

REVIEW

New aspects of allergic reactions to betalactams: crossreactions and unique specificities

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Introduction

Allergic reactions to betalactams, although not common, constitute the most frequent cause of adverse drug reactions induced by a specific immunological mechanism. Both cellular and humoral responses are involved in eliciting the reactions [1,2]. Although the incidence has decreased in recent years, perhaps as a result of improved manufacturing processes [3,4], some patients still suffer allergic reactions from these beneficial antibiotics [5–8].

These days the betalactam family consists of two major classes, penicillins and cephalosporins, and four minor, monobactams, carbapenems, oxacephems and clavams (Fig. 1). The major clavam, clavulanic acid, is included in this survey, although it is a betalactamase inhibitor and not an antibiotic. A list of different antibiotics belonging to these groups is presented in Table 1. Early studies with benzyl penicillin in man and animals [9–11] demonstrated that it was immunogenic and most of the antibody induced was directed against a structure formed by a reaction between the betalactam carbonyl and amino groups from lysines in proteins. This grouping, known as benzyl penicilloyl, was termed the major determinant accordingly. Initially it was believed that the side chain of the penicillin (Fig. 1, R group) played a minor role in the specificity of the antibody produced [11,12] and that the nuclear portion (common to all penicillins, see Fig. 1, A and B rings) was the most important part of the determinant structure. This led to the assumption that all penicillins would crossreact and patients allergic to one would react to all [13,14–16]. Whilst crossreaction between penicillins may be extensive for some patients the situation is much more complex because of the increased number of new betalactam antibiotics available and their frequency of use. So on the one hand there are studies which show that crossreactivity can be extended across classes of betalactam antibiotics, for example, penicillins with cephalosporins [17–20], penicillins with carbapenems [21], and cephalosporins with monobactams [22], whilst other studies highlight that some patients are

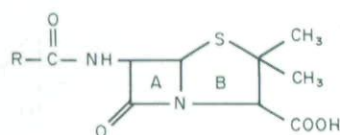
sensitive to individual penicillins [23–28], or other betalactam antibiotics [13,29–31]. This spectrum of crossreactivity is partly due to individual patients' responsiveness, but it is also related to the structures of the betalactam antibiotics in the various classes. In this review, the immunochemistry of betalactam antibiotics is discussed highlighting side chain specificity. Whilst many determinants from betalactams have been shown to be involved in allergic reactions, side chain specificity offers explanations for both crossreactivities and some selective responses. In the light of this information, our recent data on amoxycillin induced allergy are also discussed and recommendations made to aid diagnosis.

Betalactam antibiotics: structures, immunogenicity and allergenicity

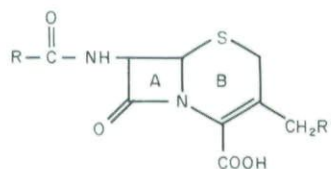
Structural comparisons between the betalactam antibiotics are a useful starting point. By definition all betalactam antibiotics contain the characteristic 4-membered betalactam ring (ring A in Fig. 1) which, except for monobactams, is fused to another 5- or 6-membered ring (ring B in Fig. 1). All, except clavams, contain a side chain joined to the betalactam ring (C-6 position or C-7 for cephalosporins and oxacephems) and some (cephalosporins, carbapenems and oxacephems) contain another side chain joined to ring B (Fig. 1). The nucleus formed by ring A (monobactams) or A and B (the rest) distinguishes the class of antibiotic and is therefore different between the classes. However the side chains, whilst of considerable diversity, can be very similar or identical for members of different classes.

Low molecular weight drugs and chemicals are too small to initiate an immune response and yet many such compounds have been shown to cause allergic reactions. Pioneering work by Landsteiner and Jacobs [32] and Eisen *et al.* [33] suggested an answer to this paradox which led to the Hapten theory of drug immunogenicity. Here the low molecular weight compound covalently couples to proteins and can thus be presented to the immune system as a hapten. All betalactam antibiotics have this ability via reaction of the betalactam ring with protein amino groups, although the outcome varies for the

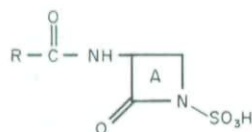
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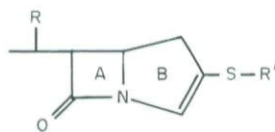
Penicillins



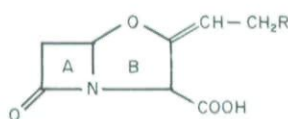
Cephalosporins



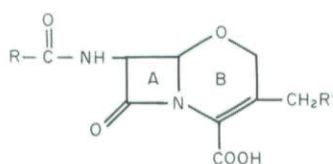
Monobactams



Carbapenems



Clavams



Oxacephems

Fig. 1. General structures of betalactam antibiotics. R, C-6 (or C-7) side chain. R', second side chain. A, betalactam ring. B, second fused ring.

various classes. For penicillins the reaction gives the penicilloyl group which is known as the major determinant. This is because initial studies [9–11] suggested that it was the major reaction product and in treated patients penicillin antibody responses seemed to be directed against this determinant. Other studies dispute this [2,34] and suggest that other so called 'minor' determinants may be more important, but penicilloyl is the most well known. The allergenicity of penicillins is not in doubt with anaphylactic cases being described very soon after treatment became available [35].

Cephalosporins also react with protein amino groups via the betalactam ring to form immunogenic conjugates [19], but unlike penicillins a 'cephalosporinyl' determinant is probably only formed transiently before degrading to simpler structures. Thus, the immunochemistry of cephalosporins has proved to be much more complex than that of penicillins.

