersensitivity reactions to penicillins with a diagnostic workup similar to that shown in Figure 1. Positive skin tests to at least one determinant were observed in 203 of the 330 subjects evaluated (61.5%); 38 (11.5%) were skin-test negative and ImmunoCAP (Thermo Fisher, Portage, Mich) positive, 49 (14.8%) were skin-test and ImmunoCAP negative and reacted to DPTs, and 40 (12.1%) were negative in allergic workups, including DPTs. In a recent study by Macy and Ngor[28] that concerned 500 subjects with histories of penicillin allergy, the rate of positive responses to skin tests with PPL and BP was 0.8; only 4 persons (0.8%) had an acute objective reaction to the oral AX challenge. These different results can be explained mainly by differences in the characteristics of the samples assessed and in the protocol used. In the study by Torres et al,[27] all 330 subjects were immediate reactors; 53.1% of them had experienced anaphylactic reactions, and 29% urticarial and/or angioedematous reactions. In the aforesaid American study,[28] only 52 participants (10.4%) had reacted within 1 hour; the index penicillin class antibiotic-associated adverse reaction in tested subjects was anaphylaxis in 14 (2.8%) and urticaria and/or angioedema in 169 (33.8%).

Regarding cephalosporins, in 3 European studies that involved adults,[26] both children and adults,[29] and children[30] with histories of immediate reactions to cephalosporins, the rate of positive responses to skin tests with cephalosporins at a concentration of 2 mg/mL was 69.7% (53/76 subjects), 30.7% (39/127), and 72.1% (31/43), respectively.

Diagnostic evaluation of children

Immediate hypersensitivity to β-lactams is particularly rare in children, but identification of these patients is particularly important because these reactions can be life threatening. Children who experienced immediate reactions should be evaluated by using the same diagnostic protocol as adults. In a large study, Ponvert et al[31] evaluated 1431 children with a suspicion of β-lactam hypersensitivity, including 162 patients who reported immediate reactions. A β-lactam hypersensitivity was confirmed in 50 of these 162 children (30.9%), the vast majority (86%) being identified by positive skin prick tests. However, they did not use PPL and MDM in skin testing. Interestingly, the likelihood of β-lactam hypersensitivity was significantly higher in the children who reported immediate hypersensitivity compared with children who reported a nonimmediate reaction ($P < .01$). Several studies confirmed the safety of skin tests in children, with a rate of 1% to 3% of systemic reactions to skin testing.[31-34] In children, the negative predictive value of the DPT has been shown to be high, and retesting has been suggested to be reserved only to patients with severe reactions.[35,36]

Nonimmediate reactions

The first approach for establishing the diagnosis is a clear-cut history. However, the identification of a nonimmediate reaction is sometimes difficult because of the heterogeneity of the clinical manifestations, which can be quite similar to the symptoms of

