

Antibiotic Allergy

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KEYWORDS

• Drug • Hypersensitivity • Allergy • Antibiotics • Immediate • Nonimmediate
• β -lactam • Non- β -lactam

KEY POINTS

- Antibiotic allergy is overdiagnosed, often resulting in the administration of less appropriate and more expensive antibiotics, with increasing costs and development of resistance through the use of more broad-spectrum drugs.
- The appropriate diagnosis and management of patients with reported antibiotic allergy are essential to good medical care and it requires the appropriate use of diagnostic tests, when these are available.
- Unfortunately, appropriate diagnosis and management are often difficult to achieve because of the lack of appropriate reagents, sometimes because of the shortsightedness of regulatory authorities. In other instances, there has been insufficient research carried out to define appropriate diagnostic techniques, except in situations such as β -lactam allergy.
- Differences exist in different parts of the world in regard to the appropriate means to investigate drug allergy, but to a large extent, these may be the result of a lack of access and standardization rather than true differences in the frequency and type of drug-induced hypersensitivity.

INTRODUCTION

Antibiotics may be classified as β -lactams or non- β -lactams. β -Lactam antibiotics contain a 4-membered β -lactam ring and consist of 2 major classes, the penicillins (penams) and cephalosporins (cephems), and the carbapenems, monobactams, oxacephems, and clavams. Non- β -lactam antibiotics, such as macrolides, sulfonamides, quinolones, and aminoglycosides, are very different chemically and also immunogenically.

PATHOGENESIS OF ANTIBIOTIC ALLERGY

Because most antibiotics are low-molecular-weight chemicals (ie, too small to stimulate an immune response), it has been assumed that the drug or its metabolite first binds

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covalently to a macromolecule such as a circulating serum protein to form a multivalent conjugate, that is processed and presented to T lymphocytes.¹ Probably the clearest example of this occurs with penicillin, which is able to bind to lysine residues on proteins such as serum albumin.^{2,3} This binding occurs because the β -lactam ring opens spontaneously and forms a stable covalent conjugate. Haptenation may also occur through the carboxyl and thiol groups to form minor antigenic determinants.^{1,4,5} A similar although slower and less efficient process occurs with cephalosporins.^{1,6} In the case of sulfamethoxazole, the drug becomes reactive through cytochrome p450 modification to a nitroso-intermediate that modifies thiol groups on proteins.⁷⁻⁹

The novel drug-conjugate undergoes antigen processing to form a small but novel Major Histocompatibility Complex (MHC) ligand, loaded on to MHC molecules, where it interacts with antigen-specific T cells.^{9,10}

However, not all antibiotics stimulate immune responses in this way. The pharmacologic interaction or p-i hypothesis suggests that chemically inert drugs may bind noncovalently to antigen-interacting structures such as the T-cell receptor or MHC and cause direct stimulation of an immune response.^{1,5,11} This situation occurs with sulfamethoxazole.¹² The drug interaction with the receptor is highly specific and may, in some cases, exhibit specificity for certain HLA alleles or receptors, possibly explaining the genetic associations of certain forms of drug hypersensitivity.^{13,14}

GENERAL PRINCIPLES

Allergy to antibiotics appears to be very common, according to patient reports, possibly with a prevalence as high as 5% to 10%.¹⁵⁻¹⁸ However, many individuals labeled as drug allergic are not truly allergic any longer or perhaps never were. Hypersensitivity reactions to antibiotics are adverse responses that resemble allergic responses and are categorized as type B according to Rawlins and Thompson classification.^{19,20} Strictly speaking, only when a definite immunologic mechanism is demonstrated should a reaction to an antibiotic be considered allergic; however, such mechanisms have not been identified for many drugs, and the assumption is usually made that similarities in presentation indicate an allergic basis. Attempts have been made to fit these reactions into the Gell and Coombs classification of type I (immunoglobulin E [IgE]-mediated), type II (cytotoxic, IgG-mediated, or IgM-mediated), type III (immune complex-mediated by IgG antibodies), and type IV (mediated by drug-specific T cells), which is subdivided into type IVa, IVb, IVc, and IVd.⁵

CLINICAL PRESENTATION

By clinical criteria, antibiotic-induced hypersensitivity reactions can be classified simply as immediate or delayed. Immediate reactions occur quickly, usually within 1 hour after the last intake of the drug and are often mediated by IgE antibodies already present in the patient.²¹ They may comprise urticaria, angioedema, bronchospasm, gastrointestinal symptoms, rhinitis, and conjunctivitis and, most seriously, anaphylaxis and anaphylactic shock. Nonimmediate reactions occur later than 1 hour and may also consist of urticaria and angioedema, the common morbilliform eruptions, fixed drug eruptions, and severe delayed reactions such as exfoliative dermatitis, acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS). Antibiotics may also cause immune-mediated interstitial nephritis, hepatitis, pneumonitis, and vasculitis.^{22,23}

