

IgE-Mediated Hypersensitivity to Cephalosporins

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Abstract: Like penicillins, cephalosporins may cause IgE-mediated reactions such as urticaria, angioedema, and anaphylactic shock, which occur because of sensitization to determinants shared with penicillins or to unique cephalosporin haptens. In particular, side-chain structures may be responsible for selective sensitization or cross-reactivity. For this reason, individual free cephalosporins are usually employed in skin testing, in addition to the classic penicillin reagents.

Cephalosporin skin tests are sensitive in diagnosing immediate hypersensitivity to these betalactams. As far as *in vitro* tests are concerned, IgE assays for cephalosporins, specifically sepharose-radioimmunoassays, are a potentially useful tool in evaluating immediate reactions and could be used as complementary tests. In selected cases displaying negative results in both skin tests and IgE assays, a graded challenge with the implicated cephalosporin can be performed.

Cephalosporin IgE-mediated hypersensitivity may be a transient condition; therefore, allergologic exams should be repeated in patients with negative initial allergologic work-ups, including challenges.

Performing allergologic tests with cephalosporins other than the culprit, as well as with penicillin reagents, allows the identification of cross-reactivity with penicillins, selective responses, or cross-reactivity among cephalosporins. In the latter group, cross-reactivity is more frequently related to R₁ than to R₂ side-chain recognition.

In assessing the selectivity of the response, negative results in skin testing with cephalosporins other than the responsible one appear to be a reliable indicator of tolerability.

Key Words: Drug allergy, anaphylactic reaction, betalactams, cephalosporins, IgE, skin testing.

INTRODUCTION

Together with penicillins, cephalosporins are the antibiotics most widely used for treating common infections [1, 2]. Like the former, they may cause immediate reactions occurring within one hour after drug administration. These reactions are clinically manifested by urticaria, angioedema, rhinitis, bronchospasm, and anaphylactic shock [3-7]. They can be life-threatening, and drug re-administration in these cases may cause even more severe reactions [8, 9]. The frequency of cephalosporin-induced cutaneous reactions, according to a study by Norrby [10], ranges from 1% (cefuroxime) to 3% (ceftriaxone). As far as IgE-mediated anaphylactic reactions to cephalosporins are concerned, some studies suggest that they are rare (frequency: 0.0001 to 0.1 percent) [5, 6, 10], although an increasing number of anaphylactic reactions, in particular to ceftriaxone, have been reported in the last few years [11-19].

The reason why patients develop an IgE-mediated reaction to a cephalosporin is unclear and may involve several

pathogenic mechanisms related to antigen presentation, class switching to IgE by B cells, and increased release of the mediators from basophils and mast cells. The drug, or a drug metabolite, reacts with IgE bound to the surface of mast cells and possibly basophils, leading to the activation, degranulation, and release of vasoactive mediators from such cells [4, 20].

1. Cephalosporin Allergenic Determinants

Although the incidence of severe immediate reactions to cephalosporins does not seem to be much different from that to penicillins, studies of cephalosporins as allergens are not nearly as numerous or thorough as those on penicillins, and very few have been dedicated to the determinants responsible for allergic reactions [21-31].

However, it is well known that cephalosporins share the four-membered betalactam ring with penicillins, but differ from the latter in that the five-membered thiazolidine ring of penicillin is replaced by a six-membered dihydrothiazine one (Fig. (1)). Other differences concern their side-chain structures and the chemistry of their degradation and transformation. Under physiological conditions, the cephalosporin betalactam ring opens and its carbonyl moiety binds a protein, forming the cephalosporoyl determinant [32], which tends to undergo extensive fragmentation, probably including the

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cleavage of the dihydrothiazine ring [22-24]. Cephalosporin side-chain structures usually survive such fragmentation and may be responsible for cross-reactivity among betalactams, including other cephalosporins, or selective sensitization [27, 33]. In fact, it has been demonstrated that antibodies to side-chain structures on cephalosporins are immunologically important and that differences in such structures may determine a lower cross-reactivity among cephalosporins than among penicillins and even between these two classes of betalactams [27, 33, 34]. On the other hand, B cells may recognize small structures [35]. Zhao *et al.* [30] performed *in vitro* studies in 1,797 subjects with hypersensitivity reactions to penicillins and/or cephalosporins, demonstrating that a structural feature as small as the methylene group was the focus of the allergenic determinant recognized on benzylpenicillin and cephalothin side chains by a single population of cross-reacting antibodies. In addition to the methylene group, recognition graded into neighboring structures, including the amide group, and extended weakly to the betalactam ring.

