

Antibiotic Allergy: Immunochemical and Clinical Considerations

Brian A. Baldo, PhD, Zhenjun Zhao, PhD, and Nghia H. Pham, PhD

Corresponding author

Brian A. Baldo, PhD

11 Bent Street, Lindfield, NSW, 2070, Australia.

E-mail: babaldo@optusnet.com.au

Current Allergy and Asthma Reports 2008, **8**:49–55

Current Medicine Group LLC ISSN 1529-7322

Copyright © 2008 by Current Medicine Group LLC

Antibiotics are among the most widely and heavily prescribed drugs, but despite this, allergic reactions to most groups of antibiotics are relatively uncommon—especially when compared with the number and frequency of type 1 hypersensitivity responses to the β -lactams (ie, penicillins, cephalosporins, and, to a lesser extent, carbopenems). Still, there remains a steady flow of reports of allergic reactions to some topically used antibiotics (eg, rifamycin SV and bacitracin). Moreover, aminoglycosides (eg, neomycin and gramicidin) may be implicated more often than previously suspected. Despite advances in our understanding of the structural basis of the allergenicity of β -lactam antibiotics, the insights have not readily transferred into routine use to improve diagnoses of reactions to individual penicillins and cephalosporins. This remains a challenge in drug allergy, as does the need for further chemical, immunologic, and clinical research on cephalosporin breakdown products and the so-called multiple antibiotic allergy syndrome.

Introduction

This review summarizes advances in our understanding of clinical and immunochemical aspects of immediate hypersensitivity responses to the most important and widely used antibiotics. Following our earlier review of this field [1], emphasis is on developments from the past 3 to 5 years along with references to earlier studies, if appropriate.

In keeping with earlier conclusions [1,2], numerous well-known and important antibiotics are rarely implicated in true allergic reactions in humans. For example, the macrolides, which comprise the important antibacterials erythromycin, azithromycin, and clarithromycin, are generally well tolerated. Although adverse reactions including rash, fever, and eosino-

philia occur, anaphylaxis seems rare. Likewise, true allergic reactions to tetracyclines, antibiotics often prescribed for weeks and months, are infrequent; the same is true for chloramphenicol. Although ostensibly covering “antibiotic” allergy, some recent reviews deal exclusively, or nearly so, with β -lactam drugs. This probably also reflects the few reports on allergies to non- β -lactam antibiotics and the overwhelming preponderance of the latter. Therefore, emphasis here is on those antibiotics most frequently featured in the recent literature as agents provoking adverse reactions identified as or strongly suspected of being immunoglobulin (Ig) E antibody-mediated immediate hypersensitivity reactions. Not surprisingly, given their well-known allergenic potential and record, heading such a list is the β -lactam group of antibiotics, especially the penicillins and cephalosporins; much less frequently vancomycin, teicoplanin, rifamycin SV, and bacitracin; and rarely, aminoglycoside antibiotics such as neomycin, gentamicin, and gramicidin.

Antibiotics Other than the β -Lactams Vancomycin and teicoplanin

The most frequently seen adverse effect of vancomycin is the so-called red man syndrome, mediated by histamine and characterized by flushing, erythema, and pruritus of the head and upper torso. Adding to the earlier reports on vancomycin allergies [1], Hassaballa et al. [3] described such a case. This individual developed anaphylaxis after intravenous (IV) infusion of vancomycin. The authors suggested that vancomycin-induced syndrome may be a marker for true vancomycin allergy. In what may be the first reported case of allergy to vancomycin in topical form, Hwu et al. [4] presented details of a patient’s ocular reaction to vancomycin eye drops following their use to treat recurrent endophthalmitis. Symptoms resolved once the eye drops were discontinued and IV treatment was started with the structurally related teicoplanin. Skin tests with vancomycin proved positive, suggesting that the reaction was at least in part an immediate hypersensitivity response. Another interesting aspect of this case was the subject’s tolerance to teicoplanin despite the known cross-reactivity between the two glycopeptide antibiotics [1].

Delayed-type hypersensitivity reactions have been reported following administration of teicoplanin, but anaphylactoid reactions to the drug are rare, especially when compared with vancomycin, which induces histamine release. A report by Asero [5] implicated teicoplanin as an allergenic molecule in rare subjects; it described anaphylaxis to the drug after IV infusion. Intradermal tests with the antibiotic induced an immediate wheal and flare reaction suggesting an IgE antibody-mediated mechanism.