European guidelines currently classify drug reactions into immediate, occurring in less than 1 hour, and delayed, occurring after 1 hour after the last drug intake. It

has been frequently implied that these timeframes also indicate likely pathogenesis, with the rapid reactions being IgE-mediated and the delayed reactions being the result of T-cell-driven responses.^{21,23,24} Although there is evidence from some studies that this may sometimes be the situation, with regard to nonimmediate reactions occurring after 1 hour, the opinion in North America and of some European experts is that such reactions, occurring even as long as 24 hours after the last drug intake, may still be IgE-mediated, depending on the individual situation.^{25–28}

Although maculopapular or morbilliform eruptions can result from rapid responses by previously sensitized T cells, diagnostic testing has shown that skin test reactivity in such cases is often delayed for several hours.²⁹ It would be difficult to explain the occurrence of hives and angioedema on the basis of a T-cell response occurring after only 1 to 2 hours. Nevertheless, it can be argued that the above classification gives some help in determining the types of skin tests that should be used.

ASSESSMENT OF ANTIBIOTIC ALLERGY

To assess drug allergy in a patient, it is necessary, but not always possible, to obtain a detailed clinical history, including the nature of the reaction, the time between the occurrence of symptoms and the first as well as the last intake of the drug, and concomitant medications.³⁰ It is also helpful to know why the antibiotic was prescribed, because reactions to many antibiotics are more frequent in the presence of unproven bacterial (and often viral) infections. Some illnesses such as HIV and other virus infections may increase the probability that an allergic reaction will occur.^{31–33} Confirmation of the diagnosis is attempted by skin tests, in vitro tests, and drug provocation tests (DPTs).^{34–39} The tests themselves are selected because of the known history, the nature of the reactions, and their presumed time of onset, whether immediate or delayed. Although immediate reactions may be assessed by skin tests, in vitro specific IgE assays, or basophil activation flow cytometry, for many antibiotics such tests are either not validated, have a high false-negative rate, or are simply not available.^{40–42} Nonimmediate or delayed reactions are even more difficult to assess, by either delayed-reading intradermal skin testing, patch testing, or specialized laboratory investigations such as lymphocyte transformation studies or cytokine release assays.^{43–48} Although delayed-reading skin tests have been validated for β -lactam antibiotics, there is less evidence for their utility for other classes of antibiotics. In vitro tests, when available, are less useful in patients with remote histories of antibiotic allergy and can be subject to false-negative/positive results, such as in the ImmunoCAP assay for penicillin, where antibodies were directed against phenylethylamine, rather than penicillin itself.⁴⁹ Confirmation or exclusion of the diagnosis of drug allergy often depends on DPT, usually when diagnostic testing is negative, when the previous reaction was not life-threatening or severe, and when there is a reasonable need to readminister the suspected drug.^{36,50,51}

β -LACTAM ANTIBIOTICS

Penicillins and cephalosporins are the antibiotics most frequently causing antibiotic-related allergic reactions, because of their ability to form conjugates with serum proteins and their widespread massive use. Penicillin allergy is the most commonly reported drug allergy, with a prevalence rate of 5% to 10% in adults and children.^{15–17,52,53}

Benzylpenicillin has progressively been replaced by amoxicillin and to a lesser extent by other penicillins in causing allergic reactions and, in European experience, this is often associated with side-chain-specific allergy.^{54,55} There is increasing

evidence supporting the role of side chains as the relevant part of the structure of the allergenic determinant. The evaluation of immediate anaphylactic β -lactam allergy combines skin tests and IgE-specific assays (when a penicillin is suspected the culprit) with a panel of common reagents, including classic penicillin reagents, such as penicilloyl-polylysine (PPL), minor determinant mixture (MDM), and amoxicillin, as well other relevant β -lactams.

In both the European Academy of Allergy and Clinical Immunology (EAACI)/ European Network for Drug Allergy (ENDA) and the American Academy of Allergy, Asthma, and Clinical Immunology (AAAAI) Practice Parameters, skin testing is the best method for diagnosing immediate hypersensitivity reactions to β -lactams.^{34,36} In patients with a recent history of anaphylactic reaction, it seems reasonable to use serum-specific IgE assays when available, to avoid the risk of reactions to skin testing (Fig. 1). The ImmunoCAP technique is the most validated technique for penicillins.

