

Immediate Hypersensitivity Reactions to Penicillins and Other Betalactams

C. Antúñez¹, E. Martín², J.A. Cornejo-García¹, N. Blanca-Lopez², R. R-Pena¹, C. Mayorga¹, M.J. Torres² and M. Blanca^{2,*}

¹Research Unit for Allergic Diseases, Carlos Haya Hospital, Málaga, Spain and ²Allergy Service, Carlos Haya Hospital, Málaga, Spain

Abstract: Immediate hypersensitivity reactions to betalactams are IgE mediated and constitute the most frequent allergic reactions mediated by specific immunological mechanisms. IgE responses to benzyl penicillin (BP), the first antibiotic producing the benzyl penicilloyl structure (BPO), are characterized by a quick release of inflammatory mediators, resulting in anaphylactic shock, urticaria and angioedema. With the progressive appearance of other structures, comprising cephalosporins, carbapenems, monobactams and clavulanic acid, IgE selective responses and cross-reactivity reactions were observed. The diagnosis of betalactam hypersensitivity, classically based on skin testing with major and minor determinants of benzyl penicillin or *in vitro* IgE antibodies to BP, has been modified by the inclusion of different determinants generated from these compounds, for which amoxicillin (AX) is the most relevant, followed by cephalosporins. Some subjects develop positive responses to several betalactams, mostly within the same family, but others develop a selective response. These are relevant for the appropriate selection of antimicrobial drugs in patients who have immediate hypersensitivity to betalactams.

Key Words: Betalactams, penicillins, amoxicillin, IgE, advances.

INTRODUCTION

Betalactam (BL) antibiotics are now formed by a large number of chemical compounds that share a common structure and mechanism of action. Penicillins constitute the most important group of antibiotics and remain the first choice of treatment for many infectious diseases [1]. The basic structure is formed by a thiazolidine ring attached to a betalactam ring. The side chain determines its antibacterial, pharmacological, and to some extent, immunological characteristics (Table 1) [1, 2].

BL are the compounds most frequently involved in immunological drug reactions induced by specific mechanisms [2-4]. Since BL were first used for treating infectious diseases, they have been considered to represent the classical prototype of drug hypersensitivity. By 1945 a wide scope of several reactions attributed to BP already existed, including urticaria, erythema nodosum, convulsions and anaphylaxis [3]. By the fifties the number of cases of anaphylaxis had increased and since then penicillin hypersensitivity has been taken into consideration, such that treatment with these antibiotics is no longer considered innocuous [3]. In their daily practice, many physicians must face the problem of evaluating persons who have experienced an allergic reaction, attributed to these compounds [4]. The literature specific to this area of knowledge has grown considerably over the years and we now possess a large corpus of knowledge that enables us to see the changes over time and to better understand the evolution of allergy to BL [5, 6]. Nevertheless,

research in this area always lags behind clinical practice, and several observations indicate that more studies are needed to answer the questions raised in daily practice.

Initially, rather than a still image, penicillin allergy was considered to be a moving picture where the actors were newly-released BL, different populations with different ages and variable rates of exposures, and wider treatment applications may be necessary for considering these factors [3, 7]. Of these, the most notorious finding contributing to variation in penicillin allergy is that benzyl penicilloyl (BPO), the major determinant generated by benzyl penicillin (BP), is becoming less relevant because BP has been progressively less used and gradually replaced by a number of new BL. These are composed of chemical structures that, although they share the BL ring, have sufficient differences that contribute to the nature of the epitope [5, 8]. Many other questions have also been raised, and these are analyzed in reference [9].

Since the late 80s, a systematic and constant series of studies from both our group and other European centers has appeared. These reports have led to changes in the classical view [5], maintained for many years by American authors [6]. In fact, a wide number of structures are now available and different patterns of consumption exist among countries [7], it is not therefore logical to assume that the same model of hapten recognition will exist everywhere [10].

Although the main clinical entities originally described remain the same [4], the frequency of occurrence, the specificities of the antibody or T cell studied, and other factors have changed [5, 7]. Data suggest that serum sickness attributed to penicillins is actually very infrequent, whereas delayed urticaria is not as frequent as before [12]. In our ex-

*Adress correspondence to this author at the Servicio de Alergología, Hospital Civil, plaza del Hospital Civil s/n, pabellón 6, 1º, 29009, Málaga, Spain; E-mail: miguel.blanca.sspa@juntadeandalucia.es

Table 1. Side Chain of Penicillin Antibiotics

Non Proprietary Name	Side Chain
Penicillin G	2-Phenylacetic acid
Penicillin V	2-Phenoxyacetic acid
Methicillin	2,6-Dimethoxybenzoic acid
Oxacillin	2-(3-phenyl-4-isoxazolyl)acetic acid
Cloxacillin	3-(2)-Chlorophenyl-5-methyl-4-isoxazolecarboxylic acid
Dicloxacillin	3-(2,6-Dichlorophenyl)-5-methyl-4-isoxazolecarboxylic acid
Nafcillin	2-Ethoxy-1-naphthoic acid
Ampicillin	2-Amino-2-phenylacetic acid
Amoxicillin	2-Amino-2-(4-hydroxyphenyl)acetic acid
Carbenicillin	2-Phenylmalonic acid
Ticarcillin	2-(3-thienyl)malonic acid
Mezlocillin	2-({[methylsulfonyl]-2-oxo-1-imidazolidinyl}carbonyl)amino-2-phenylacetic acid
Piperacillin	2-{{(4-ethyl-1,2,3-dioxopiperazine)}

perience and that of others, anaphylaxis is currently the most frequent clinical entity reported [13].