Cephalosporins such as cefaclor and cephalexin may undergo aminolysis with the formation of pyrazinone – a degradation compound produced when the molecule reacts with a carrier protein – which binds IgE antibodies in the sera of some cefaclor-allergic subjects [29]. This was shown by allowing cefaclor or cephalexin to react with propylamine in an alkaline aqueous solution and the resultant solid to stand in phosphate buffer. When cefaclor was conjugated to human serum albumin or poly-L-lysine under mild alkaline conditions and stored, an analogous degradation occurred, leading to the formation of a conjugated pyrazinone derivative. A corresponding pyrazinone-polylysine was recognized by antibodies in the serum of some cefaclor-allergic subjects.

Other specificities of antibody reactivity against cephalosporin molecules are possible. In subjects with immediate hypersensitivity to cefaclor, *in vitro* studies [26] have demonstrated IgE antibody reactivity with both ends of the cephalosporin molecule, i.e., the side-chain group (R_1 substituent) and the ring structures with the attached R_2 group (Fig. (1) and (2)).

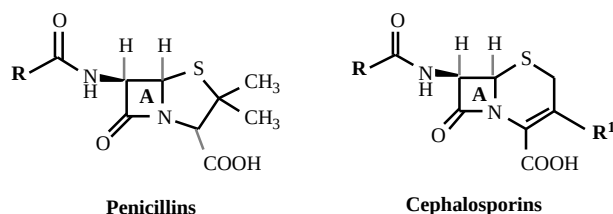


Fig. (1). Chemical structure of penicillins and cephalosporins, with the common β -lactam ring (A).

Some patients display allergologic-test positivity only to the implicated cephalosporins, which may be explained by reactivity with the entire molecule, as demonstrated by *in vitro* tests with cefaclor [26]. Such patients are not usually challenged with the other betalactams tested. However, there are also cases of selective immediate hypersensitivity to cephalosporins, such as cefazolin [36-38], cefuroxime [39, 40], cefixime [41], ceftriaxone [13], ceftazidime [42], and

cefodizime [43], in which selective responses have been confirmed by the negativity of skin tests, IgE assays, and challenges with other betalactams (including first-, second-, and third-generation cephalosporins).

The production of hybridomae has confirmed that, in addition to common determinants, cephalosporins can generate unique structures capable of inducing a specific immunologic response that does not cross-react with classic structures [25]. Thus, allergic reactions to cephalosporins may occur because of sensitization to determinants shared with penicillins (Fig. (1)) or to unique cephalosporin haptens [26, 27, 33]. Therefore, cephalosporins, like penicillins, cannot simply be considered a group of compounds with a common allergenic determinant structure.

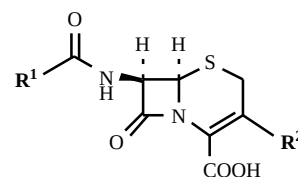
2. Diagnosing Immediate Reactions to Cephalosporins

Skin Testing

Free individual cephalosporins diluted in normal saline should be employed in skin testing, in addition to the classic penicillin reagents (penicilloylpolylysine, minor determinant mixture, and benzylpenicillin), amoxicillin, and ampicillin [12, 19, 44]. We proved that a concentration of 2 mg/mL in normal saline of several injectable and noninjectable cephalosporins was nonirritant in control groups of 30 and 40 subjects, respectively [11, 19]. In our experience, skin testing at such concentration has proved to be a very effective method for evaluating subjects with immediate reactions to cephalosporins. Recently, we studied 76 subjects (54 females, 22 males), ranging in age from 15 to 90 years, with histories of immediate reactions to cephalosporins, mostly to ceftriaxone (reactions in 20 subjects), cefotaxime (in 18 subjects), and ceftazidime (in 18 subjects) [19]. The distribution of culprit cephalosporins of this series is presented in Fig. (3). In the first allergologic work-up, we performed skin tests and serum specific IgE assays. Some subjects with negative results underwent challenges and re-evaluations. The rate of positive responses to skin tests with responsible cephalosporins was 69.7% (53 out of the 76 patients); it increased to 78.9% (positive responses in 60) when considering also the results of the re-evaluation.