For the remaining betalactam antibiotics, aztreonam has been shown to react with protein amino groups to form immunogenic conjugates [36] and a case of aztreonam allergy has been reported [29]. Edwards *et al.* [37] investigated the immunogenicity of an experimental carbapenem (MM22383) following a case of occupationally induced allergy. This carbapenem was a contact sensitizer in guinea-pigs and reacted with protein amino groups giving conjugates which resulted in specific antibody in rabbits.

Table 1. List of antibiotics belonging to the six betalactams containing groups

<i>Penicillins</i>	<i>Cephalosporins</i>
Penicillin G	Cephalothin
Penicillin V	Cefazolin
Methicillin	Cephalexin
Oxacillin	Cephalexin
Cloxacillin	Cephadrine
Nafcillin	Cefradoxyl
Ampicillin	Cefamandole
Amoxycillin	Cefuroxime
Carbenicillin	Cefonicid
Ticarcillin	Cefotetan
Azlocillin	Ceforanide
Mezlocillin	Cefotaxime
Piperacillin	Ceftixozime
Propicillin	Ceftriazone
	Cefoperazone
	Ceftazidime
<i>Monobactams</i>	<i>Clavams</i>
Aztreonam	Clavulanic acid
<i>Carbapenems</i>	<i>Oxacephems</i>
Imipenem	Moxolactam

The remaining betalactams are both very interesting and show that studies on penicillins should not be extrapolated to other betalactam classes. Clavulanic acid, a betalactamase inhibitor, which is always formulated with other penicillins, has been investigated for its intrinsic immunogenicity [37]. Although it reacts with protein amino groups, the resulting conjugates are not immunogenic and clavulanic acid itself failed to contact sensitize guinea-pigs. This unusual behaviour was attributed to its complex chemistry which results in a multitude of small 'haptens' being introduced onto proteins which would not be expected to give a good immunogen. This predicted low immunogenicity/allergenicity has been borne out in clinical use since only one example of a clavulanic acid specific reaction has been reported [38]. Likewise, moxalactam (the only oxacephem in general use), whilst protein reactive was not immunogenic and heat aggregated protein conjugates were required for antibody production [39]. The reasons for this are not known but could be similar to the clavams. This may suggest that moxalactam has a low allergenic potential and certainly we are unaware of any allergic case.

Specificity studies of betalactam antibiotic induced immune responses

Penicillins

As mentioned previously, early studies implicated the benzyl penicilloyl structure as an important determinant. The recognition of this 'major determinant' was followed by the development of an improved skin-test reagent, benzyl penicilloyl polylysine (PPL) to aid diagnosis of IgE mediated penicillin allergy [40]. However, not all penicillin allergies were detected with PPL and soon 'minor determinant mixture' (MDM) consisting of benzyl penicillin and some of its breakdown products was also being employed [41]. Radioallergosorbent test (RAST) assays capable of detecting minor determinant specific IgE antibody in patients' sera have also been developed [42,43]. More recently, Harle and Baldo [44] used radioimmunoassays employing ampicillin, amoxycillin and ticarcillin related solid phase assays and hapten inhibition studies in order to define the human IgE binding regions of these penicillins. They found that, not only the side chain but also, the betalactam and thiazolidine rings were important determinant structures. Again using RAST, Juhlin and Wide [45] employed assays with benzyl- and phenoxy methyl-penicilloyl specificities (derived from *Pen G* and *Pen V*) and found sera which were

positive in only one of the assays, implying that there was some side chain specificity. Skin-test studies carried out by Shibata *et al.* [46] employed reagents which could only present the side chain structure of benzyl penicillin and methicillin and yet 29 and nine respectively of 46 patients gave weal-and-flare responses suggesting significant side chain responsiveness.

Experimental studies using a variety of techniques have also shown that side chain specificity cannot be ignored. Atsumi [47] prepared polyclonal anti-benzyl penicilloyl antibodies which were absorbed onto a benzyl penicilloylated solid phase. The antibody was then eluted using a variety of conjugates and compounds to investigate specificity. Five populations of antibody were obtained using compounds representing discrete parts of the benzyl penicilloyl-protein determinant suggesting that antibodies recognizing parts of the side chain and nuclear (common) structures were present. It was significant that the nuclear specific antibodies recognized the penicilloyl conjugates of a range of penicillins equally well, whereas side chain specific antibodies were more discriminating. Nishida [48] using alkaline hydrolyzed penicillin and Munro *et al.* [49] using penicilloic and penilloic acids studied the crossreacting potential of benzyl penicilloyl antibodies and also found side chain specificity. Oxacillin and its halogenated analogues, all containing an isoxazole side chain grouping and penicillins substituted in the alpha position of the side chain with amino (ampicillin and amoxycillin) or alkyl (phenethicillin and propicillin) groups were all poorly recognized by the antibody. More recent studies have investigated monoclonal antibodies raised against benzyl penicilloylated bovine gamma globulin. De Haan *et al.* [50] prepared three such mouse IgG monoclonals and investigated their ability to bind benzyl penicillin, ampicillin, amoxycillin, 6-amino penicillanic acid (the parent nucleus structure of all penicillins with no side chain) and their respective penicilloyl protein conjugates. One monoclonal was strongly side chain specific, another reacted well with all native penicillins suggesting specificity for the thiazolidine ring, whilst the third recognized mostly the linkage structure between the penicillin and the protein with some side chain influence. Fukushima [51] isolated a mouse IgE monoclonal which was strongly side chain specific but also reacted with certain cephalosporins.