Although several mechanisms are involved in allergic reactions to BL [3], this review, however, will concentrate on type I, IgE mediated reactions, which are the most frequent penicillin-induced reactions. The haptenisation of cell and serum proteins by penicillins and the subsequent recognition by IgE antibodies on the surface of basophil/mast cells induce the rapid release of histamine and other inflammatory mediators that are responsible for the allergic response [14]. Well-known clinical entities include anaphylaxis, consisting of generalized pruritus, erythema, angioedema, difficulty breathing, upper/lower airway obstruction and, in more severe cases, cardiovascular collapse leading to anaphylactic shock [4]. When manifestations are limited to the skin, the clinical entity is denominated immediate urticaria. Organ-specific reactions in the absence of other symptoms may occur, such as laryngeal angioedema, rhinitis, asthma or conjunctivitis. In many instances these reactions occur in the industrial sector, including the pharmaceutical industry [15-17].

BACKGROUND

All drugs used in medicine, including BL antibiotics, are recent in comparison with the other agents to which the immune system is exposed and interacts. The immune system was not created to respond to chemical compounds now used. Consequently, information about events over the last half century, since the appearance of BL and other antibiotics, is pertinent [3, 13].

As stated above, from the early days of penicillins, the population exposed to these compounds has increased, varied and diversified over the years [7]. The older subjects with

ages of 60s and over have an immunological system that has been exposed to the whole spectrum of BL antibiotics since the first contact more than 50 years ago in many cases. No matter they develop good tolerance or in rare instances a response, the system always recognizes different structures and keep them in memory with a very low proportion of cases developing response [4]. On the other hand, the immune system in younger persons only recognizes one particular structure, e.g., amoxicillin (AX) or a third generation cephalosporins, as these persons have not been exposed to the whole range of BL.

From the beginning, when BP was the only BL used, reactions were classified into three groups, according to the time interval between drug intake and occurrence of symptoms: immediate, accelerated or delayed [18]. Immediate reactions occur within minutes to less than one hour after hapten exposure, with typical entities being urticaria and anaphylactic shock. Delayed reactions are those occurring from 48 to 72 hours after drug intake, and involve such entities as delayed urticaria, exanthema, desquamative exanthema, Stevens-Johnson syndrome, Lyell syndrome and fixed drug eruption. These reactions have been attributed to a T cell response. Accelerated reactions constitute a group of entities, mostly urticaria with or without angioedema and exanthema, which appear within an interval of several hours to 24-48 hours after drug intake. Nevertheless, a considerable overlap exists between immediate and accelerated reactions and the latter are very often classified as immediate reactions, contributing to their misclassification. Mechanisms involving an IgE mediated response have been proposed for serum sickness and delayed urticaria, though current knowledge is insufficient to confirm this [18-21]. However, a detailed analysis of this is beyond the scope of this review, although it is nevertheless an interesting hypothesis.

The clinical classification and the mechanism proposed were mostly done when the relevant methodologies were insufficient [3]. Later, the identification of IgE and the subsequent development of *in vitro* assays enabled confirmation of many of the findings obtained by skin testing. Furthermore, immunochemical studies helped in the recognition of the antigenic determinants proposed [6]. Application of these technologies to the study of the IgE response to BL has contributed to the better understanding of BL compared with other antibiotics. Other technologies used to study the mechanisms involved in immunological reactions to BL include identification of IgG and its isotypes [22, 23], identification of sensitized T cells [24, 25], development of monoclonal antibodies, and sophisticated studies with T lymphocytes with the development of T cell lines and T cell clones [24-26]. Although this armamentarium has led to further understanding of the process, researchers do not always agree and some confusion may exist [9].

THE IMMUNOLOGICAL RESPONSE TO BETALACTAMS

The reason why BL are the drugs most frequently involved in immunological reactions is attributed to their capacity to bind spontaneously to exogenous or endogenous proteins [2, 27, 28]. All BL bind to cell or serum proteins with different kinetics, generating hapten carrier conjugates in a concentration-dependent manner. Binding with serum proteins occurs in less than one hour whereas binding with cell proteins occurs in about eight hours [28]. The penicilloyl groups are mainly located within the albumin molecule and are partly inaccessible to antipenicilloyl antibodies [29, 30]. This property renders them immunogenic, with the capacity to induce T cells or antibodies, which in turn leads to a pathological response. T cells or antibodies that recognize penicillin haptens can be found in most persons, though no reaction occurs because of the induction of tolerance. However, a reaction may occur in a very small proportion of exposed subjects, though the reasons for this are not completely known [29].

The BPO results from the opening of the BL ring by an amino group of the protein, and this forms the major determinant that is recognized when, conjugated to poly-L-lysine (PLL), it is applied to the skin [29]. However, it was very soon detected that the application of penicillin G itself also induced a positive response. It was therefore believed that penicillin G generated several minor determinants (MDM) [31].

