The Complex Clinical Picture of β-Lactam Hypersensitivity: Penicillins, Cephalosporins, Monobactams, Carbapenems, and Clavams

Maria J. Torres, MD, PhD*, Miguel Blanca, MD, PhD

β-Lactam (BL) antibiotics are the most frequent elicitors of drug hypersensitivity reactions. Benzylpenicillin (BP) was the first reported BL involved, followed over the years by different penicillins and cephalosporins, with amoxicillin (AX) now being the drug most frequently inducing reactions.1 The BLs involved in hypersensitivity will increase over the years as new compounds of this family become available. Hypersensitivity has already occurred with the new cephalosporins and also recently with clavulanic acid.1,2

Hypersensitivity reactions can lead to any of the 4 immunologic effector mechanisms described by Coombs and Gell (Table 1).3 Type I (immediate) reactions occur less than 1 hour after drug administration and are mediated by drug-specific IgE antibodies, with the typical clinical manifestations being urticaria and anaphylaxis. Type II (cytotoxic) and type III (immunocomplex) reactions are mediated by drug-specific, complement-fixing IgG or IgM antibodies, with typical symptoms being hemolytic...
anemia and serum sickness. Type IVa–d, known as delayed hypersensitivity reactions, are nonimmediate reactions induced by various T-cell subsets. These reactions occur within an interval of 24 to 48 hours after drug intake, with maculopapular exanthema being the most frequent reaction.

Depending on the time interval between drug intake and the occurrence of the reaction, Levine\(^4\) classified allergic reactions to BLs as immediate, accelerated, or delayed. As a working classification, the reactions can be grouped as immediate (appearing within 1 hour of drug intake) and nonimmediate reactions (appearing more than 1 hour after drug intake). Although this classification is not strict and overlaps exist, it is useful when considering the clinical evaluation and the diagnostic workup.\(^5\)

In this article, the authors describe the clinical entities, the underlying mechanisms, and the in vivo and in vitro diagnostic methods of hypersensitivity reactions to different BLs and emphasize the role of new concepts, patterns of responses, and the emergence of compounds, such as clavulanic acid, in the elicitation of the reactions.

**EPIDEMIOLOGY**

The prevalence and incidence of allergic reactions to BLs in the general population are not well known. Although the initial incidence decreased when contaminants were reduced and chemical synthesis was introduced, it was later counterbalanced by the increasing number of exposed populations.\(^6\) Data vary depending on the study,

<table>
<thead>
<tr>
<th>Type of Reaction</th>
<th>Mechanisms</th>
<th>Clinical Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I (immediate)</td>
<td>IgE mediated</td>
<td>Urticaria, Angioedema, Anaphylaxis, Anaphylactic shock, Bronchial asthma, Rhinitis, conjunctivitis</td>
</tr>
<tr>
<td>Type II (cytotoxic)</td>
<td>Antibody mediated</td>
<td>Immune hemolytic anemia, Thrombocytopenia, Blood cell dyscrasias, Organ-specific reactions</td>
</tr>
<tr>
<td>Type III (immunocomplex)</td>
<td>Immunocomplex mediated</td>
<td>Serum sickness–like syndrome, Vasculitis, Organ-specific reactions</td>
</tr>
<tr>
<td>Type IV (delayed)</td>
<td>T cell mediated</td>
<td>Maculopapular exanthema, SJS, TEN, Organ-specific reactions, AGEP, DRESS/DHIS, Fixed drug eruption, Contact eczema, Delayed urticaria</td>
</tr>
</tbody>
</table>

*Abbreviations:* AGEP, acute generalized exanthematous pustulosis; DRESS/DHIS, drug rash with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.
with over-reporting when patients are classified only by clinical history and under-reporting of mild and severe reactions.\textsuperscript{7}

Early reports showed a frequency of allergic reactions to penicillins ranging from 0.7% to 10%, with the frequency of anaphylaxis being 0.015% to 0.004%.\textsuperscript{8} Since then, numerous studies have been published showing the prevalence of positive skin test results in patients with a clinical history of allergy or good tolerance. In a study performed by Gadde and colleagues,\textsuperscript{9} results of skin tests were positive for penicillin determinants in 7.1% of patients with a positive history and in 1.7% of those with a negative history. Studies performed in a large series of patients with cutaneous symptoms showed that only 19% were finally diagnosed as being allergic to BLs.\textsuperscript{7}

**BLS INVOLVED**

BLs include a large number of chemical compounds that share a common structure and mechanism of action, and they are the first choice for the treatment of different bacterial diseases. Depending on their chemical structure, BLs are classified into 2 major classes, penicillins and cephalosporins, and 4 minor classes, monobactams, carbapenems, oxacephems, and clavams.