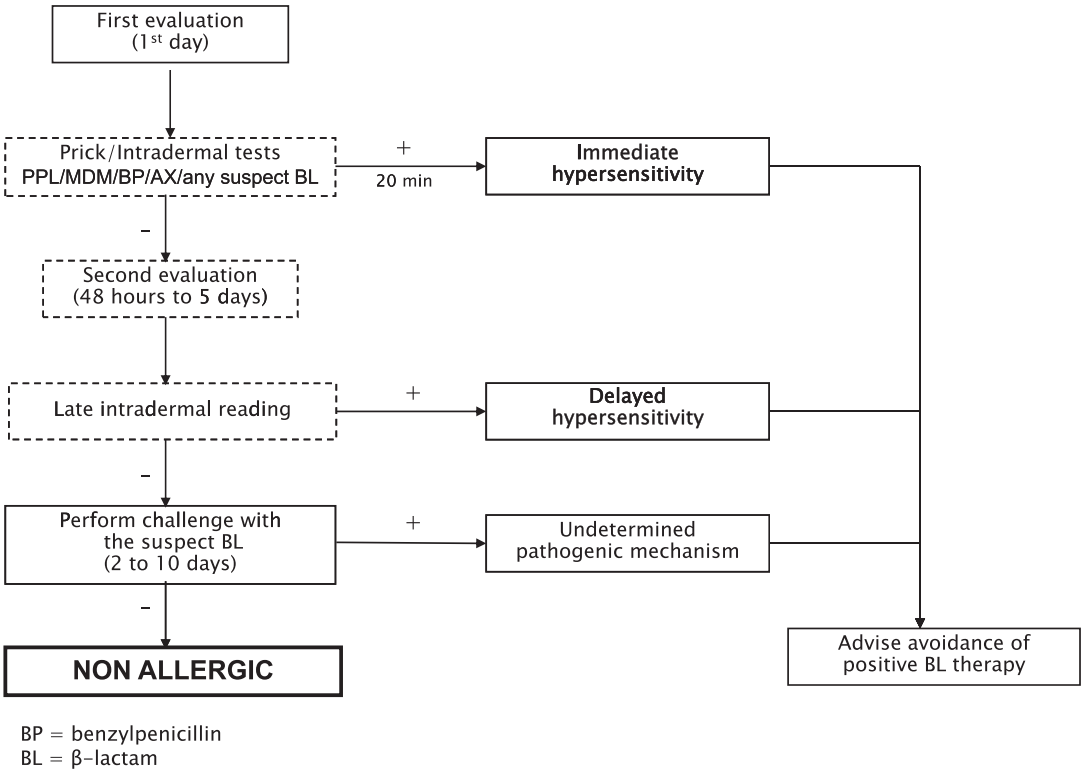

FIGURE 2. Algorithm for the diagnosis of nonimmediate allergic reactions to β-lactams.

infectious diseases. Moreover, these reactions may be favored by a concomitant viral infection, such as those caused by HIV, cytomegalovirus, human herpes virus 6, or Epstein Barr Virus.[9] Shown in Figure 2 is an algorithm for *in vivo* allergic evaluation of nonimmediate reactions to β-lactams, which combines skin prick tests with the classic penicillin reagents (PPL, MDM, and BP), AM, and AX as well as any other suspect β-lactam and DPTs. The aforesaid reagents are tested up to the highest concentrations recommended for evaluating immediate reactions. Subjects who experienced mild reactions and are negative in all of the above tests could, in addition, undergo DPTs with the suspect β-lactam. An initial dose of one-hundredth of the therapeutic one can be administered. In cases with negative results, 3 days to 1 week later (depending on the time interval between drug intake and adverse reaction), a dose of one-tenth should be given and, if the result is again negative, after the same time interval chosen before, a full dose. This algorithm does not advise retesting subjects who had nonimmediate reactions and present negative results in both patch tests and delayed-reading intradermal tests. In fact, unlike IgE-mediated hypersensitivity, delayed hypersensitivity to penicillins seems to be a persistent condition.[8]

In a recent study,[37] 162 of 433 adults (37.4%) with a history of nonimmediate reactions to penicillins had positive allergy tests; 157 of the 162 (96.9%) displayed patch-test and/or delayed-reading intradermal-test positivity to penicillin reagents, which indicates a T-cell-mediated hypersensitivity. All of these 157 patients were positive to the responsible penicillins (parent drugs); 16 of them also displayed delayed-reading intradermal-test positivity to MDM. Five of the 162 patients (3.1%) presented only immediate-reading skin-test positivity (4 to PPL and 1 to AX). In this study, 239 subjects with negative results in allergy tests underwent challenges with the suspect penicillins according to the aforesaid protocol; only 7 (2.9%) reacted.[37] Another study by the same group evaluated 105 adults with nonimmediate reactions to cephalosporins; 7 (6.6%) displayed positive results in allergy tests.[38] Of the 98 subjects who were negative, 86 accepted challenges with the suspect cephalosporins and tolerated them.[38]

Nevertheless, there are some concerns whether a single therapeutic dose is sufficient to confirm or exclude a delayed hypersensitivity to penicillins. In a recent study, 22 patients with histories of nonimmediate reactions to penicillins displayed negative results in allergic workups, including challenges, and underwent a 10-day therapeutic course: 11 patients experienced cutaneous reactions.[39] However, a multicenter study performed on subjects with either immediate or nonimmediate reactions to β-lactams, mostly penicillins,[40] demonstrated that the negative predictive value of DPTs with single doses of the suspect β-lactam was 94.1% (111 of 118 patients).