At the same time, a number of chemical structures were identified and considered as candidate haptens, though no detailed immunochemical studies have proved their existence in humans [2, 6]. To date, the chemical identity of minor haptenic determinants has not been elucidated [31].

The production of monoclonal antibodies to BPO has provided further information regarding the part that contributes to the antibody binding site within this low molecular weight compound structure. Antibodies seem to recognize three major structures: the side chain of BP, the part consisting of the binding of the carbonyl of the BL to the amino group of proteins, and the thiazolidine ring [31-33]. Similar results have been reported with ampicillin [34]. Application

of these findings to human IgE sera specific to BL has shown that the sera seem to recognize the nuclear part or the side chain of BP, but no sera have so far been detected that recognized the thiazolidine ring [35].

The most significant contribution of penicillin is related to the presence of IgE antibodies to the side chain [5]. In this context, AX, the most consumed drug worldwide, generates a specific determinant, to which an increasing number of subjects develop a specific response. This determinant, known as amoxicilloyl, is the equivalent to benzylpenicilloyl [35-37].

Important differences exist between IgE specific to AX and IgE specific to BP. In IgE responses to AX, the side chain contributes relevantly to inhibition. In IgE responses to BP, the side chain does not contribute in a similar way to the formation of the epitope, and the whole structure is required, with no significant inhibition of the molecular component [35]. This may explain why persons who are selective to AX only respond to this compound and persons positive to BP usually respond to several penicillin derivatives, such as ampicillin, metampicillin, and amoxicillin [8]. Further studies have shown that with the use of monoclonal antibodies to AX and the use of a sensitized mast cell line, the specificity is directed to the side chain of AX and in the case of BP the whole molecule is required [31].

THE IMMUNOLOGICAL RESPONSE TO CEPHALOSPORINS

Cephalosporins are BL that contain a dihydrothiazine instead of a thiazolidine ring, plus a number of different side chains at the R1 and R2 positions (Table 2). The cephamycins have a methoxy group at position 7 of the BL. Compared to penicillins, the number of cephalosporins is higher and several classifications exist. Cephalosporins are divided into four generations, according to their activity against gram-positive and gram-negative bacteria [1]. The most relevant for IgE hypersensitivity reactions is the chemical structure of the R1 side chain [38, 39].

Our knowledge concerning the immunological response to cephalosporins is more incomplete. Early during the development of first generation cephalosporins it was shown that cephalothin had the same cross-reactivity as 6-aminopenicillanic acid with anti-BPO antibodies [40]. In other instances, similarities between the thiyopene side chain of cephalothin or cephalixin and the phenylacetic of BP contributed to cross-reactivity [41]. Another explanation involved molecular impurities, but cross-allergenicity was seen to exceed the value of possible cross-contamination [42].

Although selective responses to cephalosporins were reported, since the 90s their number has increased, including responses to such compounds as cefazolin [43, 44], cefuroxime [45, 46], ceftriaxone [47-49], cefotaxime, cefepime and ceftazidime [50].

Detailed analytical studies in persons with immediate responses to cephalosporins show the presence of three patterns of response: those who respond to penicillin determinants [49, 51], those who respond to cephalosporin determinants but are negative to penicillin determinants [44, 46, 51, 52], and those who respond exclusively to one single cepha-

Table 2. Side Chain of Cephalosporins Antibiotics

Generation	Non Proprietary Name	Side Chain
First	Cephalotin	2-(2-thienyl)acetic acid
	Cefazolin	2-(1 <i>H</i> -1,2,3,4-tetraazol-1-yl) acetic acid
	Cefalexin	2-Amino-2-phenylacetic acid
	Cefadroxil	2-Amino-2-(4-hydroxyphenyl)
Second	Cefamandole	2-Hydroxy-2-phenylacetic acid
	Cefoxitin	2-(2-thienyl)acetic acid
	Cefaclor	2-Amino-2-phenylacetic acid
	Cefuroxime	2-(2-Furyl)-2(methoxyimino) acetic acid
	Loracarbef	2-Amino-2-phenylacetic acid
	Cefonicid	2-Hydroxy-2-phenylacetic acid
	Cefotetan	2-(4-carboxy-1,3-dithietan-2-yliden)malonic acid
	Ceforanide	2-[2-(aminomethyl)phenyl] acetic acid
Third	Cefotaxime	2-(4-amino1,3-thiazol-2-yl)-2-(methoxyimino)acetic acid
	Cefpodoxime	2-(4-amino1,3-thiazol-2-yl)-2-(methoximino)acetic acid
	Cefixoxime	2-(5-imino-4,5-dihydro-1 <i>H</i> -pyrrol-2-yl)-2(methoxyimino) acetic acid
	Ceftriaxone	2-(2-amino-1,3-thiazol-4-yl)- 2-(methoxyimino) acetic acid
	Cefoperazone	2-[[[(4-ethyl-2,3-dioxopiperazine)carbonil]amino}-2-(4-hydroxy-phenyl)acetic acid
	Ceftazidime	2-([[(2-amino-1,3thiazol-4-yl) (carboxy)methylidene]amino)-oxy]-2-methylpropionic acid
	Cefepime	2-(4-amino1,3-thiazol-2-yl)-2-(methoxyimino)acetic acid