These studies clearly show that in spite of their small size penicillins can still present a range of antigenic determinants to the immune system resulting in antibodies specific for discrete parts of their structure. The ability of a patient to react to other penicillins depends on the specificity of their particular response and which penicillin they have been given.

Cephalosporins

Initial studies on cephalosporin induced allergy were hampered because early cephalosporins contained penicillin contaminants [52]. However, cases of cephalosporin allergy with no penicillin involvement have been reported [31,53–55]. Regarding specificity, early experimental studies concluded that the C-7 side chains of cephalosporins play a major role in determining the specificity of antibodies [18,19,56–59]. For example, antiserum against a cefazoline conjugate crossreacted poorly with conjugates of cephalothin and cephaloridine [58,59] whereas anti-sera raised against the latter two cephalosporins crossreacted well [18,19,56]. Cephalothin and cephaloridine have the same thiophene side chain but cefazoline has a very different tetrazole group. More recent studies using monoclonal antibodies raised against a cephalixin conjugate [60] confirmed that the side chain was a determinant but also highlighted other determinants involving part of the degraded cephem nucleus and the protein-cephem linkage region.

Other betalactams

A case of allergy to aztreonam has been reported [29], apparently precipitated by the first exposure, which was confirmed by skin test and provocation. The response was very specific. Studies by Adkinson *et al.* [36] suggested that aztreonam would give side chain specific responses but see below. Documented allergy to carbapenems is restricted to one subject by occupational exposure to MM22383, an experimental carbapenem [37]. Diagnosis was confirmed using patch tests employing MM22383 and RAST with a MM22383-polylysine conjugate. The only carbapenem in clinical use, imipenem has only been investigated for its potential to crossreact in patients already allergic to penicillins [14].

'Unique' specificities and crossreactions between betalactam antibiotics: examples and explanations

Most patient studies have only employed PPL and MDM based on benzyl penicillin because no other reagents are commercially available, but it is widely believed that they are sufficient, with rare exceptions, to diagnose all penicillin allergies. Broad crossreactivity between penicillins can only occur if the nucleus (the common structural feature) is the most important part of the allergenic/immunogenic determinant, but if a patient has mounted a significant immune response against a side chain determinant of a penicillin which is different to that of a benzyl penicillin, then the patient may only respond to that penicillin and be skin-test negative to the usual reagents. Numerous studies confirm that this can occur.

Luton [28] reported a patient who was allergic to benzyl penicillin but could tolerate methicillin and more recently Antonicelli *et al.* [30] showed that patients could be selectively allergic to piperacillin. Studies which have employed semi-synthetic penicillins or related minor determinants as skin-test materials [43,46,61,62] have also concluded that significant numbers of patients do not respond to benzyl penicillin reagents but are allergic to other penicillins. Van Dellen *et al.* [61], using major and minor determinants of benzyl penicillin, ampicillin and methicillin found patients who responded to reagents from all three penicillins and some who only responded to a specific penicillin. These results were confirmed by Solley *et al.* [62]. A recent study by Silviu-Dan *et al.* [63] investigated a population of 228 patients using BPP and MDMs skin-test reagents prepared from benzyl penicillin and ampicillin. Of 40 patients who were skin-test positive to one or more reagents, six (15%) reacted only to ampicillin MDM. The authors concluded that these patients were responding to side chain specific determinants. The side chain of ampicillin differs from benzyl penicillin in having an alpha amino group. Similarly in the studies mentioned above [28,30,61,62], methicillin and piperacillin have very different side chains to benzyl penicillin and would not be expected to crossreact if side chain responses predominated.

Another aspect of side chain specific responses is the possibility of crossreaction with other betalactam antibiotics which share the same or very similar side chain although their class defining nucleus (rings A and B in Fig. 1) is different. This phenomenon could be partly involved in the widely held belief that extensive crossreaction exists between penicillins and cephalosporins in penicillin allergies. Early studies employed cephalothin, cephaloridine (both cephalosporins) and benzyl penicillin. These three antibiotics have very similar side chain, thiophene for the cephalosporins and phenyl for benzyl penicillin, and would be expected to crossreact if side chain responses were involved. Many other cephalosporins have different side chains to benzyl penicillins and studies using rabbit antibodies raised against cephalosporins of this type and direct challenge studies in cephalosporin [31] and penicillin allergies [62] have shown that crossreacting is not common. The latter study was particularly significant since 0/27 confirmed penicillin allergies (skin-test positive) responded when given cephalosporins.

Regarding monobactams, experimental and clinical studies using penicillin and cephalosporin allergies have shown that aztreonam has a low potential for crossreaction [23,36,64–68] and this has been attributed to side chain specificity [36]. Rabbit antibodies to aztreonam were only inhibited by ceftazidime which has the same side

chain and not by other penicillins, cephalosporins or monobactams. A recent clinical case [29], whilst confirming that aztreonam allergics may tolerate treatment with a number of penicillins and cephalosporins, also showed that the patient in question tolerated ceftazidime suggesting that the response was not side chain specific. Challenges with other monobactams would have been interesting but were not feasible. Carbapenems (imipenem) may not share the lack of crossreactivity enjoyed by aztreonam. Saxon *et al.* [21] investigated 40 subjects with a history of penicillin allergy using major and minor determinants of benzyl penicillin and equivalent materials from imipenem. Twenty subjects showed positive responses, 10 to penicillin reagents, nine to penicillin and imipenem reagents and one to imipenem reagents. Minor determinants from both materials appeared to demonstrate the highest level of crossreactivity suggesting that nuclear related determinants might be involved. Benzyl penicillin and imipenem have very different side chains but, as suggested by Saxon *et al.* [21], the nuclear structures may form similar minor determinants. In the carbapenem induced allergy case studied by Edwards *et al.* [37] IgE antibody from the patient was not inhibited by a benzyl penicilloyl conjugate but minor determinants were not investigated.