Patients at high risk

If it is necessary to evaluate patients who experienced severe reactions (eg, SJS, TEN, AGEP, and DRESS), then, according to the European guidelines,[8-10] patch tests should be used as the first line of investigation with BP, AM, AX, and any suspect β-lactam at a concentration of 5% in petrolatum. In case of positive results, skin prick tests should be avoided. In case of patch-test negativity, for intradermal testing, the drug should be initially tested with the highest dilution.

Diagnostic evaluation of children

Delayed-onset urticarial or maculopapular rashes are frequently observed in children treated with β-lactams, with an estimated frequency of 1% to 5% rashes per prescription.[19] In children, the percentage of penicillin-associated nonimmediate skin eruptions, particularly maculopapular exanthems and delayed-appearing urticarial eruptions, which actually represent allergic phenomena, is significantly lower than in adults.[41] In fact, in children, such manifestations are thought to be mainly caused by the infection itself.[42] An allergic reaction can be demonstrated by a DPT in fewer than 10% of the patients who developed a rash while on β-lactams.[31,36,42,43] Because there currently is no specific test to distinguish between a viral infection and an allergy in the acute phase, an allergic workup should be performed in all children with a suspicion of allergy, ideally 2 months later. Regarding the diagnostic value of allergy tests, few pediatric studies have been published. In a large study by Ponvert et al,[31] 68.4% of nonimmediate reactions were diagnosed by DPTs, which highlights the importance of such tests in the diagnosis of these reactions in children. In a study by Caubet et al,[42] 88 children with delayed-onset urticarial or maculopapular rashes associated with β-lactam therapy were evaluated by skin tests, patch tests, and DPTs. All 88 children underwent oral challenges: 6 (6.8%) reacted; 4 were intradermal-test positive, and 2 intradermal-test negative. The sensitivity of intradermal testing was 66.7%, and the specificity was 91.5%; 88 children needed to undergo skin testing to identify only 4 patients with β-lactam hypersensitivity. Based on these results and when taking into account the difficulty of performing painful intradermal tests in children, the investigators concluded that a physician-supervised DPT, administered as one dose followed by standard dosing for 48 hours at home, is a safe and efficient diagnostic procedure.[42] Several recent studies confirmed the safety of DPTs in children who developed a benign rash (no severity signs), provided that the clinician observes the initial reaction first hand or has a clear documentation of the rash in the medical record.[31,36,42-46] In the study by Caubet et al,[42] however, children with positive intradermal tests had a higher rate of positive DPTs than those without a positive test ($P < .05$), which led one of us (A.R.) to advise performing delayed-reading intradermal tests only with the suspect β-lactams at the highest concentration and, in case of negative results, DPTs. In fact, such an approach would allow the physician to diagnose by skin testing those patients with true delayed hypersensitivity, thus preventing positive responses to DPTs. Further large studies are needed in different populations to determine the optimal management of those patients.

Subjects with an undefined time interval between the last drug administration and the hypersensitivity reaction

These subjects can be considered as nonimmediate reactors and can be evaluated according to the diagnostic algorithm shown in Figure 2, which includes both immediate- and delayed-reading skin tests as well as DPTs.