losporin [44, 47]. Explanation of these differences requires analysis of how the epitopes are generated. In penicillins, due to the chemical structure resulting from the condensation of the BL with the thiazolidine ring, the high tension determines a great chemical reactivity but in cephalosporins the heterocycles are formed by four and six carbons resulting in a lower tension of the BL ring. Therefore haptensisation of proteins by cephalosporins is slower and less efficient than with penicillins. The R2 chemical structure can modulate chemical reactivity, but because it is lost after opening of the BL ring only the R1 and part of the BL ring remain bound to the carrier, contributing to the formation of the epitope [53]. Therefore, cross-reactivity between cephalosporins must be considered in terms of the chemical structure of the R1 side chain. In this context, we have found important cross-reactivity between cefuroxime and cefotaxime, compounds that have an identical side chain, and also between cefuroxime, ceftazidime and cefepime [54]. However there are cases where cross-reactivities have been found with cephalosporins with different side chains [44, 51, 52].

OTHER BETALACTAMS

Carbapenems differ from penicillins in that they are unsaturated and contain a carbon atom instead of sulphur. The two compounds used for treatment are imipenem and meropenem. The latter does not need to be coadministered with cilastin, but its therapeutic equivalence and clinical toxicity are similar to imipenem [4]. A study has shown a high degree of cross reactivity with penicillin [55], although another study has shown that selective responses may occur [56]. Because of the limited use of this group of antibiotics compared to the other BL, additional studies are required to estimate cross-reactivity.

Aztreonam (AZT) is a monocyclic BL isolated from *Chromobacterium violaceum*. AZT interacts with penicillin binding proteins of susceptible microorganisms and is resistant to many betalactamases [57]. It shares the same side chain as ceftazidime. These have been recognized by IgG antibodies [58, 59]. Three cell lines of hybridoma have been established to AZT [60]. Two of these lines recognize AZT and ceftazidime, indicating that the same acyl side chain is a relevant part of the epitope. The third line recognizes a new antigenic determinant and displays broad cross-reactivity with several BL.

Selective responses to AZT have been reported, although we are unaware of any evidence of specific IgE antibodies [61, 62]. In other instances, cross reactivity with ceftazidime has been observed [63]. However, in all patients with penicillin allergy, good tolerance to AZT has been observed [64]. Clavulanic acid is a betalactamase inhibitor produced by *Streptomyces clavuligerus*. It is an inhibitor of betalactamases produced by gram-positive and gram-negative bacteria [65]. Selective hypersensitivity reactions to clavulanic acid have been reported [62, 63], although no studies have yet shown the immunochemical characteristics of the epitope.

CLINICAL EVALUATION

The first and most accurate approach is a detailed clinical history [66]. With the implementation of a number of questions a very firm diagnosis can be proposed. The information required for establishing the diagnosis is: symptoms induced, drug or drugs involved, time occurring between drug intake and appearance of symptoms, time occurring between the occurrence of the reactions and the evaluation of the subject,

previous episodes, tolerance to other drugs and the process for which the BL was administered.

Because the sensitivity of both skin testing and radioallergo sorbent test (RAST) is not optimal, it is estimated that as many as 30% of allergic patients will fail to be diagnosed using these tests [66, 67]. Subjects with a positive history but a negative skin test and negative RAST must still be considered as allergic. The assumption that if a person has a negative skin test they will tolerate the drug is not acceptable [6]. Because sensitivity is not optimal, an important proportion of patients will still develop reactions even following these recommendations [9].

The general approach for the evaluation of subjects with immediate hypersensitive reaction to BL is described in detail in the position paper of the European Academy of Allergy and Immunology [66]. The first step is to perform skin testing with BPO, MDM, and AX determinants. This is now widely accepted and is gradually becoming routine in many European countries [7]. Cross-reactive or selective responses may occur in BL-allergic patients. In cases of cross-reaction, the offending drug is very often amoxicillin, cloxacillin or another penicillin derivative, but the skin or *in vitro* test may only be positive to BP determinants (BPO and/or MDM) [8].

DIAGNOSIS OF BL ALLERGY

Skin tests have been the most generalized approach for diagnosing immediate hypersensitivity to BL [68]. This technique must be performed by experienced personnel and is not recommended for mass campaigns. A detailed explanation of its application and the safety measures to be observed are described in reference [66, 67].

In countries where AX is the most important drug eliciting the reaction, the use of just BPO and MDM will leave more than the 60% of subjects undiagnosed [5, 8]. The addition of AX and, where necessary the culprit drug, which is very often a cephalosporin, will increase the sensitivity of skin testing.

Reasons for negative skin tests in patients with a clear history include failure to use the whole battery recommended, including if necessary the culprit drug, and a long time interval between drug reaction and the performance of the study [5].

The natural evolution of skin testing indicates that after three years follow-up, 50% of skin tests to AX become negative, and 100% after five years [69]. On the other hand, in subjects positive to penicillin determinants, 50% remain positive after five years follow-up. Although these data are not available for cephalosporins, there are reasons to suspect that these intervals may be even shorter than for AX.

A complementary approach for diagnosis is *in vitro* testing. However, considering that skin tests are not exempt from risk and that reaching the highest permitted concentration may induce a response in up to 11% of patients, this test is often the first choice [67]. Current methods available use a high density of epitope in the carrier. In our experience, use of human serum albumin (HSA), aliphatic spacers or PLL are all good choices, although PLL is preferable [36, 37].