Amoxycillin induced allergy in Spain

In 1988 [24] we described three subjects with histories of allergy to amoxycillin who were skin-test negative to PPL and MDM and tolerated therapeutic doses of benzyl penicillin and phenoxymethyl penicillin. By skin test or RAST, or in two cases by challenge, all three patients were shown to be specifically allergic to amoxycillin. These studies were extended [25] to investigate the incidence of this phenomenon. A total of 288 subjects with a history of a penicillin allergy were studied using skin tests with PPL, MDM, amoxycillin and ampicillin, RAST with benzyl penicilloyl and amoxycilloyl and challenge with benzyl penicillin, phenoxymethyl penicillin and amoxycillin. Sixty-four subjects (22%) were confirmed to be allergic and 20 of these (7% of total subjects, 31% of the allergic) only gave responses to amoxycillin. Most cases were IgE mediated but we have found some delayed reactors [21,69,70]. Others have also found significant numbers of patients specifically responding to the alpha amino penicillins [26,43,70,71]. In the latter work 26% of the subjects objectively allergic to penicillins were found to be allergic to amoxycillin and/or ampicillin alone. Ampicillin (similar to amoxycillin) specific allergies which were not diagnosed by conventional skin-test reagents were also described by Silviu-Dan *et al.* [63]. In this study 228 subjects were skin tested

for penicillin allergy and 6/40 were positive (15%), only responding to ampicillin reagents. Our studies and others mentioned previously go against the belief that conventional benzyl penicillin based reagents are suitable for the diagnosis of the vast majority of penicillin reactors. We believe that for amoxycillin, and to a lesser extent ampicillin, two factors are responsible, specificity and level of use.

Specific responses will only occur if the drug in question forms a unique structural determinant, which for the penicillins would probably have to involve the side chain. A key structural feature of amoxycillin and ampicillin is the alpha amino group in the side chain.

The remaining phenyl (ampicillin) or p-hydroxy phenyl (amoxycillin) groups are not so different to many other penicillins. The importance of the amino group was highlighted in clinical studies by Voorhorst and Spareboom [72]. Using patch tests, one penicillin allergic patient only responded to penicillins containing an alpha amino group of the correct stereochemistry. We have studied the specificity of IgE antibody in patients who are allergic to amoxycillin, benzyl penicillin and both [74,75]. Typical results are shown in Fig. 2. Using RAST inhibition employing whole determinants (benzyl penicillin and amoxycillin coupled to butyl amine), side chain only (phenyl acetic acid and para hydroxy phenyl glycine), and nuclear only structures (6-aminopenicillanic acid coupled to butyl amine and thiazolidine) we have found that amoxycillin specific IgE is markedly side chain specific whereas benzyl penicillin specific IgE is best inhibited by whole determinant. Further studies are in progress but 40 sera specific for amoxycillin or benzyl penicillin follow this tendency. Therefore we believe that amoxycillin specific allergy is a predominantly side chain specific response which would not be diagnosed by conventional skin-test reagents. An interesting observation which could relate more to cephalosporin immunochimistry is that an unexpected number of our amoxycillin-specific allergics can tolerate cephalosporins with a structurally similar side chain [75]. This could imply that although the side chain predominates for these patients, some other penicillin related structural element not available on cephalosporins does play a role.

The second factor is level of usage. A drug capable of causing specific responses may still not become prominent because it is little used. Others have reported selective allergic reactions to betalactam antibiotics, but the cases are few and antibiotic use lower than for amoxycillin; cloxacillin [27], aztreonam [29] and piperacillin [30].

In Spain, more than 50% of the antibiotic prescriptions are for amoxycillin [25] and that coupled with the propensity to give specific reactions could result in a high number of allergics who cannot be diagnosed by conven-