The basic structure of all BLs consists of a 4-member BL ring that, in penicillins, is connected with a 5-member thiazolidine ring and, in cephalosporins, with a 6-member dihydrothiazine ring. The former has 1 side chain (R1), and the latter has 2 (R1 and R2), with substitution at the R1 and R2 side chains resulting in various antibiotics with different chemical structures (Table 2). These changes, although minor in some

<table>
<thead>
<tr>
<th>Group</th>
<th>Compounds</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Natural</td>
<td>Penicillin G, penicillin V</td>
<td></td>
</tr>
<tr>
<td>Aminopenicillins</td>
<td>AX, ampicillin, bacampicillin</td>
<td></td>
</tr>
<tr>
<td>Penicillinase-</td>
<td>Methicillin, oxacillin, cloxacillin,</td>
<td></td>
</tr>
<tr>
<td>Resistant</td>
<td>nafcillin, dicloxacillin</td>
<td></td>
</tr>
<tr>
<td>Carboxypenicillins</td>
<td>Carbenicillin, ticarcillin</td>
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<tr>
<td>Acylaminopenicillins</td>
<td>Azlocillin, mezlocillin, piperacillin</td>
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<tr>
<td>Cephalosporins</td>
<td></td>
<td></td>
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<tr>
<td>First Generation</td>
<td>Cefadroxil, cephalexin, cephalotin,</td>
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</tr>
<tr>
<td></td>
<td>cephampirin, cefazolin, ceprozil,</td>
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<td></td>
<td>cefradine</td>
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<tr>
<td>Second Generation</td>
<td>Cefaclor, cefamandole, cefmetazole,</td>
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<td></td>
<td>cefminox, cefonicid, ceforanide,</td>
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<td></td>
<td>cefotetan, cefotiam, cefoxitin,</td>
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<td></td>
<td>cefuroxime, loracarbef</td>
<td></td>
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<tr>
<td>Third Generation</td>
<td>Cefdinir, cefetamet, cefixime,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>cefodizime, cefoperazone,</td>
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<td></td>
<td>cefotaxime, cefpodoxime,</td>
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<td></td>
<td>ceftizoxime, cefpiramide,</td>
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<td>cefsulodin, cefazidime,</td>
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<td></td>
<td>ceftibuten, ceftriaxone</td>
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<tr>
<td>Fouth Generation</td>
<td>Cefepime, cefpirome</td>
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</table>
instances, are sufficient to be recognized as different and be discriminated by the immunologic system, with relevant clinical consequences.10

CLINICAL MANIFESTATIONS

The skin is the organ most frequently involved in hypersensitivity reactions to BLs, sometimes accompanied by systemic symptoms.5 In a minor proportion of cases, reactions may not involve the skin and are limited to just one or several organs, such as the liver, lung, kidney, hematopoietic system, or others. Different entities can be recognized depending on the mechanisms, time interval, dose, and duration of treatment and clinical manifestations (see Table 1).

Immediate Reactions

Immediate reactions usually appear within a period ranging from minutes to no longer than 1 hour after BL administration by any route.4 The clinical entities include anaphylaxis, consisting of generalized pruritus, erythema, and angioedema; difficulty breathing; upper or lower airway obstruction; and, in more severe cases, cardiovascular collapse leading to anaphylactic shock.11 When manifestations are limited to the skin, the clinical entity is urticaria, whether or not accompanied by angioedema, which consists of rapidly evolving, transient, pruriginous wheals occurring at different sites of the body.11 In the onset of the reaction, it can sometimes be difficult to differentiate urticaria from anaphylaxis because it can be one of the initial symptoms of anaphylaxis.