Because of limitations for skin testing and the fact that in many countries it cannot be used for *in vivo* diagnosis, *in vitro* testing has the advantage that any hapten available in the solid phase can be used [36]. Unfortunately, sensitivity is not as optimal as with the *in vivo* test, although both techniques are complementary. Indeed, in many cases an *in vitro* test is positive [70].

Another method is based on basophil activation test (BAT). This is based on the capacity of basophils to release histamine after activation by a hapten. Following this, the marker, CD63, is expressed on the basophil membrane. Quantitation of CD63 and FcεRI enables the number of basophils to be calculated. In our experience, the overall sensitivity of the BAT is 48.6%, with a specificity of 93%. In cases with a negative skin test and RAST, the sensitivity is low, although more studies are required. It is important to note that the sensitivity of Pharmacia CAP assay does not match that of the basophil test, but the combination of both tests increases sensitivity to 67%. An important finding is that when a group of selective responders to cephalosporin was studied, sensitivity was around 77%. These figures appear promising, especially considering the limitations of skin testing with these compounds [71].

Solid phases have often been used for the *in vitro* quantitation of IgE antibodies. These solid phases consist of sepharose beads activated with cyanogen bromide, to which penicillin-HSA or penicillin-PLL is bound [72, 73]. These techniques are more complicated and in our experience they do not appear to represent an advantage. One refinement of these techniques is the use of sepharose activated with epoxy resins to which cephalosporins are conjugated [73, 74]. These techniques have been used to identify IgE antibodies to cephalosporins, although sensitivity and specificity studies are lacking.

THERAPEUTIC ALTERNATIVES

The current practice in subjects with proven allergy to BL is to avoid the drug, although since the reports of selective responders to amoxicillin and cephalosporins these general recommendations do not need to be applied in all cases. Recent studies indicate that third- and fourth-generation cephalosporins are well tolerated in patients who are primarily sensitized to BPO [53], and BP can be administered to patients who are primarily sensitized to AX or cephalosporins.

The question of safe tolerance within the penicillin group is more difficult to answer. At present, we know that selective responders will tolerate BP but no data are available concerning whether, in the long term, subsequent treatment will be tolerated. On the other hand, the administration of amoxicillin, ampicillin or another penicillin derivative may induce a cross-reactive response in patients who, after skin testing and/or RAST, are only positive to BP determinants (BPO and/or MDM or RAST only to BPO) [8]. These clinical observations are supported by *in vitro* studies. In those cases where side-chain specific antibodies to AX exist, this side chain contributes in a relevant way to the formation of the epitope [35].

Regarding AZT, a number of studies indicate that good tolerance to AZT exists in patients who are primarily sensitized to penicillin determinants [64]. The only restriction concerns when a patient who was originally sensitized to ceftazidime is given AZT [63, 75].

In subjects who have an IgE response to penicillin, the only alternative is often to induce desensitization to the drug. This consists of the progressive administration of the drug, usually parentally, although the oral route has occasionally been used. Different protocols have been published elsewhere. No data are available concerning the success of this approach, but some patients have developed good tolerance or only mild reactions, whereas others respond positively to the drug and this cannot therefore be administered.

ACKNOWLEDGEMENT

We thank Ian Johnstone for help with the English language version of the manuscript. Supported by Grants of the Ministerio de Sanidad (FIS PI02/0666, PI03/1165), the Ministerio de Educacion y Ciencia (BQU 2001/3624) and the Consejería de Salud de la Junta de Andalucía, Spain.

ABBREVIATIONS

AX	=	Amoxicillin
AZT	=	Aztreonam
MDM	=	Minor determinants mixture
BL	=	Betalactams
BP	=	Benzyl penicillin
BPO	=	Benzyl penicilloyl
HSA	=	Human serum albumin
PLL	=	Poly-L-lysine
RAST	=	Radio allerge sorbent test

REFERENCES

References 76-78 are related articles recently published in *Current Pharmaceutical Design*.