Rifamycin SV

Rifamycin SV is a macrocyclic antibiotic that could act as an allergen [1]; its application has an established track record of immediate allergic reaction. Two reports add to that record. The subjects experienced anaphylaxis provoked by rifamycin SV after local application.

In a study employing skin prick and Prausnitz-Küster (P-K) tests, Erel et al. [6] concluded that the patients' reactions were IgE-mediated. Magnan et al. [7] used reductive amination to conjugate rifamycin SV to poly-L-lysine before coupling to cellulose and employing the resultant complex to detect rifamycin SV-reactive IgE antibodies in the patient's serum. Recently, anaphylaxis was reported to occur during irrigation of a wound with rifamycin SV [8]. A positive skin test to the drug and a positive basophil activation test using multicolor flow cytometric analysis with specific monoclonal antibodies as basophil activation markers supported the diagnosis of anaphylaxis.

Bacitracin

Bacitracin, a polypeptide antibiotic produced by *Bacillus subtilis*, consists of three separate compounds: bacitracin A, B, and C, with bacitracin A being the chief constituent. The antibiotic is widely used in topical form after surgical procedures for acute skin injuries and chronic wounds. Adverse drug reactions include contact urticaria, contact allergy, and numerous cases of anaphylaxis. Reactions to bacitracin seem to occur particularly when the skin barrier is not intact. Surgical irrigation fluid containing bacitracin was recently identified as the agent provoking anaphylaxis in a patient undergoing knee arthroplasty [9]. Bacitracin as an allergen in adverse reactions is the subject of a recent short review [10].

Aminoglycoside antibiotics

These antibiotics are widely used topically and implicated in delayed hypersensitivity reactions. In a recent prospective study, skin tests on 119 patients with chronic otitis media and 30 patients with otosclerosis revealed positive reactions to gentamicin (13.4%), neomycin (12.8%), and gramicidin (4.5%) [11]. Overall, 14% of patients were positive to at least one aminoglycoside. Previous use of the antibiotic correlated with a higher tendency of developing a hypersensitive reaction. These interesting findings warrant further investigations to

firmly establish the immediate and/or delayed nature of the adverse reactions to these antibiotics.

β -Lactam Antibiotics

Test materials for in vivo and in vitro use

Given the need to consider side-chain determinants on individual β -lactams; the possibility of cross-reactions resulting from recognition of core or shared side-chain structures [12–18]; and the known heterogeneity of penicillin and cephalosporin allergenic determinants [1,12–14,17,18], test reagents in vivo and in vitro should not be confined to preparations like benzylpenicilloyl-polylysine (Prepen) and the so-called “minor” determinant mix (generally prepared from benzyl penicillin) [18]. In this context, and after reviewing studies [19–21] and guidelines from Europe [19], little long-term thinking seems to have occurred and little effort made to begin developing and standardizing a wider range of improved β -lactam test agents.

Immunochemical investigations have led to interesting insights into fine structural IgE antibody recognition patterns of some penicillins and cephalosporins. This suggests the need to employ not only a wider variety of individual drugs but also drugs in different hapten-conjugate linkages in skin and antibody tests. We base this conclusion on findings that include demonstration of allergic sensitivity and positive skin and IgE tests to flucloxacillin but not to benzyl penicillin [16]; antibody recognition of the amoxicilloyl but not the amoxicillinanyl determinant in one allergic subject but the reverse recognition pattern in another patient [22]; and demonstration of fine structural recognition differences on R1 and R2 side chains of cefaclor by IgE antibodies from cefaclor-allergic subjects [14].

Although assessment and comparison of the allergenic reactivities of various putative penicillin antigens is needed [17,18], the “major” or “-oyl” antigen and at least one so-called “minor” antigen, the “-anyl” derivative, are sufficiently well studied and characterized [23]. This work can at least provide the start of a collection of diagnostic reagents that may increase the detection of penicillin-allergic subjects. To start, “-oyl” and “-anyl” derivatives of benzylpenicillin, amoxicillin, and ampicillin could be prepared, standardized, and trialed [18].