Nonimmediate Reactions

Nonimmediate reactions include the accelerated and delayed reactions under the Levine classification.4 These reactions usually appear from 24 to 48 hours after drug administration, although symptoms can initiate within 1 hour of drug intake.12–14 The clinical entities can mimic the symptoms of infectious or autoimmune diseases, and it is often difficult to establish if the reaction was induced by the BL or had an infectious, mostly viral, origin.15

The most frequent entity is maculopapular exanthema, followed by urticaria, both considered benign diseases, and where aminopenicillins represent the main cause.16,17 Examples of less common but more severe reactions include acute generalized exanthematous pustulosis (AGEP). Drug rash with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome (DRESS/DIHS) is actually an uncommon manifestation of BL allergy. Rare but well documented are bullous eruptions such as erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis.18,19 Other entities such as fixed drug eruption and contact dermatitis also exist.20 Serum sickness–like syndrome has also been attributed to BLs, particularly to cephalosporins and aminopenicillins, although the role of BLs in the triggering of this entity has not yet been definitively established.21

Hematologic Reactions

The most common hematologic reaction induced by BLs is hemolytic anemia, which was first reported with penicillin and later with second and third generation cephalosporins, such as cefotetan and ceftriaxone.22 Additional cases have also been associated with piperacillin23 and with β-lactamase inhibitors (clavulanic acid, sulbactam, and tazobactam) combined with ticarcillin, ampicillin (AM), and piperacillin.24 Less frequent reactions involve neutropenia and thrombocytopenia. The former is associated with high doses and prolonged periods (14 days or more) of penicillins intake, for example, in the treatment of infective endocarditis.25
**Organ-specific Reactions**

Immediate organ-specific reactions in the absence of other symptoms may occur, such as laryngeal angioedema, rhinitis, asthma, or conjunctivitis. In many instances, these reactions are of occupational origin, for example, those in health care workers, veterinary personnel, or people involved in the pharmaceutical industry. Nonimmediate, organ-specific reactions can occur in the context of a systemic reaction such as DRESS/DIHS, although they may also appear without skin involvement. The most common organ affected is the liver, and this reaction has been reported with AX, flucloxacillin, and others. The possible symptoms include fever and jaundice. Similar to many other drugs, BLs can induce cholestasis, granulomatous hepatitis, hepatocellular damage, and acute liver failure. Clavulanic acid is a well-documented cause of cholestatic hepatitis, and flucloxacillin is that of (isolated) hepatitis.

Acute interstitial nephritis (also mainly a reaction to flucloxacillin and previously to cloxacillin) is characterized by a slowly developing impairment of renal function, mild proteinuria, and sterile pyuria, possibly containing eosinophils. Some patients have concomitant exanthema. Less common organ-specific reactions include pancreatitis, pneumonitis, and myocarditis.

**PATHOPHYSIOLOGY**

**Formation of Hapten-Carrier Conjugate**

All BLs have the capacity to bind spontaneously to exogenous or endogenous proteins that can later be processed and recognized by the immunologic system. The kinetics of binding to cell or serum proteins is rapid, generating hapten-carrier conjugates in a concentration-dependent manner. The first penicillin formulations were heterogeneous and contained BP aggregates and bacterial protein contaminants that were thought to be responsible for the high percentage of reactions. Because the formulations are now pure chemically synthesized compounds with no contaminants, the putative carrier must be endogenous proteins.

For many years, the best recognized structure has been benzylpenicilloyl (BPO), which results from the opening of the BL ring by an amino group of the protein, forming the major antigenic determinant (Fig. 1). The inclusion of BP in a poly-L-lysine (PLL) carrier has been used as the major determinant for in vivo diagnosis. It was later shown that in a certain proportion of patients, the application of BP or other metabolites, such as benzylpenicilloic or benzylpenilloic acid, to the skin could induce a positive response. These drugs were commercialized as the minor determinants mixture (MDM). Cephalosporins are BLs that also bind to proteins, although haptenization is slower and less efficient than with penicillins. In most cephalosporins, the R2 is lost after the opening of the BL ring, with the IgE antibodies recognizing the R1 and part of the BL ring structure (see Fig. 1). Cross-reactivity between cephalosporins can therefore be explained through similarity of the R1 side chain.