- Petri WA Jr. Antimicrobial agents: penicillins, cephalosporins and others betalactam antibiotics. In: Goodman and Gilman's. The pharmacological basis of therapeutics. Eds. Hardam JG and Limbird LE. McGraw-Hill, New York. 2001; 1189-218.
- Dewdney JM. Immunology of the antibiotics. In: Sela M. ed. The antigens. Academic Press, New York. 1977; Vol IV: 114-22.
- Idsoe O, Guthe T, Wilcox RR, de Weck AL. Nature and extent of penicillin side reactions, with particular reference to fatalities from anaphylactic shock. *Bull World Health Organ* 1968; 38: 159-88.
- Adkinson NF Jr. Drug allergy. In: Adkinson NF, Yunginger JW, Busse WW, Bochner BS, Holgate ST, Simmons FE. *Allergy. Principles and Practice*. Mosby, Philadelphia. 2003; 1679-94.
- Blanca M, Vega JM, Garcia J, Miranda A, Carmona MJ, Juarez C, *et al.* New aspects of allergic reactions to betalactams: crossreactions and unique specificities. *Clin Exp Allergy* 1994; 24: 407-15.
- Weiss ME, Adkinson NF. Immediate hypersensitivity reactions to penicillin and related antibiotics. *Clin Allergy* 1988; 18: 515-40.
- Blanca M. Allergic reactions to penicillins. A changing world?. *Allergy* 1995; 50: 777-82.
- 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: 875-904.
- Blanca M, Torres MJ, Mayorga C, Perez-Inestrosa E, Suau R, Montañez MI, *et al.* Immediate allergic reactions to betalactams. Facts and controversies. *Curr Op Allergy Clin Immunol* 2004; 4: 261-6.
- Torres MJ, Blanca M, de Weck A, Fernandez J, Demoly P, Romano A, *et al.* and the ENDA and the EAACI interest group on drug hypersensitivity. Diagnosis of immediate allergic reactions to betalactam antibiotics. *Allergy* 2003; 58: 854-63.
- Green GR, Roseblum AH, Sweet LC. Evaluation of penicillin hypersensitivity: Value of clinical history and skin testing with penicilloyl-polylysine and penicillin G. A cooperative prospective study of the penicillin study group of the American Academy of Allergy. *J Allergy Clin Immunol* 1977; 60: 339-45.
- Terrados S, Blanca M, Garcia J, Vega JM, Torres MJ, Carmona MJ, *et al.* Non-immediate reactions to betalactams: prevalence and role of the different penicillins. *Allergy* 1995; 50: 5 63-7.
- Blanca M, Mayorga C, Torres MJ, Warrington R, Romano A, Demoly P, *et al.* Side Chain Specific Reactions To Betalactams: Twelve Years Later. *Clin Exp Allergy* 2002; 32: 192-7.
- Siraganian RP. Biochemical events in basophil or mast cell activation and mediator release. In: Adkinson NF, Yunginger JW, Busse WW, Bochner BS, Holgate ST and Simmons FE. *Allergy. Principles and Practice*. Mosby, Philadelphia 2003; 243-78.
- Davies RJ, Pepys J. Asthma due to inhaled chemical agents: ampicillin, benzyl-penicillin, 6 aminopenicillanic acid and related substances. *Clin Allergy* 1974; 4: 222-47.
- Suh YJ, Lee YM, Choi JH, Such CH, Nahm DH, Park HS. Heterogeneity of IgE response to ceftaran pivoxil was noted in 2 patients with ceftaran induced occupational asthma. *J Allergy Clin Immunol* 2003; 11: 209-10.
- Park HS, Kim KU, Lee YM, Choi JH, Lee JH, Park SW, *et al.* Occupational asthma and IgE sensitisation to 7-aminocephalosporanic acid. *J Allergy Clin Immunol* 2004; 113: 785-7.
- Levine BB. Immunologic mechanisms of penicillin allergy. A haptenic model system for the study of allergic diseases of man. *N Engl J Med* 1966; 275: 1115-25.
- De Haan P, Kalsbeek GL. Induction of benzylpenicilloyl specific antibodies, inducing IgE by long term administration of benzylpenicillin. *Clin Allergy* 1983; 13: 563-9.
- Strannegard IL, Majeed HA, Ahlstedt S. Antibodies to penicillin in children receiving long-term secondary prophylaxis for rheumatic fever. *Allergy* 1987; 42: 502-6.
- De Haan P, Van Ketel WG. Specific reactions and cross reactions of anti-penicilloyl antibodies. *Allergy* 1987; 42: 92-6.
- Christie G, Coleman JW, Newby S, McDiarmid-Gordon A, Hampson JP, Breckenridge AM, *et al.* A survey of the prevalence of penicillin-specific IgG, IgM and IgE antibodies detected by ELISA and defined by hapten inhibition, in patients with suspected penicillin allergy and in healthy volunteers. *Br J Clin Pharmacol* 1988; 25: 381-6.
- Klein GF, Stanzl U, Fristch PO, Varga JM. Enzyme-linked immunosorbent assay for detection of antibodies to the unmodified betalactam ring. *Allergy* 1993; 48: 151-7.
- Bell SJD, Pichler WJ. Penicillin-allergic patients react to penicillin-modified "self". *Allergy* 1989; 44: 199-203.
- Brander C, Mauri-Helweg D, Rolli HP, Goldman M, Pichler WJ. Heterogeneous T cell response to betalactam modified self structures in penicillin allergic individuals. *J Immunol* 1995; 155: 2670-8.
- Luque I, Leyva L, Torres MJ, Rosal M, Mayorga C, Segura JM, *et al.* *In vitro* T lymphocyte responses to betalactam drugs in immediate and nonimmediate allergic reactions. *Allergy* 2001; 56: 611-8.
- Levine BB. Immunologic mechanisms of penicillin allergy. A haptenic model system for the study of allergic diseases of man. *N Engl J Med* 1966; 275: 1115-25.
- Warbrick EV, Thomas AL, Stejkal V, Coleman JW. An analysis of betalactam derived antigens on spleen cells and serum proteins by ELISA and western blotting. *Allergy* 1995; 50: 910-7.
- Yvon M, Anglade P, Wal JM. Identification of the binding sites of benzyl penicilloyl, the allergenic metabolite of penicillin on the serum albumin molecule. *FEBS Lett* 1990; 263: 237-40.
- Lafaye P, Lapresle C. Fixation of penicilloyl groups to albumin and appearance of anti-penicilloyl antibodies in penicillin-treated patients. *J Clin Invest* 1988; 82: 7-12.