The situation with the cephalosporins is more complicated. Their allergenic structures are not as well identified and studied. Even though preparation of intended “-oyl” conjugates of cephalosporins under alkaline conditions are known to yield labile compounds, especially those with a good leaving group in the 3'-position [24–26], test materials already used by more than one group and prepared by nucleophilic β -lactam ring cleavage have successfully detected cephalosporin-reactive IgE antibodies in allergic patients' sera [18,27–30]. So far, few immunochemical studies [14,18,28] have used other cephalosporin antigens but the “-oyl” conjugates. In a recent study of the heterogeneity of IgE responses to cefaclor, the chemical

nature of the drug-solid phase complex remains unclear (see below) [31•].

Interpretation of cephalosporin immunoassay findings

Despite criticism [30,32,33] of interpretations of IgE recognition results obtained by our group after using cephalosporin derivatives that were likely derived, at least in part, by nucleophilic β -lactam ring opening [27], and uncertainty about the nature of the resulting products [24,25], the critics continue using cephalosporins chemically modified the same way for serum immunoassays [29,30]. These labile products' uncertain number and nature have prompted questions [30,32,33] about interpretations of cephalosporin allergenic determinants identified in radioimmunoassay (RIA) hapten inhibition studies, and in particular, implication of R2 structures in IgE recognition and binding. In response, we draw attention to three relevant considerations.

First, in a study of fine structural differences identified by heterogeneous populations of cefaclor-reactive IgE antibodies [14], cephalosporin solid phases used in immunochemical binding studies were not prepared by β -lactam ring opening, which leads to subsequent decomposition. Instead, coupling via a carbodiimide was carried out by linking human serum albumin (HSA) to the 2'-carboxyl at pH 5.5 with the intention of maintaining structural integrity. Second, immunologic recognition (direct binding and inhibition) experiments, using so-called cephalosporoyl- and 2'-linked HSA solid phases, repeatedly identified R1 cephalosporin side-chains and whole molecules as determinants. Careful selection for use as inhibitors of free, intact, unmodified cephalosporin analogues with different R2 groups revealed clear recognition at that molecule's end [14, 27]. Clearly, even without knowing the different possible structures attached to the solid phase following coupling of intended "-oyl" derivatives, some IgE antibodies formed in vivo to intact cephalosporins, and/or their metabolites, have been shown to recognize whole molecules and R2 side-chains. The finding that a free, unmodified drug complements the combining sites of antibodies from an allergic patient is compelling evidence of recognition of the inhibiting substance's structural features and the substance's involvement in the allergic process. Closer investigations of coupled breakdown products of cephalosporins should help explain the immunologic findings. Certainly, in view of the direct antibody binding and hapten inhibition results they cannot be dismissed without further insights. Finally, as previously noted, cephalosporin derivatives prepared by nucleophilic β -lactam ring cleavage rapidly undergo decomposition especially in the presence of a good leaving group at position 3' [24–26]. When the substituent at this position is a methyl group (as in, for example, cephalixin), breakdown of the dihydrothiazine ring would be expected to be minimal or, at most, proceed with difficulty.

In relation to derivative preparation of β -lactams used for in vitro tests, in our [13] and others' [29] hands, the extensive use of bifunctional oxiranes (eg, 1,4-butanediol diglycidyl ether) for the preparation of drug-solid supports for detection of drug-reactive IgE antibodies in RIAs has been extremely successful. Although the methodology is well described and defined [13], the procedure has recently been described as "not well defined" and has been compared poorly to so-called "validated techniques such as RAST [radioallergosorbent test] and other immunoassays" [34]. Given the well-understood coupling chemistry and standard procedures that are at least as well defined as many other assays to detect IgE, this criticism seems curious and selective. As with so many drug-solid phase complexes used to detect antibodies, chemical characterization studies are needed [13].

β -Lactam allergenic determinants

In an often repetitive output, one group [30,32–34] has maintained that advanced immunochemical analyses of IgE-binding penicillin determinants are lacking; that a lack of knowledge hinders understanding of cross-reactivity between penicillins and cephalosporins; and that little is known of the nature of cephalosporin determinants. The latter belief has also been expressed by Romano et al. [29]. Our knowledge of cephalosporin breakdown products is certainly deficient; few antigens apart from those formed after β -lactam ring opening have been prepared; and, as with many coupled substances, the exact natures of substituents bound to solid phases remain unknown [13]. Also, as for many drugs, the differences, if any, among structures recognized by IgE antibodies in vivo and in vitro remain to be defined.