The production of murine monoclonal antibodies to BP molecules has led to the identification of 3 epitopes: the side chain, the part formed by the binding of the carbonyl of the BL to the amino group of proteins, and the thiazolidine ring. Monoclonal antibodies have also been produced with other BLs such as AX, AM several cephalosporins, and aztreonan, which indicates that any of these structures can generate specific epitopes, thus supporting the concept that any particular BL can induce selective responses. Detailed immunochemical studies using polyclonal IgE with monomeric and polymeric penicillin conjugates showed that although
differences in the chemical structures are relevant for the antigenic determinant, the whole structure that includes the protein carrier is necessary for the constitution of the antigen. The relevant parts of the penicillin are the common BL ring, including the thiazolidine and the side chain.50

Immediate Reactions

In the lymph nodes, the BL, free or conjugated, is taken up by the dendritic cell, processed, and presented to T and B cells. Within the context of a Th2 response, specific IgE antibodies to the hapten-carrier complex are produced. On further reexposure, the penicillin-protein complex is recognized by IgE antibodies, which are bound to high-affinity FcεRI on the surface of the mast cell and basophils. Cross-linking of the IgE molecules leads to activation of a calcium-dependent protein kinase cascade and the subsequent release of inflammatory mediators such as histamine, prostaglandin D2, sulfidoleukotrienes, tryptase, and many cytokines. This release of mediators is responsible for the immediate reactions described earlier. The peculiarities of hapten-specific IgE molecules and their facilitated ability to cross-link are described in another article by Pichler and colleagues elsewhere in this issue.

Immediate reactions are generally induced by therapeutic doses, although they may occur with much lower amounts that can be in micrograms, picograms, or even less. These reactions can occur on exposure to minimum amounts of BL, such as those used for skin testing or traces present in foods.51,52

The IgE response to BLs is not a long-lasting phenomenon. After the reaction, there is an increase in IgE production that decreases over time at a variable rate, depending on the specificity of the antibody.53 Those subjects with IgE antibodies specific to side chain AX determinants test negative before those recognizing the BPO determinant.52 These findings have been shown by skin testing and in vitro studies.54,55
Nonimmediate Reactions

In nonimmediate reactions, effector T cells are responsible for the immunologic cellular mechanisms. This group includes a variety of clinical entities formerly subclassified as type IV reaction, according to Coombs and Gell. To account for the clinical and immunologic heterogeneity, 4 additional subclassifications have been proposed (type IVa–d). These subclassifications correspond to different subsets of T cells, with distinct functions and tissue damage. BLs are involved in all 4 type IV reactions: BLs can cause macrophage activation (type IVa [Th1] reaction), eosinophil-rich exanthemas (type IVb), bullous skin diseases (type IVc), as well as neutrophil-rich inflammations, such as AGEP (type IVd).

Immunohistochemical studies performed in the skin have shown a mononuclear cell infiltrate composed mainly of T cells, expressing activation markers (CD25, CD69, and HLA-DR) and the skin homing receptor, cutaneous leukocyte-associated antigen receptor, in CD4 and CD8 subsets, with CD4 cells generally predominating over CD8 cells. Other cells, such as neutrophils, eosinophils, macrophages, or keratinocytes, can also be involved; for example, in the case of maculopapular exanthema, an increased number of eosinophils in the papillary dermis has been found.

Monitoring the acute response in peripheral blood helps to understand the mechanisms involved, and the authors have found increased production of interferon-γ, tumor necrosis factor α, interleukin (IL) 2, the transcription factor T-bet, and the cytotoxic markers, perforin and granzyme B.

Hematologic Reactions

Most hematologic reactions concern hemolytic anemia. In such reactions, at least 2 mechanisms may occur; those reactions where BLs bind to cell membrane proteins and those where immunocomplexes are formed in serum and later adsorbed to red blood cells, resulting in hemolysis. Most cases induced by BLs depend on the presence of BL-dependent antibodies (mainly IgG), which react with BLs that bind firmly to cell membranes and can be detected by incubating the patient’s serum with erythrocytes coated with the BL. This mechanism induces extravascular red cell destruction.

Organ-specific Reactions

In hepatitis, the formation of drug-modified hepatic protein adducts is thought to play an important role in the hepatotoxicity of BLs, and the presence of hepatic protein adducts has been shown in patients with hepatitis induced by flucoxacillin. About 1 in 10,000 treatments with flucoxacillin results in hepatitis; quasi all affected patients were HLA-B5701+, which means that the clinical manifestation of hepatitis is strongly associated with HLA-B5701, although the penetrance of this gene to cause hepatitis is very low.