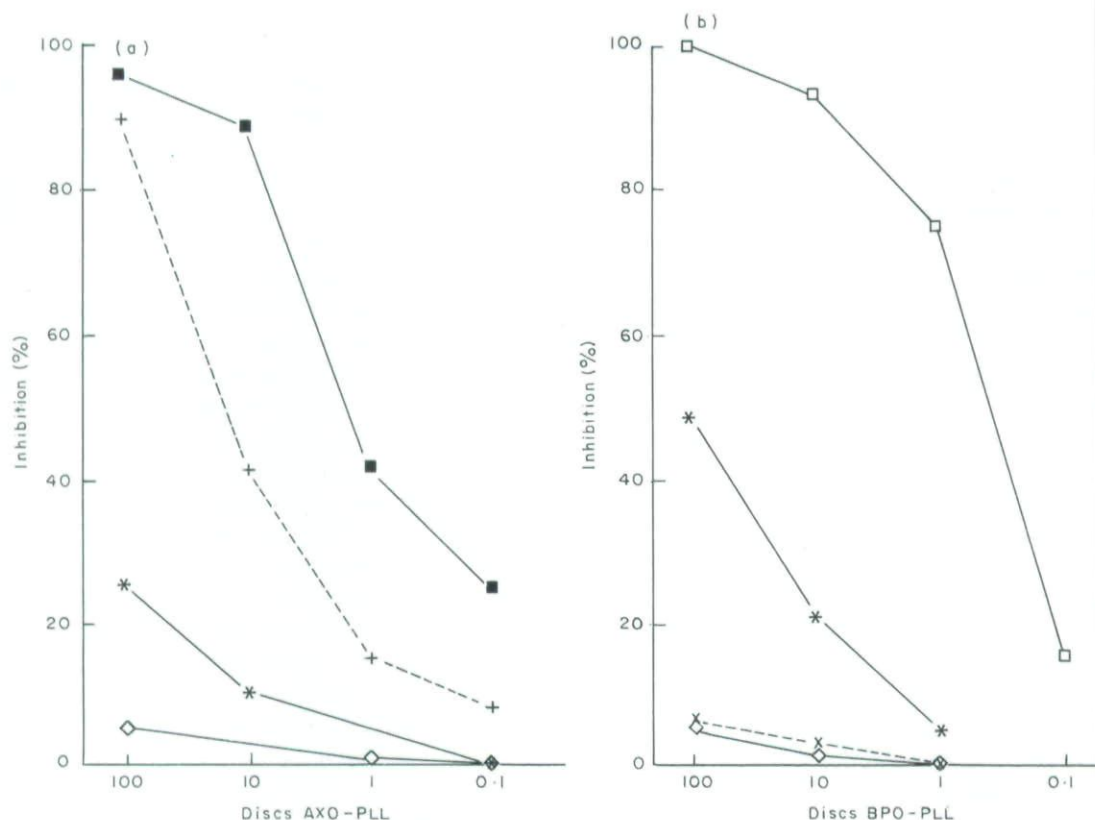


Fig. 2. RAST inhibition studies showing results using one serum specific to amoxycillin and one for benzyl penicillin. Concentration of the different monomers used are expressed in mM. In (a), the side chain of AX (PHPG) inhibited 92% and the binuclear portion (6-APA-BA) inhibited 23% at 100 mM. In (b) the side chain of benzyl penicillin (PHA) did not inhibit and the 6-APA-BA (6-amino penicillanic acid-butylamine conjugate) inhibited 52%; (a) Serum 1. —■—, AX-BA. *, 6-APA-BA. —+—, PHPG. —◇—, THIAZ. (b) Serum 2. —□—, BPO-BA. —*—, 6-APA-BA. —x—, PHA. —◇—, THIAZ.

tional reagents. For example, in our study [25] 50% of the allergic group had received amoxycillin compared with only 28% receiving benzyl penicillin and 18 (90%) of the amoxycillin specific allergics had knowingly received amoxycillin. A similar phenomenon has been observed before. Using RAST assays specific for penicilloyl determinant from benzyl penicillin and phenoxymethyl penicillin, Juhlin and Wide [45] showed that a higher percentage of sera collected over the period 1974–1978 was specifically positive to *PenV*-oyl RAST than during the period 1967–1971. The authors suggested that the results reflected the increased use of *PenV* since 1971 and both RAST systems should be employed for diagnostic purposes.

Our findings could also suggest that amoxycillin has a higher inherent immunogenicity than some other betalactams as has recently been described for cefaclor [76]. However, information mentioned in the latter work

clearly shows that this is not the case. Overall we believe that our discovery of relatively large numbers of specific amoxycillin allergics is due to the high usage and specific responsiveness of this valuable antibiotic in Spain.

Relevance of these findings in the clinical evaluation of subjects allergic to betalactams

As already mentioned, only benzyl penicillin related skin tests are commercially available; PPL and MDM are available in Europe, but PPL is only available in USA. Therefore, unless amoxycillin reagents are specifically prepared and used, cases of selective amoxycillin allergy will be under-evaluated. In our studies the criteria used to diagnose a subject as being selectively allergic to amoxycillin are as follows: history of an immediate reaction to amoxycillin with negative skin test to PLL and MDM and good tolerance to benzyl penicillin and phenoxymethyl

penicillin. In addition the subject should have a positive skin test and/or be RAST positive to amoxycillin. If, in the presence of a strong suggestive history, both the amoxycillin and the skin test and RAST are negative, a controlled challenge with amoxicillin needs to be made to confirm the case as selectively allergic [23,27,30].

Summary and future prospects

This review highlights data from the last 30 years which clearly shows that the side chain of penicillins and other antibiotics make an important contribution to the specificity of the immune responses [73]. Our very recent studies show that under certain circumstances side chain responsiveness can lead to a significant number of allergic subjects who cannot be diagnosed by the only commercially available reagents. This is not to say that other determinants are not important, as shown by the work of Saxon *et al.* [21] with imipenem showing unexpected crossreactivities with penicillins probably due to nuclear determinant similarities. However, many clinical and experimental studies carried out over the years with a relatively small number of penicillins and cephalosporins have extrapolated crossreactivity data to include families of antibiotics rather than considering some of the individual members. Studies similar to those carried out on the more recent betalactams, imipenem and aztreonam should be carried out on the more recent cephalosporins to establish crossreactivity profiles so that objective judgments can be made.

Our studies show that in populations where amoxycillin is used extensively there is a well defined phenomenon of selective amoxycillin allergy which is related to the specificity of the amoxycillin responsiveness. These patients represent a sub-group of amoxycillin allergies where the side chain contributes in a more selective way to the antigen binding site. These results have not been observed for benzyl penicillin [77] but may apply to other antibiotics. We believe that the limited range of skin-test materials available at present should be extended to include conjugates of amoxycilloyl-polylysine in addition to amoxycillin itself. The development of sensitive *in vitro* assays for quantifying amoxycillin specific antibodies is also required. Perhaps side chain only specific reagents for the more common antibiotics would also be of value. Pharmaco-epidemiological studies are required to establish the relationship existing between the use of different betalactam compounds and the appearance of allergic reactions to them. In addition, genetic studies are needed in order to elucidate the mechanisms whereby some subjects develop a response to common antigenic determinants and others more selectively to the side chain.