Despite these deficiencies, considerable advances have been made in precisely identifying structures that are complementary to combining sites on different populations of heterogeneous IgE antibodies from the sera of β -lactam-allergic patients. Side chain determinants on penicillins and cephalosporins and some important small antigenic differences have been identified, demonstrating the power and resolution of the careful application of classical quantitative hapten inhibition studies [13]. For example, for the penicillins, allergic specificities distinguish structural differences between benzylpenicillin and amoxicillin [12,15], ampicillin and amoxicillin [12], and amoxicilloyl and amoxicillanyl determinants [22]. A similar spectrum of specificities has been found with cephalosporins [14,18,27], and at the level of cross-reactivity of β -lactams, structures that at first appear not closely related, namely benzylpenicillin and cephalothin, were shown to share a common allergenic structure recognized by cross-reacting IgE antibodies [27,28]. These few examples and the progress made in identifying allergenic structures of other drugs [13] provide some satisfaction and optimism about our knowledge of structure-activity details for allergies to β -lactams.

As another example of the value and utility of hapten inhibition methodology, Kim et al. [31•] studied the heterogeneity of IgE antibody responses to a cephalosporin in sera from patients with anaphylaxis provoked by cefaclor. They detected two antibody recognition patterns for cefaclor—one in which the R1 side chain comprised the complementary allergenic structure, and the other in which the entire molecule (presumably including the R2 side chain) was recognized. Interestingly, the drug-protein complex was prepared by using the cross-linking agent sulfosuccinimidyl-4-(p-maleimidophenyl) butyrate to couple cefaclor to HSA. Given this agent's reactivity, linkage to cefaclor may have occurred via the free primary amine on the R1 side-chain. The same group has also reported occupational asthma to 7-aminocephalosporanic acid in two subjects. One case was shown to be mediated by IgE antibodies, whereas in the other, the mechanism appeared to be non-immune [35].

The involvement of β -lactam side-chains as allergenic determinants is becoming widely recognized as more experimental findings confirm it [36] and more clinical findings are interpreted in light of it [37–39]. Based on their analysis of an apparent case of selective cefodizime allergy, Romano et al. [39] concluded that the patient probably recognized the entire cefodizime molecule or the R2 side-chain.

Rodriguez-Pena et al. [34] advanced a curious interpretation of allergenic side-chain recognition. They stated that RIA results, which demonstrated selective responses to flucloxacillin in patients with clear clinically documented flucloxacillin-induced anaphylaxis, could not be considered selective because of the absence of skin tests, despite evidence that such a test was provided [16]. Inaccurate interpretations such as this underline the need for investigators to refer to the original publications rather than derive conclusions from the sometimes deficient summaries of others.

Unfortunately, some major reviews of β -lactam hypersensitivity [40–42] continue to discuss topics such as “penicillin cross-reactivity with β -lactams” and important questions such as, “Is it safe to give a cephalosporin drug to patients who have histories of penicillin allergy?” without consideration of the drugs' structural differences and similarities. Although a reliable, complete case history, skin test, challenge, and in vitro IgE test still form the basis of an accurate diagnosis, some knowledge of structures, especially R1 and R2 side-chains on commonly prescribed β -lactams, can greatly assist the clinician in diagnosis and alternative drug selection.

Carbapenem hypersensitivity

One retrospective study compared the incidence of carbapenem reactivity in 100 patients with reported or documented penicillin allergy to that in 111 patients with no history [43]. Analysis showed that carbapenem reactivity was 11% in the penicillin-allergic group—3.2 times greater than the

finding in the nonallergic group. Investigators observed no difference in the occurrence of allergic reactions between the two carbapenems imipenem-cilastatin and meropenem. The incidence found by Prescott et al. [43] was markedly lower than the 47% incidence found by Saxon et al. [44] among subjects with true penicillin allergy but similar to the figures from the retrospective studies of McConnell et al. [45] (9.4%) and Sodhi et al. [46] (9.2%). Clearly, a prospective study was required and was recently provided [47•]. Skin testing and antibiotic challenges showed that the reactivity to penicillins and meropenem in patients with well-demonstrated IgE antibody-mediated allergy to penicillins was no higher than 5.2%. The authors concluded that IgE antibodies from penicillin-allergic patients recognize specific penicillin determinants rather than a determinant shared with the carbapenem, namely, the β -lactam ring. Since little or nothing appears to be known about the allergenic structures involved in imipenem and meropenem, simple direct antibody binding and classic quantitative immunochemical studies should be undertaken to identify determinants.