Hypersensitivity reactions to monobactams (aztreonam), carbapenems (imipenem, meropenem), and clavulanic acid

Allergic reactions to these β-lactams appear to be uncommon. In any case, they can be assessed by using the diagnostic algorithms shown in Figures 1 and 2, depending on the reaction type, immediate or nonimmediate. Skin testing with a nonirritating concentration of native aztreonam (2 mg/mL in normal saline solution) has proved to be useful in diagnosing single cases of immediate hypersensitivity to this monobactam.[47-49] Chen et al[50] reported a case of IgE-mediated anaphylaxis to imipenem-cilastatin diagnosed on the basis of a positive skin prick test with imipenem-cilastatin (at a concentration of 1 mg/mL of each component in normal saline solution) as well as a positive serum-specific IgE assay. A case of occupational allergic contact dermatitis from meropenem, with a positive patch test at 5% in petrolatum has also been reported.[51]

Recent studies have demonstrated that clavulanic acid (CLV) is responsible for several IgE-mediated reactions to pharmaceutical preparations in which it is combined with AX.[31,52,53] Therefore, CLV should also be tested in subjects with reactions to AX-CLV, especially in those who display negative results in allergy tests with AX. In some of the aforesaid studies,[52,53] subjects with reactions to AX-CLV have been evaluated by both skin tests at concentrations up to 20 mg/mL and *in vitro* (serum-specific IgE assays and BATs). However, CLV alone is not available for skin testing; therefore, AX-CLV (20 mg/mL AX and 4 mg/mL CLV) can be used.

Safe administration of alternate β-lactams to β-lactam-allergic subjects

Cross-reactions are frequent among penicillins as well as among cephalosporins; they also can occur among classes, particularly between penicillins and cephalosporins.[54] Therefore, subjects with a well-demonstrated hypersensitivity to penicillins or other β-lactams should avoid the responsible drug as well as those potentially cross-reactive. Specifically, patients allergic to AX should avoid cephalosporins with identical R-group side chains (cefadroxil, cefprozil, cefatrizine). Similarly, patients allergic to AM should avoid cephalosporins and carbacephems with identical R-group side chains (cephalexin, cefaclor, cephradine, cephaloglycin, loracarbef).[12] Cross-reactivity related to the common β-lactam ring appears to be very rare. However, subjects who present IgE antibodies against such a ring, which is shared by all β-lactams, have been found.[55-57] More frequently, cross-reactivity is connected with the antigenic determinants of side chain structures.

The clinician faced with a patient with a documented allergic hypersensitivity (positive allergy tests) to a β-lactam and a compelling need for an alternate one should perform skin tests with the latter; if skin test results are negative, she or he can give the β-lactam concerned with a graded challenge. This approach has proved to be safe in administering cephalosporins,[58] aztreonam,[59,60] and carbapenems[55,56,61,62] to subjects allergic to penicillin as well as in administering penicillins, aztreonam, and carbapenems to individuals allergic to cephalosporin.[57] In fact, pretreatment skin testing allows the physician to detect not only cross-reactivity among β-lactams sharing common antigenic determinants but also any concomitant sensitizations.[58]

NON-β-LACTAM ANTIBIOTICS

Quinolones

Quinolones can be classified according to their generation: first (cinoxacin and nalidixic acid), second (ofloxacin, norfloxacin, ciprofloxacin, and enoxacin), third (levofloxacina), and fourth (gemifloxacin and moxifloxacin). Hypersensitivity