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References

- 1 Amos HE. Antigenic determinants of the penicillin molecule. In: Amos HE, ed. Allergic drug reactions. Oxford: Edward Arnold, 1976;64-72.
- 2 Dewdney JM. Immunology of the antibiotics. In: Sela M, ed. Antigens 5, New York: Academic Press, 1977;73-245.
- 3 Ahlstedt S, Kristofersson A. Experimental evidence of decreased incidence of penicillin allergy through use of pure penicillins. *Infection* 1979; 7:499-502.
- 4 De Weck AL. Penicillins and cephalosporins. In: De Weck AL & Bundgaard H, eds. Allergic reactions to drugs. Berlin: Springer Verlag, 1983;423-64.
- 5 Weiss ME, Adkinson NF. Immediate hypersensitivity reactions to betalactams. *Clin Allergy* 1988; 18:515-40.
- 6 Blanca M, Vega JM, Garcia J, Carmona MJ, Miranda A. Immediate hypersensitivity reactions to penicillin and related antibiotics. *Clin Exp Allergy* 1989; 19:556-7.
- 7 Blanca M, Suau R, Perez E *et al.* Allergy to betalactams. New aspects of an old problem. In: Patriarca G, ed. Food and drug allergy, Rome: UCB Pharma, 1990;11-8.
- 8 Shepherd GM. Allergy to beta lactam antibiotics. In: Van Arsdel PP, ed. Immunology and Allergy Clinics of North America, Philadelphia: WB Saunders, 1991;635-44.
- 9 Parker CW, de Weck AL, Kewrn M, Eisen HN. The preparation and some properties of penicillenic acid derivatives relevant to penicillin hypersensitivity. *J Exp Med* 1962a; 115:803.
- 10 de Weck AL. Studies on penicillin hypersensitivity. I. The specificity of rabbit antipenicillin antibodies. *Int Arch Allergy Appl Immunol* 1962;21:20.
- 11 Levine BB, Ovary Z. Studies of the mechanism of the formation of the penicillin antigen III: The N(D(Benzyl penicilloyl) group as an antigenic determinant responsible for hypersensitivity to penicillin G. *J Exp Med* 1961; 114:875.
- 12 de Weck AL. Studies in penicillin hypersensitivity. The role of the side chain in penicillin antigenicity. *Int Arch All Appl Immunol* 1962; 21:38-50.
- 13 Sullivan T. Drug allergy. In: Middleton E, Reed CE, Elliot EF, Adkinson NF, Yunginger JW, eds. Allergy, Principles and Practice. St Louis: C.V Mosby Company, 1988;1523-36.
- 14 Saxon A, Bell GN, Rohr AS, Adelman DC. Immediate hypersensitivity reactions to betalactams antibiotics. *Am Int Med* 1988; 107:204-15.
- 15 Steward GT. Cross-allergenicity of penicillin G and related substances. *Lancet* 1962;509.
- 16 Grieco MH. Cross-allergenicity of the penicillins and cephalosporins. *Arch Int Med* 1967; 119:141-46.
- 17 Petz DL. Immunologic cross-reactivity between penicillins and cephalosporins: A review. *J Infect Dis* 1978; 137s:574-9.