Multiple Antibiotic Allergy Syndrome

In a recent clinical review, Macy [48] drew attention to the inadequacies of our understanding of this curious and poorly defined syndrome and the factors needed for diagnosis and effective treatment. In a detailed study of the structural basis of multiple drug allergies in seven patients, Pham et al. [49] demonstrated that drug recognition was related to the presence of tertiary and quaternary mono-, di-, and trialkyl amino groups but only if the alkyl groups were “small” viz. methyl or ethyl. These structural groups are present on many pharmacologically active agents. IgE antibodies to non- β -lactam drugs and IgE to β -lactam antibiotics were found to occur as separate populations.

Antibiotic Desensitization

When no alternative exists for treating life-threatening bacterial infection because the patient is allergic to the only effective antibiotic(s), desensitization to the antibiotic(s) may be the only remaining course of action. In what is likely the largest antibiotic desensitization study undertaken, Turvey et al. [50•], over a 5-year period, carried out 57 desensitizations in 21 patients using 12 antibiotics. They achieved successful outcomes in 75% of the treatments, demonstrating that in most patients with IgE antibody-mediated antibiotic allergy, antibiotics may be administered safely following desensitization.

Conclusions

There is a small but steady output of reports of allergic reactions, including anaphylaxis, to topical antibacterial agents, especially in cases in which application is to

mucous membranes or areas of denuded skin. Antibiotics in this category include rifamycin SV and bacitracin; on closer examination, aminoglycoside antibiotics may eventually be included. As with chlorhexidine, for which reports of anaphylaxis have recently increased, allergic reactions to rifamycin SV and bacitracin may reflect wider usage or, more likely, the realization of these drugs' capacity to provoke reactions and the subsequent implication in the reactions.

Vancomycin is known to provoke anaphylactoid reactions, but whether or not many of these reactions are exclusively due to the histamine-releasing property of the drug or also involve an IgE-antibody-mediated mechanism is not always clear. Reports mentioned here and elsewhere suggest that the possible involvement of type 1 hypersensitivity in apparent anaphylactoid reactions to vancomycin and the structurally related teicoplanin should be considered [1].

Except for preliminary studies of IgE antibodies to rifamycin [1,7], no investigations of structure-activity recognition relationships appear to have been undertaken with any of the above-mentioned antibiotics. Although the immunochemical procedures and strategies for such studies are well defined [13], each molecule is complex. Precise identification at the fine structural level of allergenic determinants may be difficult.

Publications on allergic reactions to β -lactam antibiotics still constitute the biggest number of reports by far of such reactions to any drug. Although progress in identifying allergenic determinant structures of β -lactams and studying the molecular basis of cross-reactions has been disputed [29,30,33,34], significant insights have arguably been gained at the immunochemical level [1,12–18,22,28,31•,32]. These advances could and should be used to introduce improved test agents for diagnosing allergies to penicillins and cephalosporins. Certainly, questions remain on the structures of cephalosporin breakdown products but even so, procedures already applied have demonstrated that even without well characterized chemical entities, drug-reactive IgE-antibodies can readily be detected and the antibodies can be used to identify complementary allergenic structures [13,27,31•]. When this information is obtained using unmodified cephalosporins and carefully selected analogues with precisely known structures as inhibitors of cephalosporin-reactive antibodies [14,27], it is difficult to dismiss the relevance of such *in vitro* recognition studies, especially if the findings correlate with the clinical picture.

A good case can be made for the introduction of penicilloyl and penicillanyl conjugates into routine skin prick testing and as test antigens for *in vitro* immunoassays for the detection of penicillin-reactive IgE antibodies. For the cephalosporins, knowledge of the number and nature of the breakdown products formed following opening of the β -lactam ring (ie, formed during attempted preparation of the so-called cephalosporoyl derivatives) is still

incomplete, but this has not totally restricted the successful use of such labile derivatives to detect drug-reactive antibodies in the sera of allergic patients [27–30]. The so-called cephalosporanyl derivatives, formed by covalent coupling to the 2'-carboxyl and prepared with the aim of avoiding nucleophilic-mediated β -lactam ring opening, have also been successfully used for *in vitro* testing [14,18,28]. Characterization of possible antigenic products of such electrophilic coupling reactions should now be a priority.