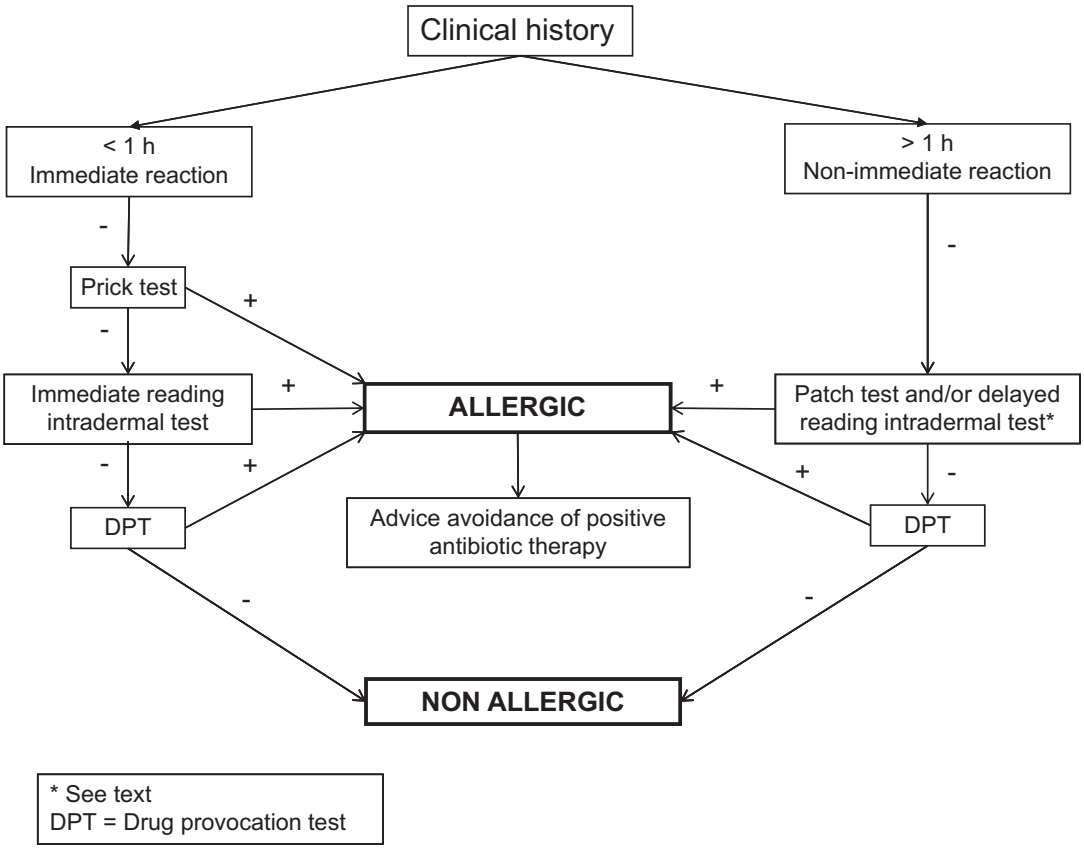

FIGURE 3. Algorithm for the diagnosis of allergic reactions to non-β-lactams antibiotics.

reactions to quinolones have been increasing over the past decade.[63] Quinolones also have been increasingly used in children, particularly in those with cystic fibrosis, and allergic reactions have become more commonly reported in the past decade.[63]

Most hypersensitivity reactions to quinolones are of the nonimmediate type, the most frequent manifestation being maculopapular rash. The estimated incidence of skin rashes varies between different quinolones, which range from 1% to 7%, gemifloxacin being associated with a higher incidence of skin rashes (particularly in female patients younger than 40 years old).[64-66] Fixed drug eruptions, AGEP, SJS, and TEN to quinolones are rare.[16,63] A T-cell-mediated pathogenic mechanism has been demonstrated in some patients with maculopapular exanthemas or AGEP on the basis of positive responses to patch tests and/or LTTs.[16,67] Immediate reactions to quinolones are less frequent than nonimmediate ones,[63,68-72] with a reported incidence between 1:1000 and 1:1,000,000.[73,74] Two studies, performed in 55 subjects[68] and 38 subjects,[71] respectively, with immediate reactions to quinolones, demonstrated an IgE-mediated pathogenic mechanism in more than 50% of patients, who underwent either sepharose-radioimmunoassays [68] or both sepharose-radioimmunoassays and BATs.[71]