DIFFERENCES IN PRACTICE ACROSS THE WORLD

In Europe, the highest concentration accepted for epicutaneous prick and intradermal testing are 5×10^{-5} M for PPL, 2×10^{-2} M for MDM, 25,000 IU/mL for benzyl penicillin (BP), 25 mg/mL for amoxicillin and other penicillins, and 2 mg/mL for cephalosporins. Both PPL and MDM are available in some but not all countries in Europe (DAP; Diater, Madrid, Spain), whereas in North America, only PPL (PRE-PEN; AllerQuest LLC, West Hartford, CT, USA) is available commercially. In some centers, PPL and MDM may be prepared locally, but standardization is a problem. It has been estimated that skin testing with only PPL and BP, and not using the penilloate and penicilloate, may miss 10% to 20% of penicillin-allergic subjects, but studies from North America have found that DPTs after skin testing only with PPL and BP produce a similar rate

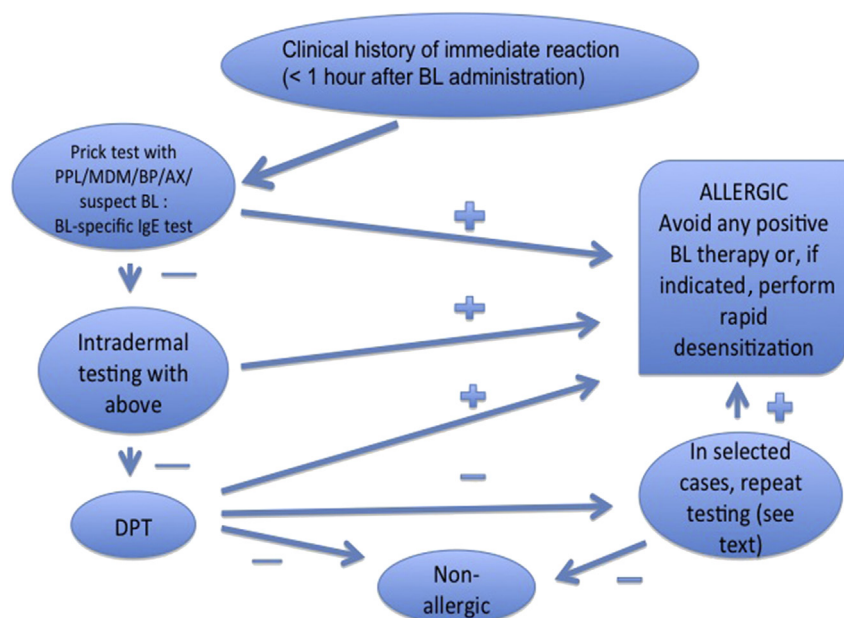


Fig. 1. Algorithm for the diagnosis of immediate hypersensitivity reactions to β -lactams. AX, amoxicillin; BL, β -lactams; BP, benzyl penicillin; DPT, drug provocation test; IgE, immunoglobulin E; MDM, minor determinant mixture; PPL, penicilloyl-polylysine.

of reactions to that seen in patients testing negative to both PPL and BP or MDM reagent.^{39,56–60} Lin and colleagues⁵⁸ assessed 243 patients with self-reported penicillin allergy, of whom 20.6% reacted to BP derivatives, 9% only to penilloate and penicilloate, and 5.8% to amoxicillin. Even more striking were the findings of Macy,³⁹ in 242 patients with self-reported penicillin allergy. Only 2 reacted to benzylpenicilloyl polylysine, and on challenge with penicillin or amoxicillin, only 1.66% reacted.³⁹ The experience of one of the authors, over the last 3 years in Canada, supports these findings. In 350 patients skin test–negative to PPL, BP, and ampicillin, only a single patient suffered a delayed but mild rash after challenges with penicillin V or amoxicillin (Warrington RJ, personal communication, 2013).

It seems clear that over the past 20 years, the incidence of proven allergy to penicillin itself in patients reporting penicillin allergy has fallen steadily from a high of perhaps 20% to 5% or even less.¹⁶ However, European experience suggests an increasing role for side-chain-specific determinants in penicillin allergy, particularly for amoxicillin.⁶¹ In Europe, amoxicillin and ampicillin for intravenous use are used for skin testing, at concentrations of up to 25 mg/mL.^{62,63} In North America, although ampicillin is available, the trihydrate of amoxicillin has been used, which limits the concentration that can be prepared for testing to about 4 mg/mL.^{38,64} Nevertheless, this is still approximately equivalent to the concentration used for minor determinants and the above DPT studies suggest that allergic patients are not missed by using the lower concentration.⁶⁵