Two cases of nephritis induced by BLs, flucoxacillin, and BP have been reported, in which the immunohistochemistry of kidney biopsies showed T-cell (CD4+ and/or CD8+) infiltration, with an increase in IL-5 level and eosinophil and neutrophil counts. These investigators postulate that drug-specific T cells are activated in situ and orchestrate local inflammation via secretion of various cytokines, which are probably responsible for the renal damage.

DIAGNOSIS

The clinical history enables 2 approaches for diagnosing allergic reactions, immediate and nonimmediate, to BL. In both reactions, in vivo and in vitro methods can be performed.
**Immediate Reactions**

**Skin testing**
The recommended procedure is skin testing with penicilloyl polylsine (PPL) (PRE-PEN) and with MDM consisting of BP and benzylpenilloico acid. However, in countries where AX is the most important drug involved in sensitization, this determinant is also required for diagnosis. Furthermore, when any other BL is involved in the reaction and the results of skin tests for PPL, MDM, and AX are negative, skin testing with the culprit BL, such as cephalosporin or clavulanic acid, can be done if it is available.

For the procedure, it is recommended to do prick testing first, and if results are negative, the intradermal test can be performed. General procedures have been described by the European Academy of Allergy and Clinical Immunology. Positive prick and intradermal test results are shown in **Fig. 2**, and the doses recommended for skin testing are shown in **Table 3**.

Rates of 1.3% of systemic symptoms in all tested patients and 8.8% in those with a positive skin test result and a history of anaphylaxis have been reported. Consequently, precautions must be taken, particularly in severe cases, reducing the hapten concentration by as much as 1000-fold dilution, using each determinant separately in time, or even considering performing an in vitro test first.

**In vitro testing**
For immediate reactions, methods widely used for detecting BL-specific IgE are antibody-based immunoassays that use solid phases (agarose (Sepharose), cellulose discs), carrier molecules (human serum albumin, aliphatic spacers, or PLL), and different determinants such as BP, AX, and cephalosporins. A commercial platform for routine analysis is the CAP System FEIA (fluorescence immunoassay) method (Phadia AB, Uppsala, Sweden), which works by a high surface-capacity solid-phase assay using a secondary fluorescent-labeled antibody. The specificity of this method ranges from 83.3% to 100% and the sensitivity from 12.5% to 45%, depending on the clinical manifestations.

Another procedure being progressively used is the basophil activation test, which is based on the capacity of basophils to release histamine or to upregulate activation markers such as CD63 or CD203c after activation. How surface-bound drug-specific IgE is cross-linked if a free drug is added is not yet clear. The method has a sensitivity of

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**Fig. 2.** Immediate skin test results positive for BL. (A) Prick test results positive for cefadroxil. (B) Intradermal test results positive for AX and AM.
of 48.6% and a specificity of 93%.\textsuperscript{67,68} Both in vitro tests, although less sensitive than skin testing, have proved to be complementary, and some cases have tested negative for the skin test and positive for the in vitro test.\textsuperscript{69}

Drug provocation testing

Drug provocation testing (DPT) can be considered for those patients who have tested negative for the skin test and in vitro test, who have no risk factors, and for whom diagnosis is mandatory.\textsuperscript{70} In contrast to earlier investigations, where a sensitivity of 95% was found, recent research suggests the sensitivity of penicillin tests to be substantially lower, and European researchers have estimated that up to 30% of patients with immediate allergic reactions to BL will fail to be diagnosed if DPT is not done.\textsuperscript{70,71}

The general guidelines for performing a DPT are a single-blind placebo-controlled test under strict hospital surveillance with emergency room facilities.\textsuperscript{61,62} The drug is administered at increasing doses, with a minimum interval of 30 to 60 minutes between each administration if good tolerance is established at the previous dose, until the full therapeutic dose is reached. In patients with a history of severe reactions, this dose can be as low as 0.1 to 5 mg. The doses recommended for DPT is shown in Table 3.