- [31] De Haan P, Jonge AJ, Verbrugge E, Boorsma DM. Three epitope-specific monoclonal antibodies against the hapten penicillin. *Int Arch Allergy Appl Immunol* 1985; 76: 42-6.
- [32] 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: 427-36.
- [33] Mayorga C, Obispo T, Jimeno L, Blanca M, Moscoso del Prado J, Carreira J, *et al.* Epitope mapping of betalactam antibiotics with the use of monoclonal antibodies. *Toxicology* 1995; 97: 225-34.
- [34] Nagakura N, Souma S, Shimizu T, Yanagihara Y. Antiampicillin monoclonal antibodies and their cross-reactivities to various β -lactams. *J Antimicrob Chemother* 1991; 28: 357-68.
- [35] Moreno F, Blanca M, Mayorga C, Terrados S, Moya C, Pérez E, *et al.* Studies of the specificities of IgE antibodies found in sera from subjects with allergic reactions to penicillins. *Int Arch Allergy Immunol* 1995; 108: 74-81.
- [36] Blanca M, Mayorga C, Sanchez F, Vega JM, Fernandez J, Juarez C, *et al.* Differences in serum IgE antibody activity to benzylpenicillin and amoxicillin measured by RAST in a group of penicillin allergic subjects. *Allergy* 1991; 46: 632-8.
- [37] Blanca M, Mayorga C, Perez E, Suau R, Juarez C, Vega JM, *et al.* Determination of IgE antibodies to the benzylpenicilloyl determinant. A comparison between poly-L-lysine and human serum albumin as carriers. *J Immunol Methods* 1992; 153: 99-105.
- [38] Fernandez M, Warbrick EV, Blanca M, Coleman JW. Activation and hapten inhibition of mast cells sensitised with IgE anti-penicillin antibodies: evidence for two-site recognition on the penicillin derived determinant. *Euro J Immunol* 1995; 25: 2486-91.
- [39] Sanchez-Sancho F, Perez-Inestrosa E, Suau R, Montañez MI, Mayorga C, Torres MJ, *et al.* Synthesis, characterization and immunochemical evaluation of cephalosporin antigenic determinants. *J Mol Recognit* 2003; 16: 148-56.
- [40] Batchelor FR, Dewdney JM, Weston RD, Wheeler AW. The immunogenicity of cephalosporin derivatives and their cross-reaction with penicillin. *Immunology* 1966; 10: 21-33.
- [41] de Weck AL. Penicillins and cephalosporins. In: de Weck AL, Bundgaard H, Ed. *Allergic reactions to drugs*. Springer, Berlin 1983; 63: 423-82.
- [42] Stewart GT. Allergenic residues in penicillins. *Lancet* 1967; 1:1167-83.
- [43] Anne S, Reisman RE. Risk of administering cephalosporin antibiotics to patients with histories of penicillin allergy. *Ann Allergy* 1995; 74: 167-70.
- [44] Warrington RJ, McPhillips S. Anaphylaxis to cefazolin without allergy to other betalactam antibiotics. *J Allergy Clin Immunol* 1996; 98: 460-2.
- [45] Romano A, Quarantino D, Venuti A, Venemalm L, Mayorga C, Blanca M. Selective type-1 hypersensitivity to cefuroxime. *J Allergy Clin Immunol* 1998; 101: 564-5.
- [46] Saenz de San Pedro B, Mayorga C, Torres MJ, Florido JF, Quirarte J, Blanca M. Boosted IgE response after anaphylaxis reaction to cefuroxime with cross-reactivity with cefotaxime. *Ann Allergy Asthma Immunol* 2002; 89: 101-3.
- [47] Romano A, Piunti E, Di Fonso M, Viola M, Venuti A, Venemalm L. Selective immediate hypersensitivity to ceftriaxone. *Allergy* 2000; 55: 415-6.
- [48] Ernst MR, Van Dikjen PJ, Kabel PJ, Draaisma JM. Anaphylaxis after first exposure to ceftriaxone. *Acta Paediatr* 2002; 91: 355-9.
- [49] Astanaskovich-Markovic M, Gavroci-Jankulovic M, Circovic-Velickovic T, Vuckovic O, Todoric D. Type I hypersensitivity to ceftriaxone and cross reactivity with cephalixin and ampicillin. *Allergy* 2003; 58: 537-8.
- [50] Orhan F, Odemis E, Yaris N, Okten A, Erduran E, Durmaz M, *et al.* A case of IgE mediated hypersensitivity to cefepime. *Allergy* 2004; 59: 239-41.
- [51] Romano A, Mayorga C, Torres MJ, Artesani MC, Suau R, Pérez E, *et al.* Immediate allergic reactions to cephalosporins: cross-reactivity and selective responses. *J Allergy Clin Immunol* 2000; 106: 1177-83.
- [52] Demoly P, Messaad D, Sahla H, Hillaire-Buys D, Bousquet J. Immediate hypersensitivity to ceftriaxone. *Allergy* 2000; 55: 418-9.
- [53] Perez-Inestrosa E, Suau R, Montañez MI, Rodriguez R, Mayorga C, Torres MJ, *et al.* Cephalosporin chemical reactivity and its immunological implications. *Curr Opin Allergy Clin Immunol* 2005; 5: 323-30.