An article by Torres and colleagues,⁶² in which 330 patients with a history of immediate hypersensitivity reactions to penicillins were assessed, reported that 78.3% of the initial reactions were caused by either amoxicillin or ampicillin. Sixty-one percent showed positive skin tests to at least one reagent. There were 11.5% who were skin test–negative and ImmunocAP positive, whereas 14.8% were skin test and ImmunocAP–negative but reacted to DPT (in 55% cases to amoxicillin). Therefore, 12.1% had a negative drug-allergy workup. A study by Montanez and colleagues⁶⁶ of 276 patients with a history of immediate reactions to the association of amoxicillin/clavulanic acid found 19.9% positive to skin tests, 62% of these reacting to amoxicillin and tolerating benzylpenicillin challenge, whereas 29% reacted to clavulanic acid alone and tolerated benzylpenicillin and amoxicillin. One hundred ninety patients were negative to all testing. In contrast, Macy and Ngor³⁹ found a rate of positive skin tests to PPL and BP in only 0.8% of 500 subjects, with only 4 (0.8%) subjects with negative skin tests reacting acutely to challenge. The difference seems to relate to the studied population, with immediate reactions occurring in all positive subjects in the studies by Torres and colleagues,⁶² but only in 10.4% in the study of Macy and Ngor.³⁹

With regard to cephalosporins, injectable forms are used for testing, usually at approximately 2 mg/mL, or even higher. Solutions can be made from oral capsules or pills.^{67–70} However, the latter method is not as straightforward as the use of injectable forms of the drugs and requires careful standardization. Most often, specificity of IgE antibodies to cephalosporins is directed to the side-chain determinants, rather than the β -lactam ring, except in first-generation cephalosporins.^{67,71} Studies conducted in both adults and children with histories of immediate reactions to these antibiotics have found the rate of positive skin tests to vary from 30.7% to 72.1%, using 2 mg/mL solutions. However, the negative predictive value of such testing remains uncertain, but may be approximately 82%.^{67,71,72}

IgE-mediated hypersensitivity to β -lactams may decrease with time. It is therefore advised in European guidelines that patients who have suffered immediate reactions to β -lactams and are negative on the first evaluation, including provocation test, should be retested later.^{73–77} In one of these studies, resensitization in the region

of 27%, based on skin testing, was shown, but this was not confirmed when the skin test-positive patients were challenged. In this study, positive challenges were present in only a very small percentage of skin test-positive patients and not significantly more than was seen in skin test-negative patients.⁷⁷ These data are also supported by Solensky and colleagues,⁷⁸ who found that skin test-negative patients with a history of prior penicillin allergy were not resensitized after 3 full courses of therapy with penicillins. US Practice Parameters state that resensitization after treatment with oral penicillin is rare, and therefore, penicillin skin testing does not need to be routinely repeated in patients who have tolerated one or more courses of treatment with β -lactams.⁷⁹ It remains possible that resensitization may be more frequent after parenteral therapy but these data are not available.

It is important to raise the issue of what is considered to be a positive skin test for antibiotic allergy, because differences exist between Europe and North America. This difference is particularly an issue when there is little information available regarding DPT testing in skin test-positive patients. A positive response to skin testing with β -lactam reagents in Europe is considered to be a reaction that is 3 mm or more greater than the saline control, or an increase of 3 mm or more in the intradermal test, whereas in North America, with regard to Pre-Pen, a positive response is defined as a 5-mm or greater increase in either the prick test or the intradermal test. What is known of the reaction rates in skin test-positive subjects? The most recent data come from the study by Goldberg and Confino-Cohen, who used the criteria of a 3-mm increase in skin test reaction for prick tests and 5-mm increase for intradermal tests.⁷⁷ Seven of 67 skin test-positive patients reacted to penicillin or amoxicillin challenge (10.4%), whereas 4 of 94 skin test-negative subjects reacted, with positive and negative predictive values of 10.4% and 95.7%, respectively. At a second evaluation 2 to 5 months later, the positive predictive value of the repeated skin tests as assessed by DPT was 2.9%, and the negative predictive value was 97.6%. It is important to note that the patients in this study had non-life-threatening reactions to β -lactams more than 3 years before the allergy workup, and therefore, the results cannot be extrapolated to those individuals with more recent and more serious immediate hypersensitivity reactions.

When it comes to skin testing itself, European guidelines suggest that this can be spread out over several days, because of the risk of reactions occurring from the skin testing itself.⁸⁰ Although occasionally a patient may react to skin testing with an anaphylactic reaction, usually but not always this is after intradermal testing, and this would seem to be inordinately rare. It would seem unlikely to result if the testing were carried out using only standardized penicillin reagents and the β -lactam antibiotic to which the patient initially reacted. A review of the data on which this suggestion to delay testing is based indicates that 61% of the subjects who reacted to skin testing reacted to what would be considered to be standard skin test reagents used on the first day of testing.⁸¹ What was striking was that reactions occurred in patients who had had immediate or anaphylactic reactions and who were tested within 5 months of that reaction, whereas in the non-reacting group, the delay to testing was approximately 18 months. Therefore, it is reasonable in patients with a recent history of an immediate reaction to start at lower concentrations and to limit the number of tests to major and minor determinants and the implicated β -lactam.