With the goal of applying research results on the immune recognition of different β -lactam antibiotics to improve diagnosis of immediate allergic reactions to these drugs, the following important and relevant findings are summarized. Penicillin and cephalosporin allergenic determinants show heterogeneity. Different allergic subjects may recognize different determinants, and account must be taken of side-chain and core-structure determinants and possible cross-reactions within and between the two families of drugs [18]. Indeed, an additional and even finer level of specificity may sometimes occur: for example, a patient who shows allergic recognition of a penicilloyl but not the corresponding penicillanyl determinant and another allergic patient who shows the reverse [22]. In light of these insights, investigators should be working toward achieving the "ideal" diagnostic protocol for the accurate diagnosis of immediate hypersensitivity reactions to β -lactam antibiotics [18]. Of course, such an "ideal" may change as new information accumulates.

Allergic reactions to more than one—and sometimes many—antibiotics are not uncommon but, as with so-called multiple drug allergy syndrome, multiple antibiotic allergy has not been studied and clarified to the point where there is universal agreement on its origins and underlying mechanisms [48,49]. In fact, it is also not clear whether multiple antibiotic allergies occur as part of a generalized allergic response to many different drugs or as reactions to antibiotics only. In the only study so far on mechanisms, cross-reactions due to IgE antibody recognition of "small" alkyl groups seemed to explain multiple drug reactions in the patients examined, but coincident allergic reactions to β -lactam antibiotics appeared to be mediated by separate populations of IgE antibodies [49]. Clearly, more careful analysis and cataloging of clinical cases and fundamental cellular and humoral immunologic studies are required to advance understanding of this puzzling recognition response shown by some drug-allergic patients.

Acknowledgment

Correspondence may also be addressed to the following: Zhenjun Zhao, PhD, Institute for Eye Research, Level 4, Rupert Myers Building (North Wing), University of

New South Wales, Sydney, NSW 2052, Australia, e-mail: Z.Zhao@ier.org.au; and to Nghia H. Pham, PhD, e-mail: ptr96335@bigpond.net.au.