- [54] Torres MJ, Mayorga C, Rodríguez-Bada JL, Perez-Inestrosa E, Montañez MI, Suau R, *et al.* Study of *in vitro* cross reactivity by determining specific IgE in patients with immediate adverse reactions to cephalosporins. *J Allergy Clin Immunol* 2005; 115: S32.
- [55] 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.
- [56] Sodhi M, Axtell SS, Callahan J, Shekar R. Is it safe to use carbapenems in patients with a history of allergy to penicillins? *J Antimicrob Chemother* 2004; 54: 1155-7.
- [57] Sykes RB, Cimarusti CM, Bonner DP, Bush K, Floyd DM, Georgopadakou NH, *et al.* Monocyclic β -lactam antibiotics produced by bacteria. *Nature* 1981; 291: 489-91.
- [58] Adkinson NF, Swabb EA, Sugarman AA. Immunology of the monobactam aztreonam. *Antimicrob Agents Chemother* 1984; 25: 93-7.
- [59] Saxon A, Swabb EA, Adkinson NF. Investigation into the immunologic cross-reactivity of aztreonam with other betalactam antibiotics. *Am J Med* 1985; 78: 19-26.
- [60] Shimizu T, Souma S, Nagakura N, Masuzawa T, Iwamoto Y, Yanagihara Y. Epitope analysis of aztreonam by anti-aztreonam monoclonal antibodies and possible consequences in beta-lactams hypersensitivity. *Int Arch Allergy Immunol* 1992; 98: 392-7.
- [61] Candarso AI, Saez Jiménez SA, Vidal C, Rodríguez M. Aztreonam induced anaphylaxis. *Lancet* 1990; 336: 746-7.
- [62] de la Fuente-Prieto R, Armentia-Medina A, Sanchez-Palla P, Diez-Perez JM, Sanchos-Merino ME, Fernandez-Garcia A. Urticaria caused by sensitization to aztreonam. *Allergy* 1993; 48: 634-6.
- [63] Perez Pimiento A, Gomez Martinez M, Minguez Mena A, Trampal Gonzalez A, *et al.* Aztreonam and ceftazidime: evidence of *in vivo* cross allergenicity. *Allergy* 1998; 53: 624-5.
- [64] Vega JM, Blanca M, García JJ, Miranda A, Carmona MJ, García A, *et al.* Tolerance to aztreonam in patients allergic to beta-lactam antibiotics. *Allergy* 1991; 46: 196-202.
- [65] Neu HC, Fu KP. Clavulanic acid, a novel inhibitor of beta-lactamases. *Antimicrob Agents Chemother* 1978; 14: 650-5.
- [66] Torres MJ, Blanca M, Fernández J, Romano A, de Weck A, Aberer W, *et al.* Diagnosis of immediate allergic reactions to beta-lactam antibiotics. *Allergy* 2003; 58: 961-72.
- [67] Torres MJ, Romano A, Mayorga C, Moya MC, Guzman AE, Reche M, *et al.* Diagnostic evaluation of a large group of patients with immediate allergy to penicillins: the role of skin testing. *Allergy* 2001; 56: 850-6.
- [68] Adkinson NF Jr, Thompson WL, Maddrey WC, Lichtenstein L. Routine use of penicillin skin testing on an inpatient service. *N Eng J Med* 1971; 285: 22-4.
- [69] Blanca M, Torres MJ, Garcia JJ, Romano A, Mayorga C, de Ramon E, *et al.* Natural evolution of skin test sensitivity in patients allergic to betalactam antibiotics. *J Allergy Clin Immunol* 1999; 103: 918-24.
- [70] Torres MJ, Mayorga C, Cornejo-Garcia JA, Romano A, Blanca M. IgE antibodies to penicillin in skin tests negative patients. *Allergy* 2002; 57: 965.
- [71] Torres MJ, Padial A, Mayorga C, Fernandez T, Sanchez-Sabaté E, Cornejo-Garcia JA, *et al.* The diagnostic interpretation of basophil activation test in immediate allergic reactions to betalactams. *Clin Exp Allergy* 2004; 34: 1768-75.
- [72] Harle DG, Baldo BA. Drugs as allergens: An immunoassay for detecting IgE antibodies to cephalosporins. *Int Arch Allergy Appl Immunol* 1990; 92: 439-44.
- [73] 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: 1063-71.
- [74] Pham NH, Baldo BA. β -lactam drug allergens: Fine structural recognition patterns of cephalosporin-reactive IgE antibodies. *J Mol Recognit* 1996; 9: 287-96.
- [75] Moss RB. Sensitization to aztreonam and cross-reactivity with other beta-lactam antibiotics in high-risk patients with cystic fibrosis. *J Allergy Clin Immunol* 1991; 87: 78-88.
- [76] Gillor O, Nigro LM, Riley MA. Genetically engineered bacteriocins and their potential as the next generation of antimicrobials. *Curr Pharm Des* 2005; 11(8): 1067-75.
- [77] Li L, Xu B. Multivalent vancomycins and related antibiotics against infectious diseases. *Curr Pharm Des* 2005; 11(24): 3111-24.
- [78] Wu Z, MacPhee IA, Oliveira DB. Reactive oxygen species in the initiation of IL-4 driven autoimmunity as a potential therapeutic target. *Curr Pharm Des* 2004; 10(8): 899-913.

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.