DPTs or graded challenges are recommended in appropriate cases, according to international guidelines. The AAAAI Practice Parameters recommend that DPT be carried out in patients who, after diagnostic testing or clinical evaluation, are considered unlikely to be allergic to the challenge drug.³⁶ Therefore, after negative skin and in vitro tests, the patient is given a full dose of the β -lactam in North America. The

EAACI/ENDA guidelines consider the DPT to be the gold standard to establish a definitive diagnosis in patients with convincing histories of drug hypersensitivity but negative diagnostic tests.⁵⁰ In such cases, challenge is begun with one-hundredth (or lower if the reaction was of rapid onset and/or severe) of the therapeutic dose, and if negative, one-tenth of the therapeutic dose is given half an hour to 1 hour later, followed by the full dose after a further half an hour to 1 hour. Challenges are obviously prohibited in cases of severe and serious reactions, such as SJS, TEN, AGEP, and DRESS.

Key issues outstanding between European and North American practice are as follows:

1. Availability and need for MDMs
2. Requirement for retesting after skin tests and challenge
3. Challenge protocols after negative testing
4. Importance of side-chain-specific allergy to penicillins

IMMEDIATE β -LACTAM ALLERGY IN CHILDREN

Although immediate β -lactam allergy in children is rare, it may occur and is evaluated by the diagnostic protocols used in adults. Atanaskovic-Markovic and coworkers assessed 1170 children who had histories of immediate reactions to penicillins and/or cephalosporins by skin tests, specific IgE in vitro testing, and challenge.⁸² Positive tests were found in 58.3%; of these, 94.4% were positive to penicillins and 35.3% to cephalosporins (ie, there was some cross-reactivity). Only approximately 40% were positive to amoxicillin or ampicillin. Tests were more likely to be positive when carried out within 6 months of the reaction. A later study by Ponvert and colleagues⁸³ of 1431 children found positive reactions in 30.9%, most by skin testing. Positive reactions were more likely when the reaction was immediate rather than delayed. The rate of systemic reactions from skin testing is low, only 1% to 3%, and the negative predictive value of challenge testing is high.

NONIMMEDIATE REACTIONS

Nonimmediate reactions to drugs can be extremely heterogeneous and similar to the symptoms of an infectious disease. In addition, the presence of a concomitant viral and possibly also a bacterial infection may favor the development of an apparent allergic reaction.³⁴

To investigate a nonimmediate allergic drug reaction, unless the reaction is consistent with a life-threatening reaction, such as SJS, TEN, AGEP, or DRESS, when patch testing with appropriate concentrations of the drug is usually advised, intradermal skin tests and patch tests with the same reagents used to investigate immediate reactions are performed. Reactions to these tests may occur after several hours or days, so patients should be warned appropriately (Fig. 2).

Patch tests are administered in those who have suffered severe reactions listed above, and only if it is essential. Usually a concentration of 5% in petrolatum is used. Intradermal testing can be used in AGEP/DRESS, in case of negative results to patch tests and starting with lower concentrations. Intradermal testing is preferred in those with mild morbilliform reactions.

In a study by Romano and colleagues,⁶¹ 36.2% of 433 adults with histories of delayed reactions to penicillins had positive skin tests, 96.9% of which were positive by patch or delayed-reading intradermal testing. Two hundred thirty-nine patients who were negative on skin testing had challenges and only 2.9% reacted.