In other studies, different concentrations of drugs ranging from 0.5 to 250 mg/mL in normal saline have been used to diagnose immediate hypersensitivity to injectable cephalosporins such as cefazolin, ceftriaxone, and cefuroxime by intradermal testing [14, 17, 18, 36, 39, 45-47]. Specifically, Pichichero and Pichichero [45] evaluated 26 patients (ranging in age from 6 months to 18 years) with adverse reactions to cephalosporins using classic penicillin reagents, as well as ampicillin and some cephalosporins (cefazolin, cefuroxime and ceftriaxone at 10 mg/mL for prick testing and 1 mg/mL for intradermal testing). Although most subjects had reacted to cephalosporins – such as cephalexin, cefadroxil, cefaclor, and loracarbef – other than those used for skin testing, an IgE-mediated hypersensitivity in about half of them was diagnosed. More recently, Atanasković *et al.* [47] diagnosed an IgE-mediated hypersensitivity in 682 (58.3%) out of 1,170 children with histories of adverse reactions to penicillins and/or cephalosporins. Among allergic subjects, the rate of positive skin tests to the cephalosporins (cefaclor, cephalexin, ceftriaxone, and cefotaxime) assessed at a concentra-

Basic structure:
derivatives of 7-amino-cephalosporanic acid



Group	Derivative	R ¹	R ²
I generation	Cephalothin (C1)		
	Cephalexin		CH_3
	Cefaclor		Cl
	Cefatrizine		
II generation	Cefamandole (C2)		
	Cefonicid		
	Cefuroxime (C5)		
III generation	Cefodizime		
	Cefoperazone		
	Cefotaxime (C6)		
	Ceftriaxone (C4)		
	Ceftazidime (C3)		

Fig. (2). Chemical structure of cephalosporins.

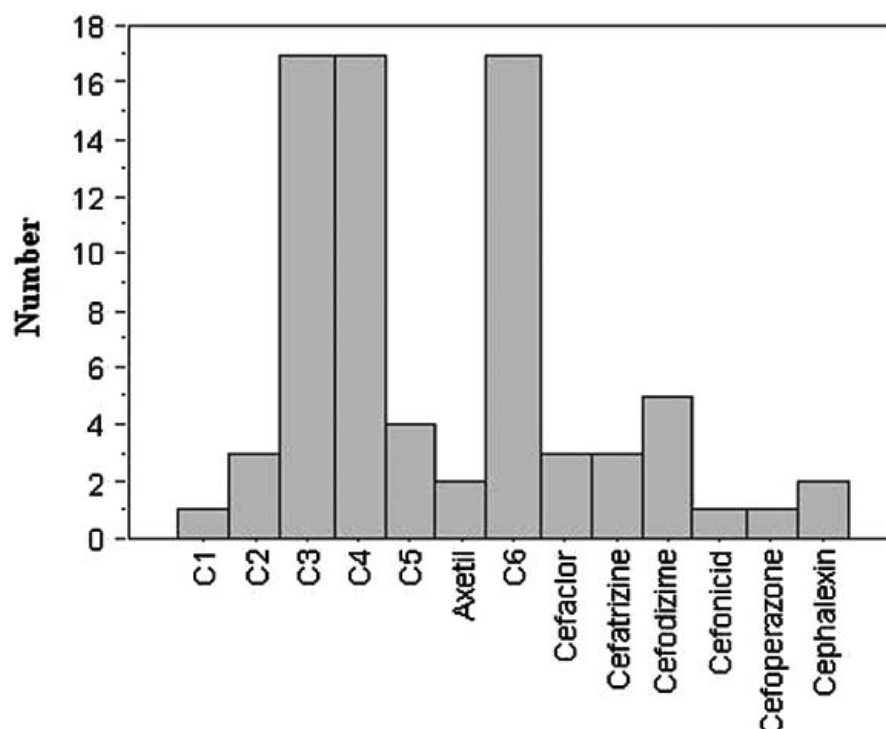


Fig. (3). Histogram of the distribution of culprit cephalosporins in a series of 76 patients who had suffered an immediate reaction to a cephalosporin and who were prospectively recruited in Italy [19].