- 18 Batchelor FR, Dewdney JM, Weston RD, Wheeler AW. The immunogenicity of cephalosporin derivatives and their cross-reactivity with penicillin. *Immunology* 1966; 10:21-23.
- 19 Shibata K, Atsumi T, Horiuchi Y, Mashimoto K. Immunological cross-reactivities of cephalothin and its related compounds with benzyl penicillin (penicillin G). *Nature* 1966; 212:419-420.
- 20 Blanca M, Fernandez J, Miranda A, Terrados S, Torres MJ, Vega JM, Avila MJ, Perez E, Garcia J, Suau R. Cross-reactivities between penicillin and cephalosporins. Clinical and immunological studies. *J Allergy Clin Immunol* 1989; 83:381-5.
- 21 Saxon A, Adelman A, Petel A, Hajdu R, Calandra GB. Imipenem cross-reactivity with penicillin in humans. *J Allergy Clin Immunol* 1988; 82:213-7.
- 22 Adkinson NF, Saxon A, Spence MR, Swabb EA. Cross-allergenicity and immunogenicity of aztreonam. *Rev Infect Dis* 1985; 7(S):613-621.
- 23 Martin JA, Igea JM, Fraj J, Lezaun AA, Parra F, Losada E. Allergy to amoxycillin in patients who tolerated benzyl penicillin, aztreonam and ceftazidime. *Clin Infect Dis* 1992; 14:592-3.
- 24 Blanca M, Perez E, Garcia J, Miranda A, Fernandez J, Vega JM, Terrados S, Avila MJ, Suau R. Anaphylaxis to amoxycillin with good tolerance to benzylpenicillin. *Allergy* 1988; 43:812-814.
- 25 Blanca M, Vega JM, Garcia J, Carmona MJ, Terrados S, Avila MJ, Miranda A, Juarez C. Allergy to amoxycillin with good tolerance to other penicillins. Study of the incidence in patients allergic to beta lactams. *Clin Exp Allergy* 1991; 20:475-481.
- 26 Lazaro JF, Cancedo SQ, Ceballer B, de la Hoz C. Choque anafilactico a amoxicilina con buena tolerancia a penicilina. *Med Clin* 1990; 94:56.
- 27 Panadero P, Senent C, Moreno F, Blanca M. Allergy to cloxacillin with good tolerance to PG, PV and ampicillin. *Allergy* (in press).
- 28 Luton EF. Methicillin tolerance after penicillin G anaphylaxis. *JAMA* 1964; 190:39.
- 29 Candarso AI, Saez Jimenez SA, Vidal C, Rodriguez M. Aztreonam induced anaphylaxis. *Lancet* 1990; ii:746-47.
- 30 Antonicelli L, Garitaini MS, Bilo MB, Sachi GF, Bonifazi F. Allergy to piperacillin. *Allergologie* 1989; 12:86.
- 31 Abraham GN, Petz LD, Funderberg HH. Cephalothin hypersensitivity associated with anti-cephalothin antibodies. *Int Arch Allergy Appl Immunol* 1968; 34:65-74.
- 32 Landsteiner K, Jacobs J. Sensitization of animals with simple chemical compounds. II. *J Exp Med* 1936; 63:625.
- 33 Eisen HN, Orris L, Belman S. Elicitation of delayed allergic skin reactions with haptens: the dependence of elicitation on hapten combination with protein. *J Exp Med* 1952; 95:473-87.
- 34 Horiuchi Y, Shibata K. Immunochemical studies on the antigenic binding of benzyl penicillin and five synthetic penicillins with proteins. *Int Arch Allergy Appl Immunol* 1965; 28:306.
- 35 Gorevic PD. Drug allergy. In: Kaplan A, ed. *Allergy*. New York: Churchill Livingstone. 1985;473-506.
- 36 Adkinson NF Jr, Swab EA, Sugarman AA. Immunology of the monobactam aztreonam. *Antimicrob Agents Chemother* 1984; 25:93-97.
- 37 Edwards RG, Dedney JM, Dobrzansky RJ, Lee D. Immunogenicity and allergenicity studies on two betalactam structures, a clavam, clavulanic acid, and a carbapenem: structure activity relationships. *Int Arch Allergy Appl Immunol* 1988; 85:184-89.
- 38 Fernandez-Rivas M, Perez Carral C, Garcia Lazaro MA, Cuevas M, Martin C, Senent C. Hipersensibilidad al ácido clavulánico. *Rev Esp Alerg Imuno Clin* 1992; 7:76(suppl 2).
- 39 Branch DR, Beatty BG, Sy Siok Hian AL, Vlahos WG, Hawthorn AW, Petz LD. Immune response to moxalactam in rabbit and in humans. *J Lab Clin Med* 1986; 107:15-22.
- 40 Parker CW, Shapiro J, Kern M, Eisen HN. Hypersensitivity to penicillenic acid derivatives in human beings with penicillin allergy. *J Exp Med* 1962b; 115:821.
- 41 Levine BB, Redmond AP. Minor haptenic determinant-specific reagents of penicillin hypersensitivity in man. *Int Arch Allergy Appl Immunol* 1969; 35:445-455.
- 42 Kraft D, Berglund A, Rumpold H, Roth A, Ebner H. Radioallergosorbent test with conjugates specific for minor haptenic determinants in the diagnosis of IgE-mediated penicillin allergy in man. *Clin Allergy* 1981; 11:579.
- 43 Edwards RG, Speckman DA, Dewdney JM. Development and use of three radioallergosorbent tests in the diagnosis of penicillin allergy. *Int Arch Allergy Appl Immunol* 1982; 68:352-358.
- 44 Harle DG, Baldo BA. Identification of penicillin allergic determinants that bind IgE antibodies in the sera of patients with penicillin allergy. *Mol Immunol* 1990; 27:1062-1071.
- 45 Juhlin L, Wide L. Detection of penicillin allergy by the radioallergosorbent test. *Lancet* 1979; ii:261.
- 46 Shibata K, Atsumi T, Horiuchi Y. The heterogeneity of human anti penicillin skin sensitising antibodies. *J Allergy Clin Immunol* 1968; 42:63-73.
- 47 Atsumi T, Nishida K, Kinoshita Y, Shibata K, Horiuchi Y. The heterogeneity of combining sites of the penicillin antibodies obtained from single rabbit. *J Immunol* 1967; 99:1286-93.
- 48 Nishida K, Kinoshita Y, Atsumi T, Shibata K, Horiuchi Y. The analysis of combining sites of rabbit antibenzyl penicilloyl antibodies. *Immunochemistry* 1972; 9:1195-202.
- 49 Munro AC, Caine MG, Woronieczki SR. Preparation and immunological cross-reactions of penicilloic and penilloic acids. *J Pharm Sci* 1978; 67:1197-1204.
- 50 de Haan P, de Jonge AJR, Vergrugge T, Boersma DM. Three epitope specific monoclonal antibodies against the hapten penicillin. *Int Arch Allergy Appl Immunol* 1985; 76:42-6.
- 51 Fukushima H, Misaki R, Takechi M, Niinomi Y, Harada M. Mouse anti benzyl penicilloyl IgE monoclonal antibody: preparation, characterization and cross-reactivity. *Clin Exp Immunol* 1987; 68:427-436.