Nonimmediate Reactions

Skin testing

Results of skin testing with immediate readings are often negative in nonimmediate reactions like many forms of exanthemas. However, this does not rule out a delayed, mainly T-cell–based reaction. Intradermal and/or patch tests with a late reading at 24 to 48 hours have usually been recommended for the diagnosis of nonimmediate reactions to BL, such as nonimmediate exanthematic reactions or delayed-appearing urticarial reactions. Some evidence indicates that the former test has a higher sensitivity, and patch testing is recommended for BLs where no preparation for parenteral use is available.\textsuperscript{70}

Intradermal testing is done in the same way as for immediate reactions. Readings are taken at 48 and 72 hours, and any infiltrated erythema with a diameter greater than 5 mm is considered as a positive result (Fig. 3).\textsuperscript{72} These reactions should be documented by the diameter of the erythema and the papulation or infiltrate, as well

| Table 3
<p>| Reagents and concentrations recommended for prick and intradermal skin testing and DPT |
|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Reagent</th>
<th>Skin Testing</th>
<th>DPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPL</td>
<td>$5 \times 10^{-5}$ mmol/L</td>
<td>Not done</td>
</tr>
<tr>
<td>MDM</td>
<td>$2 \times 10^{-2}$ mmol/L</td>
<td>Not done</td>
</tr>
<tr>
<td>BP</td>
<td>$10,000$ IU/mL</td>
<td>$10^3$, $10^4$, $10^5$, $5 \times 10^5$ IU/mL Cumulative dose (6 $\times 10^5$ IU/mL)</td>
</tr>
<tr>
<td>AX</td>
<td>20 mg/mL</td>
<td>5, 50, 100, 150, 200 mg Cumulative dose (500 mg)</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>20 mg/mL</td>
<td>5, 50, 100, 150, 200 mg Cumulative dose (500 mg)</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>2 mg/mL</td>
<td>5, 50, 100, 150, 200 mg Cumulative dose (500 mg)</td>
</tr>
</tbody>
</table>

Abbreviation: DPT, drug provocation testing.
as a morphologic description (erythematous swelling, erythematous infiltrate, only erythema, eczema with papulation with or without vesicles).

Patch tests can be done with BP, AM, AX, and the culprit BL, using a concentration of 5% in petrolatum. Readings should be taken according to the European Environmental and Contact Dermatitis Research Group patch test classification, 15 minutes after removal of the strips and again 24 and 48 hours later (see Fig. 3).

Aminopenicillins are the drugs that most frequently induce a skin test positive response, with most patients tolerating BP. Previous studies showed sensitivity to be around 60%, although recent studies have shown figures ranging between lower than 10% to 20% and 37.8%, which can be explained by a selection bias of positive cases and, although less likely, by loss of sensitivity.56,72

In vitro testing
The lymphocyte transformation test (LTT), although not routinely recommended, can be used for evaluation of nonimmediate reactions.73,74 In the authors’ experience with LTT, 57% of patients tested positive to at least one of the penicillins; although, when different BLs were used in the stimulation, a heterogeneous response was seen in selective responders.74

Drug provocation testing
Although skin testing and in vitro testing have been proposed for the diagnostic evaluation of nonimmediate reactions to BL, major limitations exist because of the low sensitivity of skin testing and difficulties in training of personnel to perform the LTT.12,13,61,72 Because exanthematic reactions are mild in nature and, in many instances, subjects may have good tolerance, DPT can be performed.

The methodology is not yet standardized. Most centers use the same as that for immediate reactions, that is, the administration of the BL at increasing doses. Depending on the severity of the earlier reactions, provocations should be done in a specialized center under careful clinical observation, paying particular attention to symptoms that may usually start after more than 1 hour and giving increasing doses up to a maximum amount of one-fifth of the therapeutic dose. If good tolerance exists in this first step, then at least 48 hours later, increasing doses are usually given up to a full therapeutic dose (mostly on an outpatient basis in milder reactions). Questions remain as to whether, after completing these steps, a full therapeutic dose should be given for a number of days similar to a therapeutic regimen, because delayed appearing reactions highly depend on the cumulative dose. The dose recommended for DPT is shown in Table 3.

Because the most frequent drug involved is AX, this drug must be used in many cases, with most of those patients who test positive tolerating BP and, consequently,
other BLs. DPT is contraindicated in the case of severe reactions, such as DRESS/ DIHS, bullous eruptions, and AGEP or hematologic reactions.