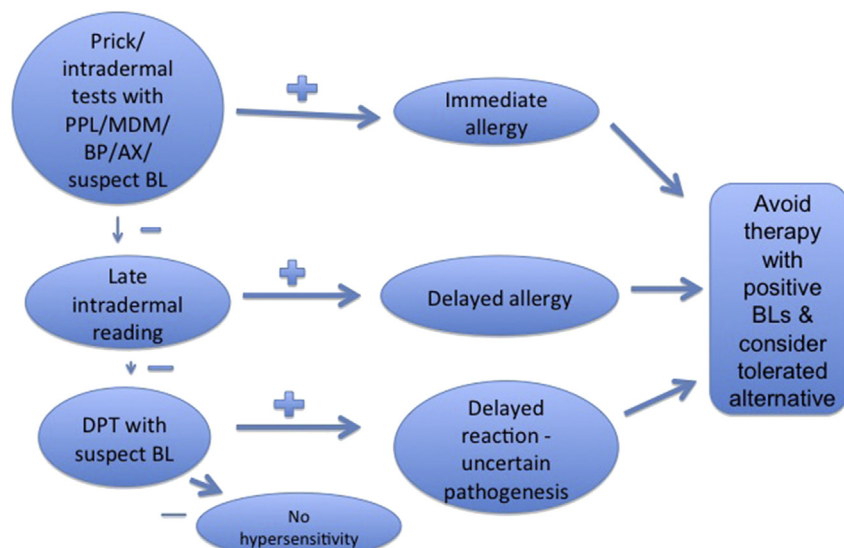


Fig. 2. Algorithm for the diagnosis of nonimmediate hypersensitivity reactions to β -lactams. AX, amoxicillin; BL, β -lactams; BP, benzyl penicillin; DPT, drug provocation test; MDM, minor determinant mixture; PPL, penicilloyl-polylysine.

The same group also assessed 105 adults with delayed reactions to cephalosporins. It was found that 6.6% were positive on skin testing, and of the 86 who were skin test-negative and were challenged, none reacted.⁸⁴

Barbaud and colleagues⁴³ carried out patch tests to different drugs, including antibiotics, on 134 patients with AGEP, DRESS, and SJS/TEN within 1 year of the reaction. Positive tests were found in 64% of DRESS, 58% of AGEP, and 24% of SJS/TEN, with only one relapse of AGEP.

There are some concerns about whether a single therapeutic-dose drug challenge is sufficient to confirm or exclude a delayed reaction to penicillins. Borch and Bindsvle-Jensen⁸⁵ found that of 22 patients with negative delayed-reading skin tests and single-dose challenge, 11 reacted during a 10-day therapeutic course. Nevertheless, in a multicenter study of patients with immediate or delayed reactions to β -lactams, the negative predictive value of a 1-day drug challenge was 94.1% (11 false negatives of 118 patients).⁸⁶

Hjortlund and colleagues⁸⁷ studied 342 patients of whom 36 were considered to have had immediate reactions, 235 had nonimmediate reactions, and 71 could not be classified. All were assessed by immediate and delayed-reading skin testing, patch testing, and specific serum IgE assays. Of the 291 patients who tested negative, 10 reacted to a single-dose challenge and 23 to a 7-day challenge. There was no correlation between the history of the reaction and the time to reaction on challenge.

HYPERSENSITIVITY REACTIONS TO MONOBACTAMS, CARBAPENEMS

Allergic reactions to these antibiotics also containing the β -lactam ring are relatively uncommon, but are assessed in a similar manner to that used in the diagnosis of penicillin and cephalosporin allergy. Skin testing with aztreonam at 2 mg/mL has been of value in immediate allergy.^{88–90} In a case of anaphylaxis to imipenem/cilastatin, this was diagnosed by skin testing at 1 mg/mL and by a positive serum-specific IgE assay.⁹¹

THE ADMINISTRATION OF ALTERNATIVE β -LACTAMS TO β -LACTAM-ALLERGIC PATIENTS

Cross-reactions may occur between β -lactams, particularly if the specific reaction is directed to the β -lactam ring or identical side-chain determinants.⁹² However, in recent years, allergy to the common β -lactam ring seems to have become much less frequent than previously noted. Reactions may still occasionally occur in penicillin-allergic subjects given first-generation cephalosporins, but this is unusual and is rarely seen with second-generation or third-generation cephalosporins.^{93–95} A meta-analysis by Pichichero and Casey⁹⁶ found an increased incidence of reactions to first-generation cephalosporins in penicillin-allergic subjects (OR = 4.8, CI = 3.7–6.2), but this analysis included studies from the 1970s, when the purity of cephalosporins was in question.⁹⁶ Macy and Burchette⁷⁹ found that of 42 penicillin skin test–positive patients receiving 129 courses of cephalosporins, 5.4% had reactions, compared with 3.2% in 80 skin test–negative controls who received 221 courses of cephalosporin therapy.⁷⁹

Patients who have been shown to be allergic to amoxicillin should avoid cephalosporins with identical R-group side-chains, which include cefadroxil, cefprozil, and cefatrizine, while ampicillin-allergic subjects should avoid the cephalosporins, cephalexin, cefaclor, cephadrine, cephaloglycin, and the carbacephem loracarbef.^{82,97} It has also been noted that there is cross-reactivity between the cephalosporins with identical or similar side-chains, such as cefuroxime, cefotaxime, ceftriaxone, and ceftazidime.^{67,71}

The best approach in someone with proven β -lactam allergy is to skin test with the drug that it is proposed to use, and if negative, give a graded challenge.⁹⁸