Hypersensitivity reactions to quinolones can be assessed by using the diagnostic algorithm shown in Figure 3. With regard to skin testing, analysis of the literature data indicates that skin prick tests with levofloxacin up to 5 mg/mL, ciprofloxacin up to 2 mg/mL, and moxifloxacin up to 5 mg/mL are nonirritant, as are intradermal tests with levofloxacin up to 0.05 mg/mL, ciprofloxacin up to 0.006 mg/mL, and moxifloxacin up to 0.004 mg/mL.[63,75,76] However, skin testing is not considered a completely reliable tool for diagnosing hypersensitivity reactions to quinolones, mainly because it can induce both false-positive and false-negative results.[69,70,72] Seitz et al[70] evaluated 64 subjects with immediate reactions to quinolones; 3 of the 6 subjects with positive skin tests, who underwent challenges, tolerated them, whereas 3 of the 45 subjects with negative skin tests, who accepted challenges, reacted. Therefore, DPTs are considered the gold standard in the diagnosis of hypersensitivity reactions to quinolones. Cross-reactivity is common between first- and second-generation quinolones, and, to a lesser extent, between the third and fourth generations.[63] In particular, a broad pattern of cross-reactivity among quinolones was demonstrated by Manfredi et al [68] in 24 of 30 patients with an IgE-mediated hypersensitivity. In any case, the pattern of cross-reactivity is complex and difficult to predict.[63]

Macrolides

Macrolides are classified according to the number of carbon atoms in their lactone ring: 14 membered (erythromycin, troleandomycin, roxithromycin, dirithromycin, and clarithromycin), 15 membered (azithromycin), and 16 membered (spiramycin, rokitamycin, josamycin, and midecamycin). Hypersensitivity reactions to macrolides are relatively uncommon (0.4%-3% of treatments).[77] Cases of immediate reactions in the form of urticaria and/or angioedema; rhinoconjunctivitis; and anaphylaxis; and

nonimmediate reactions, such as maculopapular rash, delayed-appearing urticaria, contact dermatitis, fixed drug eruptions, and TEN, have been reported in children and adults.[77-82]

Hypersensitivity reactions to macrolides can be assessed by using the diagnostic algorithm shown in Figure 3. As far as skin testing is concerned, a study by Empedrad et al[75] found nonirritating concentrations for intradermal testing of erythromycin (0.05 mg/mL) and azithromycin (0.01 mg/mL). In single cases, skin prick tests proved to be useful in diagnosing IgE-mediated hypersensitivity to macrolides such as erythromycin, spiramycin, azithromycin, and roxithromycin.[77,83-85] There also are reports of positive responses to patch tests at concentrations up to 10% in petrolatum or dimethylsulfoxide in subjects with nonimmediate reactions (eg, fixed drug eruptions and contact dermatitis) to macrolides such as erythromycin and azithromycin.[77,78,80] However, analysis of the data in the literature indicates that, in evaluating hypersensitivity reactions to macrolides, the sensitivity of skin tests is low; therefore, DPTs often are necessary.[77,79,82] Specifically, Benahmed et al[79] evaluated 139 patients with adverse reactions to these antibiotics. DPTs allowed the investigators to diagnose macrolide hypersensitivity in 8 of the 107 patients (7.5%) who accepted such tests: 7 patients reacted to spiramycin and one to roxithromycin; intradermal tests with spiramycin at the concentration of 10 mg/mL were positive in only 4 of these 7 patients.

Seitz et al [82] assessed 125 subjects with suspected macrolide allergy. Intradermal tests with erythromycin, clarithromycin, and azithromycin were performed at the concentration of 0.01 mg/mL. All skin tests were negative in the 53 patients with immediate reactions, whereas one of the 72 subjects with nonimmediate reactions displayed a delayed prick-test positivity to roxithromycin at 50 mg/mL. DPTs were negative in the 47 subjects with immediate reactions who underwent such tests, whereas they were positive in 4 of 66 patients with nonimmediate reactions. However, in a study by Mori et al,[81] which evaluated all the 64 children with a history of clarithromycin hypersensitivity by performing intradermal tests at the concentration of 0.5 mg/mL and DPTs, intradermal-test sensitivity and specificity were 75% and 90%, respectively.

Cross-reactivity among 14-membered macrolides (erythromycin, clarithromycin, and roxithromycin) has been detected in single patients with either immediate [84] or nonimmediate[78] reactions to erythromycin on the basis of positive responses to skin prick tests or patch tests. Milkovic-Kraus et al[80] described 2 subjects with allergic contact dermatitis to azithromycin who showed cross-reactivity with azithromycin intermediates, including erythromycin. However, the scarcity of reports of allergic contact dermatitis to azithromycin makes it difficult to advise avoidance of other macrolides. In any case, it would appear that macrolide hypersensitivity is unlikely to be a class hypersensitivity.