Disclosure

No potential conflicts of interest relevant to this article were reported.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. Baldo BA, Zhao Z, Pham NH: Structural determinants of antibiotic allergy. *Curr Allergy Rep* 2001, 1:23–31.
 2. Tilles SA, Slatore CG: Hypersensitivity reactions to non- β -lactam antibiotics. *Clin Rev Allergy Immunol* 2003, 24:221–228.
 3. Hassaballa H, Mallick N, Orlowski J: Vancomycin anaphylaxis in a patient with vancomycin-induced red man syndrome. *Am J Ther* 2000, 7:319–320.
 4. Hwu J-J, Chen K-H, Hsu W-M, et al.: Ocular hypersensitivity to topical vancomycin in a case of chronic endophthalmitis. *Cornea* 2005, 24:754–756.
 5. Asero R: Teicoplanin-induced anaphylaxis. *Allergy* 2006, 61:1370–1372.
 6. Erel F, Karaayvaz M, Deveci M, et al.: Severe anaphylaxis from rifamycin SV. *Ann Allergy Asthma Immunol* 1998, 81:257–260.
 7. Magnan A, Venemalm L, Porri F, et al.: Anaphylactic reaction to rifamycin SV: presence of specific IgE antibodies. *J Allergy Clin Immunol* 1999, 103:954–956.
 8. Ebo DG, Verheecke G, Bridts CH, et al.: Perioperative anaphylaxis from locally applied rifamycin SV and latex. *Brit J Anaesth* 2006, 96:738–741.
 9. Antevil JL, Muldoon MP, Battaglia M, et al.: Intraoperative anaphylactic shock associated with bacitracin irrigation during revision total knee arthroplasty. *J Bone Joint Surg* 2003, 85A:339–342.
 10. Schalock PC, Zug KA: Bacitracin. *Cutis* 2005, 76:105–107.
 11. Yung MW, Rajendra T: Delayed hypersensitivity reaction to topical aminoglycosides in patients undergoing middle ear surgery. *Clin Otolaryngol* 2002, 27:365–368.
 12. Harle DG, Baldo BA: Identification of penicillin allergenic determinants that bind IgE antibodies in the sera of subjects with penicillin allergy. *Mol Immunol* 1990, 27:1063–1071.
 13. Baldo BA, Pham NH: Structure-activity studies on drug induced anaphylactic reactions. *Chem Res Toxicol* 1994, 7:703–721.
 14. Pham NH, Baldo BA: β -Lactam drug allergens: fine structural recognition patterns of cephalosporin-reactive IgE antibodies. *J Mol Recognit* 1996, 9:287–296.
 15. Blanca M, Mayorga C, Sanchez F, et al.: Differences in serum IgE antibody activity to benzylpenicillin and amoxicillin measured by RAST in a group of penicillin allergic patients. *Allergy* 1991, 46:632–638.
 16. Baldo BA, Pham NH, Weiner J: Detection and side-chain specificity of IgE antibodies to flucloxacillin in allergic subjects. *J Mol Recognit* 1995, 8:171–177.
 17. Baldo BA: Penicillins and cephalosporins as allergens: structural aspects of recognition and cross-reactions. *Clin Exp Allergy* 1999, 29:744–749.
 18. Baldo BA: Diagnosis of allergy to penicillins and cephalosporins. Structural and immunochemical considerations. *Allergy Clin Immunol Int* 2000, 12:206–212.
 19. Torres MJ, Blanca M, Fernandez J, et al.: Diagnosis of immediate allergic reactions to beta-lactam antibiotics. *Allergy* 2003, 58:961–972.
 20. Bousquet PJ, Co-Minh HB, Arnoux B, et al.: Importance of mixture of minor determinants and benzylpenicilloyl poly-L-lysine skin testing in the diagnosis of β -lactam allergy. *J Allergy Clin Immunol* 2005, 115:1314–1316.
 21. Matheu V, Perez-Rodriguez E, Sanchez-Machin I, et al.: Major and minor determinants are high performance skin tests in β -lactam allergy. *J Allergy Clin Immunol* 2005, 116:1167–1168.
 22. Zhao Z, Baldo BA, Baumgart KW, et al.: Fine structural recognition specificities of IgE antibodies distinguishing amoxicilloyl and amoxicillanyl determinants in allergic subjects. *J Mol Recognit* 2001, 14:300–307.
 23. Zhao Z, Batley M, D'Ambrosio C, et al.: In vitro reactivity of penicilloyl and penicillanyl albumin and polylysine conjugates with IgE-antibody. *J Immunol Methods* 2000, 242:43–51.
 24. Hamilton-Miller JMT, Newton GGF, Abraham EP: Products of aminolysis and enzymic hydrolysis of the cephalosporins. *Biochem J* 1970, 116:371–384.
 25. Hamilton-Miller JMT, Richards E, Abraham EP: Changes in proton-magnetic-resonance spectra during aminolysis and enzymic hydrolysis of cephalosporins. *Biochem J* 1970, 116:385–395.
 26. Bundgaard H: Chemical studies related to cephalosporin allergy. I. Kinetics of aminolysis of cephalosporins and effect of C-3 substituents on β -lactam reactivity. *Archiv for Pharmaci og Chemi* 1975, 5:94–123.
 27. Harle DG, Baldo BA: Drugs as allergens: An immunoassay for detecting IgE antibodies to cephalosporins. *Int Arch Allergy Appl Immunol* 1990, 92:439–444.
 28. Zhao Z, Baldo BA, Rimmer J: β -Lactam allergenic determinants: fine structural recognition of a cross-reacting determinant on benzylpenicillin and cephalothin. *Clin Exp Allergy* 2002, 32:1644–1650.
 29. Romano A, Gueant-Rodriguez RM, Viola M, et al.: Diagnosing immediate allergic reactions to cephalosporins. *Clin Exp Allergy* 2005, 35:1234–1242.
 30. Antunez C, Blanca-Lopez N, Torres MJ, et al.: Immediate allergic reactions to cephalosporins: evaluation of cross-reactivity with a panel of penicillins and cephalosporins. *J Allergy Clin Immunol* 2006, 117:404–410.
 31. Kim S-H, Choi J-H, Park H-S: Heterogeneity of the IgE response to allergenic determinants of cefaclor in serum samples from patients with cefaclor-induced anaphylaxis. *Ann Allergy Asthma Immunol* 2005, 94:700–704.
- Despite uncertainties concerning the drug solid phase employed, immunochemical identification of cephalosporin IgE-binding structures adds to and supports our evolving understanding of the spectrum of cephalosporin allergenic determinants.
32. Sanchez-Sancho F, Perez-Inestrosa E, Suau R, et al.: Synthesis, characterization and immunochemical evaluation of cephalosporin antigenic determinants. *J Mol Recognit* 2003, 16:148–156.
 33. Blanca-Gomez M, Torres MJ, Mayorga C, et al.: Immediate allergic reactions to betalactams: facts and controversies. *Curr Opin Allergy Clin Immunol* 2004, 4:261–266.
 34. Rodriguez-Pena R, Antunez C, Martin E, et al.: Allergic reactions to β -lactams. *Expert Opin Drug Saf* 2006, 5:31–48.
 35. Park H-S, Kim K-U, Lee Y-M, et al.: Occupational asthma and IgE sensitization to 7-aminocephalosporanic acid. *J Allergy Clin Immunol* 2004, 113:785–787.
 36. Orhan F, Odemis E, Yaris N, et al.: A case of IgE-mediated hypersensitivity to cefepime. *Allergy* 2004, 59:239–241.
 37. Poston SA, Jennings HR, Poe KL: Cefazolin tolerance does not predict ceftriaxone hypersensitivity: unique side chains precipitate anaphylaxis. *Pharmacotherapy* 2004, 24:668–672.