Abbreviations: Cephalothin (C1), Cefamandole (C2), Ceftazidime (C3), Ceftriaxone (C4), Cefuroxime (C5) and Cefotaxime (C6).

tion of 1-2 mg/mL in normal saline ranged from 0.3% (cefotaxime) to 29.2% (cefaclor).

Some authors diagnosed cases of IgE-mediated hypersensitivity to noninjectable cephalosporins such as cefapirin and cefixime by prick testing with the pure drug in powder [48] or at 200 mg/mL in normal saline [41].

The reliability of skin tests in patients with immediate reactions to cephalosporins has convinced us to avoid challenges with cephalosporins to which patients are positive. On the other hand, authors who have performed such challenges in single patients elicited immediate urticarial or anaphylactic reactions to the responsible cephalosporins [14, 39, 41, 49].

Cephalosporin Challenges

In selected cases displaying negative results in allergologic tests, a graded challenge with the implicated cephalosporin can be done according to the recommendations of the recent position paper by Aberer *et al.* [50].

It is important to note that negative skin-test results should be interpreted in light of the time elapsed since the subject's last exposure to the drug. In fact, there are indications that in cases of IgE-mediated hypersensitivity, skin tests are more likely to be positive the less time has elapsed since the clinical reaction [19, 45]. Therefore, in subjects with immediate reactions to cephalosporins who present negative skin tests when evaluated more than one year after their immediate reactions, the pathogenic mechanism can be clarified by performing challenges with suspect cepha-

losporins and, in case of negative responses, by administering a full therapeutic course. However, it is advisable to retest such patients after 4 weeks to exclude a possible re-sensitization after loss of sensitivity [19, 44]. In fact, re-sensitization – diagnosed on the basis of renewed skin-test positivity – has been described in patients retested about one month after either negative challenges, whether followed or not by full therapeutic courses, or positive ones [19, 45]. In the study by Pichichero and Pichichero [45], one patient suspected of cefuroxime allergy, who had been skin-test negative initially, was skin-test positive to cefuroxime on retesting after a negative cefuroxime axetil oral challenge. In our recent study [19], 8 out of the 13 patients with immediate reactions to cephalosporins and negative results in the first allergologic work-up agreed to undergo challenges with the suspect drug. A conversion to skin-test positivity was observed in the 2 patients who had reacted to challenges and in 5 of the 6 who had tolerated provocation tests followed by full therapeutic courses.

Serum Specific IgE Assays

In vitro assays of serum specific IgE, such as the CAP System FEIA (CAP-FEIA, Pharmacia, Uppsala, Sweden), are commercially available for benzylpenicillin, phenoxymethylpenicillin, ampicillin, amoxicillin, and cefaclor. Some researchers performed assays of serum specific IgE for cephalosporins other than cefaclor in samples larger than 10 patients [12, 19, 26, 30, 51, 52]. However, such assays are not commercially available, and thus are not routinely used [6]. Specifically, we performed IgE assays in 30 subjects with immediate hypersensitivity – diagnosed on the basis of