Sulfonamides

Sulfonamide antibiotics (eg, sulfamethoxazole, sulfadoxine, and sulfapyridine) are sulfonyl arylamines, characterized by a sulfonamide (SO_2-NH_2) moiety directly attached to a benzene ring, which carries an unsubstituted amine (-NH_2) at the N4 position.[86,87] Hypersensitivity reactions to sulfonamide antibiotics occur in approximately 2% to 4% of healthy persons but in as many as 50% to 60% of patients with AIDS.[88] Immediate reactions (ie, urticaria and anaphylaxis) are rare.[89] Sulfonamides are more frequently associated with nonimmediate manifestations, such as maculopapular rashes and fixed eruptions. More serious hypersensitivity reactions, such as SJS, TEN, and DRESS, also have been reported.[87,88] The risk of SJS-TEN is higher for sulfonamide antibiotics than for other antibiotics.

The allergic workup (Figure 3) includes both skin tests and DPTs. Intradermal tests may be helpful in both immediate and nonimmediate reactions. Sulfamethoxazole in a concentration of 0.8 mg/mL has been shown to be nonirritating in intradermal testing.[75] Regarding immediate reactions, both *in vitro* assays and skin prick tests with multivalent sulfamethoxazole-poly-L-tyrosine have revealed IgE antibodies to sulfamethoxazole in some patients with immediate reactions to this sulfonamide antibiotic.[90] Moreover, Shapiro et al[91] evaluated 28 patients with adverse reactions to sulfonamide antibiotics by skin prick tests or specific IgE assays with sulfamethoxazole and found that 4 of the 28 who had had a skin prick test and 2 of the 10 who had undergone *in vitro* testing were positive.

Patch testing is used in Europe in nonimmediate reactions; however, its sensitivity seems to be lower than delayed-reading intradermal tests. Positive topical provocations by patch tests have been reported in patients with sulfamethoxazole-induced fixed eruptions.[92] Cross-reactivity among sulfonamide antibiotics has been reported.[86] However, laboratory analysis of T-cell reactions and clinical data indicate that nonantibiotic sulfonamides, such as glibenclamide, furosemide, and celecoxib, are not stimulatory and are tolerated by patients allergic to sulfonamide antibiotics.[87]

Aminoglycosides

Aminoglycosides are classified into 2 groups: the streptidine group (eg, streptomycin) and the desoxystreptamine group (eg, kanamycin, amikacin, gentamicin, tobramycin, and neomycin). Aminoglycosides can cause both immediate and nonimmediate hypersensitivity reactions.[93] The former are uncommon, especially anaphylactic ones. With regard to the diagnosis (Figure 3), skin testing with the native drug can be useful in evaluating immediate reactions.[10] In most anaphylactic reactions provoked by subtherapeutic doses of streptomycin, an IgE-mediated pathogenic mechanism has been demonstrated on the basis of skin-test positivity.[94,95] However, a cautious approach is advisable when evaluating anaphylactic reactions to streptomycin because systemic reactions have been observed after skin prick tests.[94] The streptomycin concentrations used for skin tests range from 0.1 ng/mL to 20 mg/mL.

There also are reports of single cases of anaphylactic reactions to other aminoglycosides, in which there were positive skin tests to the culprit drug, namely gentamicin (skin prick test at 40 mg/mL),[96] bacitracin (topical application or prick test with ointment),[97,98] and ribostamycin (skin prick test at 1 mg/mL and intradermal test at 0.1 mg/mL).[99] However, because the native antibiotic may not contain all the relevant antigenic determinants that may elicit IgE-mediated reactions, a negative skin test must be interpreted with caution. In selected cases, DPTs may be performed. Contact dermatitis is the most frequent nonimmediate reaction to aminoglycosides, and neomycin is the most common sensitizer among topical medications. Some geographic differences have been observed because contact allergy to neomycin is much more prevalent in the United States (10%-11.8%) than in Europe (1.2%-5.4%).[100]