NON- β -LACTAM ANTIBIOTICS

Quinolones

The quinolones are classified in generations: first (cinoxacin and nalidixic acid), second (ofloxacin, norfloxacin, ciprofloxacin, and enoxacin), third (levofloxacin), and fourth (gemifloxacin and moxifloxacin). With increasing use, hypersensitivity reactions have become more frequent.⁹⁹

The main immediate reactions are urticaria, angioedema, and anaphylaxis, particularly in patients with cystic fibrosis.^{99,100} Specific IgEs have been demonstrated to be present in more than 50% of patients by radioimmunoassay or basophil activation tests.^{101,102} Nonimmediate reactions have also been described, including maculopapular rashes, fixed drug eruptions, AGEP, and SJS/TEN. Gemifloxacin seems to be the more frequent culprit and the incidence of such rashes is reported as 1% to 7%, especially in younger female patients.^{103,104} T-cell-mediated responses have been demonstrated by patch testing or lymphocyte transformation testing.^{99,105}

Skin testing with presumably nonirritant concentrations of quinolones has been carried out, but this has not been clearly shown to be reliable, because both false positive and false negative results may be obtained based on subsequent drug challenge (Fig. 3). In 64 subjects with immediate reactions to these drugs, 3 of 6 patients with positive skin tests tolerated challenges, whereas 3 of 45 subjects with negative skin tests reacted to challenge.¹⁰⁶ A recent study of 218 patients with histories of hypersensitivity reactions to fluoroquinolones using Basophil Activation Test (BAT) and DPTs found that 32.1% (69) had evidence for hypersensitivity, the majority for immediate and only 3 for nonimmediate. Risk factors for true hypersensitivity were an immediate reaction, a reaction to moxifloxacin, and past confirmed reactions to β -lactams.¹⁰⁰

Cross-reactivity is unpredictable, appearing to be common between first-generation and second-generation quinolones (cinoxacin, nalidixic acid and ofloxacin,

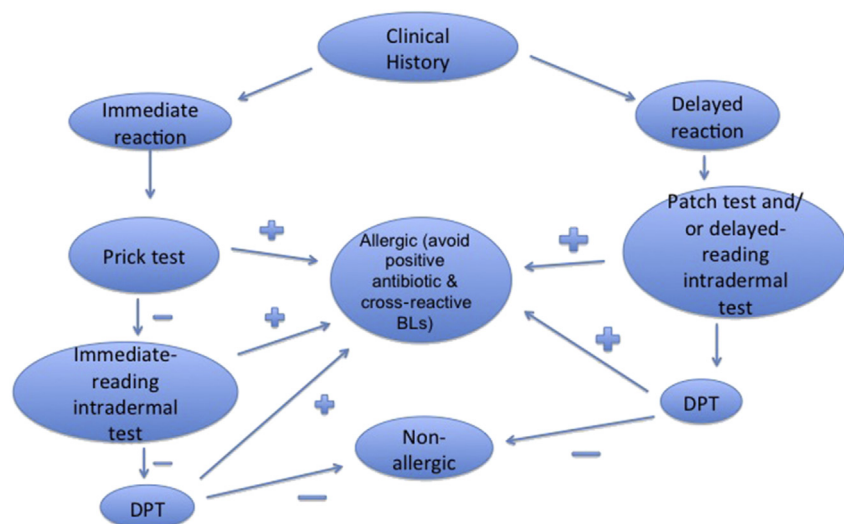


Fig. 3. Algorithm for the diagnosis of hypersensitivity reactions to non- β -lactam antibiotics. DPT, drug provocation test.

norfloxacin, ciprofloxacin, enoxacin), but less common with third (levofloxacin) and fourth generations (gemifloxacin, moxifloxacin).^{99,101}

Macrolides

The macrolide antibiotics are classified according to the number of carbon atoms in the lactone ring: 14-membered (erythromycin, troleandomycin, roxithromycin, dirithromycin, and clarithromycin), 15-membered (azithromycin), and 16-membered (spiramycin, rokitamycin, josamycin, and midecamycin).

Hypersensitivity to these antibiotics is relatively uncommon (0.4%–3% of treatments), but immediate and nonimmediate reactions have been reported, including fixed drug eruptions and TEN.^{107–110} There is little evidence with regard to the reliability of skin testing, with only single cases reported as positive.^{107,111–113} Nonirritating concentrations are 0.05 mg/mL for erythromycin and 0.01 mg/mL for azithromycin. Positive skin tests have been described by patch testing at 10% in petrolatum or dimethylsulfoxide in fixed drug eruptions and contact reactions, but the sensitivity of skin tests is low.^{107,109,114} Seitz and colleagues¹¹⁵ found that only 1 of 125 patients with immediate or delayed reactions to macrolides had a positive skin test and challenges in 47 subjects with immediate reactions were negative, whereas 4 of 66 patients with delayed reactions were positive. In contrast, Mori and colleagues¹¹⁰ reported that intradermal skin test sensitivity was 75% and specificity was 90% in 64 children with clarithromycin sensitivity.

