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

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**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

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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: $5 \times 10^{-5}$ mmol/L for PPL (ie, undiluted), $2 \times 10^{-2}$ 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