ASSESSMENT OF CROSS-REACTIVITY

As a result of similarities in their structures, cross-reactivity, especially in type I imme-
diate reactions, has been shown to exist among different penicillins and even between penicillins and first generation cephalosporins. Subjects who tested positive for PPL and/or MDM in skin testing have developed reactions with cloxacillin, AM, methicillin, or AX, among others.\(^5,11,50,52,71\) The discovery of side chain–specific determinants in immediate reactions and the observation that in nonimmediate reactions to BLs subjects with a positive response to aminopenicillins could tolerate other compounds such as BP and penicillin V led to the idea that cross-reactivity is not equal among all BLs and that the immunologic mechanism and the primary drug inducing the sensiti-
zation need to be taken into account.\(^12,13,16,17\)

The rate of cross-reactivity with cephalosporins is around 10% in patients with a primary IgE-mediated allergy to penicillins.\(^75\) It is assumed that first generation ceph-
alosporins can cross-react with penicillins because their structural features are more similar to those of penicillin, whereas second and third generation cephalosporins are less likely to induce cross-reactivity owing to differences in their chemical structure. Cross-reactivity increases to more than 30% in cases where penicillins and cephalo-
sporins share the same side chain, as occurs between AX and cefadroxil.\(^76\)

When cross-reactivity is evaluated in immediate allergic reactions to cephalospo-
rins, 2 patterns of response have been observed: those who test positive for penicillin determinants in skin testing and those who respond only to cephalosporin determi-
nants. In the second group, patients can react to several cephalosporins that share similarities or identity in the R1 side chain. In these cases, cross-reactivity has been detected among ceftriaxone, cefotaxime, and cefepime, which share an identical side chain at the R1 position, and between cefuroxime and ceftazidime, which have similar R1 side chains. The possibility of response only to one single cephalosporin also exists.\(^43,44\)

Cross-reactivity between other BL groups seems to be very low. A rate of 0.9% has been reported between imipenem and penicillins.\(^77\) In patients with penicillin allergy, good tolerance to aztreonam has been described.\(^78\)

Less is known about cross-reactivity in nonimmediate hypersensitivity reactions to amopenicillins and cephalosporins. It seems to be very low between penicillins and cephalosporins and, even within penicillins, cross-reactivity to other penicillins with different side chains is infrequent.\(^12,13,16,17\)

NATURAL EVOLUTION

Observations that in patients with clear anaphylactic reactions, the results of skin tests were not always positive and that positivity was in part caused by the time interval between drug occurrence and the time of evaluation led to the suspicion that time interval was critical in the evaluation. In a prospective study of allergic subjects who tested positive in skin tests at the initial evaluation, after a 5-year follow-up, only 40% of those with positive skin tests results to BP determinants tested negative, whereas 100% of those with a selective response to AX tested negative.\(^54\) Similar results have been shown with in vitro testing, radioimmunoassay, and the basophil activation test.\(^55\) It is not yet known what happens in those cases with immediate allergic reactions to other BLs, such as selective responders to cephalosporins or clavulanic acid.
In the case of nonimmediate reactions to BLs, sensitivity seems to be maintained over time, although the possibility of a decrease in the response also exists.\textsuperscript{12,13,16,17}

**DESENSITIZATION**

Desensitization has been shown to be useful in BL hypersensitivity, especially in immediate reactions. Oral and parenteral protocols have been published.\textsuperscript{79} Desensitization is indicated when a BL cannot be replaced or when a particular BL is more effective or has fewer side effects than other alternatives. Before desensitization, an accurate diagnosis needs to be done, and the benefits must outweigh the risks.

**SUMMARY**

The world of BLs has changed over the years, with more BLs becoming involved, although penicillin, the initial sensitizing agent, is now less involved. Other BLs are taking on a relevant role, and AX is the drug most frequently involved. Sensitization is related with patterns of consumption. The latest widely used BL reported to produce allergic reactions is clavulanic acid. Any BL can induce a hypersensitivity response. Diagnosis in immediate reactions is less sensitive than earlier because the BP molecule is not responsible for the allergic reaction and the BPO group is therefore less relevant. In addition to IgE responses such as anaphylaxis and urticaria, nonimmediate reactions occur, of which the most common are exanthemeatic or nonimmediate urticaria.

Improvement of diagnostic tests is based on the use of the relevant BL that induces sensitization and on the progress of research to identify the relevant proteins to which BLs are bound in the body. Allergy to these antibiotics will always exist, and as new molecules are introduced, they can be considered as putative causes of drug hypersensitivity. This assumption is related with consumption and other currently unknown genetic factors.

**REFERENCES**