- 52 Pederson-Bjergaard J. Cephalothin in the treatment of penicillin sensitive patients. *Acta Allergologica* 1967; XXII: 299-306.
- 53 Kaplan E, Weinstein L. Anaphylaxis to cephaloridine in a nurse who prepared solution of drug. *JAMA* 1967; 193:159.
- 54 Abraham GN, Petz LD, Funderberg HH. Immunohematological cross-allergenicity between penicillin and cephalothin in humans. *Clin Exp Immunol* 1968b; 3:343.
- 55 Saleh Y, Tischler E. Severe anaphylactic reaction to intravenous cephaloridine in a pregnant patient. *Med J Austr* 1974; 2:490.
- 56 Brandriss MW, Smith JW, Steinman HG. Common antigenic determinants of penicillin G, cephalothin and 6-aminopenicillanic acid in rabbits. *J Immunol* 1965; 94:696.
- 57 Hamilton-Miller JMT, Abraham EP. Specificities of haemagglutinating antibodies evoked by members of the cephalosporin C family and benzyl penicillin. *Biochem* 1971; 123:183-90.
- 58 Kuwahara S, Mine Y, Nishida M. Immunogenicity of cefazolin. *Antimicrob Agents Chemother* 1970;374.
- 59 Mine Y, Nishida M, Goto S, Kuwahara S. Cefazoline, a new semisynthetic cephalosporin antibiotic IV. Antigenicity of cefazolin and its cross-reactivity with benzyl penicillin, ampicillin and cephaloridine. *J Antibiot* 1970; 23:195.
- 60 Nagakura N, Shimizu T, Masuzawa T and Yanagihara Y. Anti cephalixin monoclonal antibodies and their cross-reactivities to cepheims and penams. *Int Arch Allergy Appl Immunol* 1990; 93:126-132.
- 61 Van Dellen RG, Walsh WE, Peters GA, Gleich GJ. Differing patterns of wheal and flare skin reactivity in patients allergic to the penicillins. *J Allergy* 1971; 47:230-236.
- 62 Soley GO, Gleich GJ, Van Dellen RG. Penicillin allergy: Clinical experience with a battery of skin test reagents. *J Allergy Clin Immunol* 1982; 69:238-44.
- 63 Silviu Dan F, McPhilips S, Warrington R. The frequency of reactivity to side chain determinants in immediate hypersensitivity to penicillins. *J Allergy Clin Immunol* 1991; 87:228.
- 64 Saxon A, Hassner A, Swabb EA, Wheeler B, Adkinson NF Jr. Lack of cross-reactivity between the monobactam aztreonam and penicillin in penicillin allergic subjects. *J Infect Dis* 1984; 149:16-22.
- 65 Saxon A, Swabb EA, Adkinson NF Jr. Investigation into the immunologic cross-reactivity of aztreonam with other betalactam antibiotics. *Am J Med* 1985; 78:19-26.
- 66 Adkinson NF, Wheeler B, Swabb EA. Clinical tolerance to the monobactam aztreonam in penicillin allergic subjects. Abstract (S 16-13) presented at the 14th International Congress of Chemotherapy, 23-28 June 1985, Kyoto, Japan.
- 67 Graninger et al. Aztreonam, an alternative to beta-lactam in patients with hypersensitivity to penicillin and cephalosporins. Abstract (S-36-13) presented at the 14th International Congress of Chemotherapy, 23-28 June 1985, Kyoto, Japan.
- 68 Vega JM, Blanca M, Garcia JJ, Miranda A, Carmona MJ, Garcia A, Moya MC, Sanchez F, Terrados S. Tolerance to aztreonam in patients allergic to beta lactam antibiotics. *Allergy* 1991a; 46:196-202.
- 69 Vega JM, Blanca MM, Carmona MJ, Claros A, Juarez C, Moya MC. Delayed allergic reactions to betalactams. *Allergy* 1991b; 46:154-7.
- 70 Terrados S, Vega JM, Blanca M, Garcia JJ, Juarez C, Aceves JM, Fernandez J, Carmona MJ. Evaluation of delayed allergic reactions to penicillins. *J Allergy Clin Immunol* 1993; 91:263.
- 71 Audicana M, Bernaola G, Urrutia I, Echechipia S, Gastaminza G, Muñoz D, Fernandez E, Fernandez de Corres L. Allergic reactions to betalactams: studies in a group of patients allergic to penicillins and evaluation of cross-reactivity with cephalosporins. *Allergy* 1993 (in press).
- 72 Voorhorst JM, Sparreboom S. The use of stereoisomers in patch testing. *Ann Allergy* 1980; 45:100-103.
- 73 Blanca M, Moreno F, Mayorga C, Perez E, Fernandez J, Terrados S, Vega JM, Torres MJ, Juarez C, Garcia J. Immunochemical analysis of the specificities of IgE antibodies directed to benzyl penicilloyl. *Int Arch Allergy Appl Immunol* 1992;439-442.
- 74 Moreno F, Blanca M, Mayorga C *et al.* Studies on the specificities of IgE antibodies to amoxycillin and benzyl penicillin using different parts of these molecules. *J Allergy Clin Immunology* 1993; 91:361.
- 75 Garcia J, Blanca M, Carmona MJ, Vega JM, Miranda A, Burgos F, Rondón MC. Cross-reactivity between penicillin and cephalosporin with identical side chain. *J Allergy Clin Immunol* 1992; 89:300.
- 76 Hama R, Mori K. High incidence of anaphylactic reactions to cefaclor. *Lancet* 1988; i:1331.
- 77 Blanca M, Vega JM, Perez E, Carmona MJ, Miranda A, Terrados S, Fernandez J, Saua R. Determination of IgE antibodies to benzyl penicillin and amoxycillin in sera of patients allergic to beta lactams. *Int Arch Allergy Appl Immunol* 1991; 94:376.

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