Other nonimmediate reactions, such as maculopapular rash, fixed drug eruption, and TEN, have been reported.[93] Patch tests are recommended for the diagnosis of nonimmediate reactions, especially for contact dermatitis. The concentration recommended for neomycin, gentamicin, and tobramycin is 20% in petrolatum, whereas that for streptomycin is 1%.[101] Recently, a case of DRESS associated with amikacin treatment that displayed positive responses to both patch tests and INF-γ ELISpot assays has been reported.[102] Cross-reactivity among aminoglycosides is common, approaching 50% or more among those that belong to the desoxystreptamine group. A study by Liippo and Lammintausta[103] demonstrated that positive responses to patch tests with gentamicin reflect sensitization to different aminoglycosides, particularly neomycin, and kanamycin, for which gentamicin seems to be a sensitive indicator. Streptomycin does not share common antigenic structures with other aminoglycosides that belong to the desoxystreptamine group, and cross-reactivity to the latter has not been reported.[104]

Other antibiotics

Clindamycin. Clindamycin can provoke hypersensitivity reactions, mainly nonimmediate ones, such as maculopapular exanthemas. A study by Notman et al[105] demonstrated a very limited usefulness of prick and intradermal testing with clindamycin up to 15 mg/mL in evaluating such reactions. Of the 31 subjects evaluated because of histories of hypersensitivity reactions, only 2 displayed positive responses to delayed-reading skin tests, whereas 10 of 31 patients, including 1 of the 2 subjects who were positive, reacted to challenges.[105] Two studies evaluated subjects with hypersensitivity reactions to clindamycin by performing patch tests with clindamycin at a concentration of 150 mg/mL in normal saline solution[106] or 10% in petrolatum[107]; the rate of positive tests was 15% (5 of 33 patients) and 30% (9 of 30), respectively. In the study by Seitz et al,[106] 26 subjects with negative patch tests underwent oral challenges; 6 reacted.

Rifamycins. Anaphylactic reactions to rifampicin and rifamycin SV[108,109] have been reported. In some of these reports, an IgE-mediated pathogenic mechanism has been demonstrated on the basis of positive responses to intradermal tests at concentrations up to 0.006 mg/mL for rifampicin[110] and range from 50 to 5000 μg/mL for rifamycin SV.[111,112]

Glycopeptides. The most frequent immediate reaction to vancomycin is the "red man syndrome," which is associated with its rapid intravenous administration and is characterized by flushing, warmth, pruritus, and hypotension. Anaphylactic reactions are rare; in 1 case, a positive response to intradermal testing at 0.1 μg/mL was observed.[113] Vancomycin also can elicit a variety of nonimmediate reactions, including severe ones, such as SJS, TEN, and DRESS. Positive vancomycin patch tests at concentrations that range from 0.005% to 5% in water have been reported in subjects with nonimmediate reactions.[16,114,115] Asero[116] described a subject who had experienced an anaphylactic reaction to teicoplanin and was positive to intradermal testing at 75 mg/mL.

CONCLUSION

Antibiotic allergy is clearly overdiagnosed both in children and adults, the negative consequences include the development of resistance by unnecessary use of broad-spectrum antibiotics and increasing medical costs. Therefore, the proper identification, evaluation, and management of patients with a reported history of antibiotic allergy are essential components of patient care. In case of suspicion of an allergy, a complete allergy workup should be performed, based on carefully selected diagnostic tests, depending on whether an immediate or a nonimmediate reaction is suspected. The DPT remains an essential diagnostic tool and has gained importance, particularly in children who present a benign rash while taking antibiotic treatment. However, the DPT potentially exposes subjects to a significant risk of severe anaphylactic reactions and, moreover, has significant costs and is time consuming. Currently, research efforts focus on developing new diagnostic tests and improving current ones to assess the presence and severity of an antibiotic allergy.

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