38. Pichichero ME: A review of evidence supporting the American Academy of Pediatrics recommendation for prescribing cephalosporin antibiotics for penicillin-allergic patients. *Pediatrics* 2005, **115**:1048–1057.
 39. Romano A, Viola M, Gueant-Rodriguez R-M, et al.: Selective immediate hypersensitivity to cefodizime. *Allergy* 2005, **60**:1545–1546.
 40. Thethi AK, Van Dellen RG: Dilemmas and controversies in penicillin allergy. *Immunol Allergy Clin North Am* 2004, **24**:445–461.
 41. Cunha BA: Antibiotic selection in the penicillin-allergic patient. *Med Clin N Amer* 2006, **90**:1257–1264.
 42. Solensky R: Drug hypersensitivity. *Med Clin North Am* 2006, **90**:233–260.
 43. Prescott Jr WA, De Pestel DD, Ellis JJ, et al.: Incidence of carbapenem-associated allergic-type reactions among patients with versus patients without a reported penicillin allergy. *Clin Infect Dis* 2004, **38**:1102–1107.
 44. Saxon A, Adelman DC, Patel A, et al.: Imipenem cross-reactivity with penicillin in humans. *J Allergy Clin Immunol* 1988, **82**:213–217.
 45. McConnell SA, Penzac SR, Warmack TS, et al.: Incidence of imipenem hypersensitivity reactions in febrile neutropenic bone marrow transplant patients with a history of penicillin allergy. *Clin Infect Dis* 2000, **31**:1512–1514.
 46. Sodhi M, Axtell SS, Callahan J, et al.: Is it safe to use carbapenems in patients with a history of allergy to penicillin? *J Antimicrob Chemother* 2004, **54**:1155–1157.
 47. Romano A, Viola M, Gueant-Rodriguez R-M, et al.: Brief communication: Tolerability of meropenem in patients with IgE-mediated hypersensitivity to penicillins. *Ann Intern Med* 2007, **146**:266–269.
- In probably the most significant study of this subject since 1988, 104 patients with immediate hypersensitivity and a positive skin test to a penicillin(s) were prospectively studied to detect cross-reactivity between meropenems and penicillins. Results indicated that the practice of avoiding meropenem therapy in penicillin-allergic patients should be reconsidered.
48. Macy E: Multiple antibiotic allergy syndrome. *Immunol Allergy Clin North Am* 2004, **24**:533–543.
 49. Pham NH, Baldo BA, Puy RM: Studies on the mechanism of multiple drug allergies. Structural basis of drug recognition. *J Immunoassay Immunochem* 2001, **22**:47–73.
 50. Turvey SE, Cronin B, Arnold AD, et al.: Antibiotic desensitization for the allergic patient: 5 years of experience and practice. *Ann Allergy Asthma Immunol* 2004, **92**:426–432.
- Although desensitization employing free drug is carried out by some allergists, the literature has lacked reports on large combined series of antibiotic desensitizations. This paper covers selection of candidates for desensitization and presents standard protocols employed for a range of commonly used antibiotics.