Cross-reactivity among the 14-membered macrolides has been reported in single cases but it seems likely that there macrolide allergy is not a class hypersensitivity.^{108,111,114}

Sulfonamides

Sulfonamide antibiotics are characterized by a sulfonamide ($\text{SO}_2\text{-NH}_2$) moiety attached to a benzene ring, carrying an unsubstituted amine at the N4 position.^{116,117} Hypersensitivity reactions to sulfonamide antibiotics are common, occurring in 2% to 4% of healthy individuals and even more common in patients with AIDS, affecting as

many as 50% to 60%.¹¹⁸ Although immediate reactions are relatively uncommon, delayed reactions, such as maculopapular rashes, fixed drug eruptions, SJS/TEN, and DRESS, are more frequently reported.^{117–119}

Intradermal tests may be useful in immediate and delayed reactions, when used at a concentration of 0.80 mg/mL.¹²⁰ Studies have shown IgE antibodies in some patients with immediate reactions.¹²¹ However, Shapiro and colleagues¹²² found positive skin tests in 4 of 28 patients tested and positive in vitro tests in 2 of 10. Recently, Kavadas and colleagues¹²³ reported on 6 of 11 patients with a history of immediate reactions to cotrimoxazole who had positive intradermal skin tests to the drug, but only one was challenged and reacted. Patch testing has been performed but the sensitivity is low, except when applied at the site of fixed drug eruptions.¹²⁴ Cross-reactivity between antibiotic sulfonamides has been reported,¹¹⁶ but does not include nonantibiotic sulfonamides.¹¹⁷

Aminoglycosides

Aminoglycosides are subdivided into the streptidine group (streptomycin) and the deoxystreptamine group (kanamycin, amikacin, gentamicin, tobramycin, and neomycin). Immediate and nonimmediate reactions may occur. Immediate reactions may be diagnosed by skin testing, and streptomycin has been used at concentrations ranging from 0.1 ng/mL to 20 mg/mL.^{125–127} Anaphylaxis from skin testing has been reported.¹²⁶

Cases of anaphylaxis to other aminoglycosides have been occasionally reported, diagnosed by skin prick tests.^{128–131} Hypersensitivity reactions to aminoglycosides occur frequently from contact. Such reactions may be immediate, like those with bacitracin and neomycin, or delayed. In the latter, patch tests are carried out with 20% concentration in petrolatum for neomycin, gentamicin, and tobramycin, but only at 1% for streptomycin.¹³² There is significant cross-reactivity within the deoxystreptamine group.¹³³

Clindamycin

This antibiotic may cause reactions, usually delayed maculopapular exanthemas. Notman and colleagues¹³⁴ have demonstrated the limited usefulness of skin testing in such cases, with only 2 of 31 patients showing positive delayed-reading skin tests, whereas 10 of the 31 reacted to challenge.

Patch testing for clindamycin allergy may have some value, with 30% positive tests at 10% in petrolatum.¹³⁵ However, in a study by Seitz and colleagues¹³⁵ of 26 patch test-negative subjects, 6 reacted.

Rifamycins

Anaphylactic reactions have occurred with both rifampicin and rifamycin, with positive intradermal skin tests at 0.006 mg/mL for rifampicin and 50 µg/mL to 5 mg/mL for rifamycin.^{136–140}

Glycopeptides

Vancomycin most commonly causes “red man syndrome,” associated with too rapid intravenous administration of the drug, and characterized by flushing, warmth, pruritus, and hypotension. Rarely, allergic reactions are reported, and a positive intradermal skin test with 0.1 µg/mL has been reported.¹⁴¹ Nonimmediate reactions, including severe reactions such as SJS, TEN, and DRESS, can occur. Positive patch tests have been reported in delayed eruption.^{43,142}

SUMMARY

Antibiotic allergy is overdiagnosed, often resulting in the administration of less appropriate and more expensive antibiotics, with increasing costs and development of resistance through the use of more broad-spectrum drugs. The appropriate diagnosis and management of patients with reported antibiotic allergy is essential to good medical care and it requires the appropriate use of diagnostic tests, when these are available. Unfortunately, this is often difficult to achieve because of the lack of appropriate reagents, often because of the shortsightedness of regulatory authorities. In other instances, there has been insufficient research carried out to define appropriate diagnostic techniques, except in situations such as β -lactam allergy. Differences exist in different parts of the world in regard to the appropriate means to investigate drug allergy, but to a large extent, these may be the result of a lack of access and standardization rather than true differences in the frequency and type of drug-induced hypersensitivity.

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