histories and positive skin-test responses – to one or more of the following cephalosporins: cefuroxime, ceftazidime, cefotaxime, and ceftriaxone [12]. The responsible drugs were conjugated to poly-L-lysine, and assays were made as previously described with penicillins [53]; only 9 patients proved to be positive to the implicated cephalosporins (4 to cefuroxime, 4 to ceftriaxone, and 1 to cefotaxime) [12]. Several groups [19, 26, 30, 51, 52] carried out a radioimmunoassay (RIA) of serum specific IgE for cephalosporins using the drug covalently coupled to sepharose as a solid reactive phase (sepharose-RIA). These *in vitro* assays have also been performed in subjects with immediate reactions to penicillins [30, 54], muscle relaxants [55-58], and quinolones [59]. They require several validation steps prior to interpretation [57, 58], but have proved to be very useful in evaluating subjects with immediate reactions to cephalosporins [19, 52]. In one of our previous studies [52] assessing 12 subjects with immediate hypersensitivity reactions to cephalosporins, the sepharose-RIA detected specific IgE to such drugs in 2 skin-test-negative subjects, confirmed skin-test positivity in 5, and was negative in 5 skin-test-positive ones. In the previously cited study by our group [19], assays for serum specific IgE to penicilloyl G, penicilloyl V, ampicilloyl, and amoxicilloyl were performed with the CAP-FEIA in the 76 patients with immediate reactions to cephalosporins; the sepharose-RIA with cefaclor was carried out in all 76 patients, while that with responsible cephalosporins could be done in only 70 of them. Specific IgE to the culprit cephalosporins were detected in 41 (58.6%) of these 70 patients; 5 of them were skin-test negative. The rate of sepharose-RIA positivity increased to 64.3% (positive responses in 45) when considering also the results of the re-evaluation. In this study, the usefulness of performing the sepharose-RIA in addition to skin testing can be inferred from the 5 patients who displayed skin-test and CAP-FEIA negative results and were sepharose-RIA positive, and from 3 other patients who presented skin-test positivity to penicillin reagents, together with skin-test negativity and sepharose-RIA positivity to the culprit cephalosporins.

We have also reported single cases of immediate allergic reactions to individual cephalosporins like ceftriaxone [11, 13], cephaloridine [60], cefuroxime [40], and ceftazidime [42]. In such studies, specific IgE antibodies for cephalosporins were determined in serum using prototypes of the CAP-FEIA. The drugs were conjugated to a macromolecule and covalently coupled to the solid phase by methods similar to those used for the penicilloyl derivatives. However, such assays did not always confirm skin-test positivity [13, 42, 60]. In some cases the assays were performed more than a year after the reactions and it is possible that meanwhile the IgE titer had fallen below the cut-off value, as has been observed with penicilloyl IgE antibodies [61].

Specific IgE assays seem to be less sensitive than skin testing [19, 44]; moreover, their sensitivity decreases more rapidly [62], although lengthy persistence of specific IgE antibodies to cefaclor has been reported [63].

In Vitro Cellular Tests

In the last few years, the flow cytometric basophil activation test has proved to be helpful in diagnosing IgE-mediated hypersensitivity to betalactams [64, 65]. However,

the total number of subjects with immediate reactions to cephalosporins evaluated with this method is not yet large enough to provide a definitive assessment of its sensitivity and specificity.

3. Cross-Reactivity Between Cephalosporins and Penicillins and Among Cephalosporins in Subjects Allergic to Cephalosporins

The process of allergenic cross-reactivity among cephalosporins is similar to that among penicillins, i.e., recognition of the core ring structures may result in cross-reactivity with all cephalosporins, regardless of their side-chain structures. However, because the R₂, as well as the R₁ side-chain group may differ from cephalosporin to cephalosporin, the situation is more complex. Cross-reactivity may take place *via* R₁ recognition, where side-chain groups are the same (for example, cefaclor and cephalixin, cefotaxime and ceftriaxone) or similar (cefaclor and cefadroxil), or it may be influenced by R₂ recognition (cephalexin and cephradine, cephalothin and cefotaxime) (Fig. (2)) [27].

In a previously cited study [52] – which assessed 12 patients with immediate allergic reactions to different cephalosporins by means of skin tests and IgE assays with the culprit drugs and also by evaluating responses to classic penicillin reagents as well as to ampicillin and amoxicillin – 50% of the subjects reacted positively only to cephalosporins, while the others also displayed positivity to one or more penicillin determinants.

In the more recent study by our group [19], an IgE-mediated hypersensitivity was diagnosed in 70 patients out of the 76 evaluated (in 7 after retesting); in these 70 patients, we evaluated cross-reactivity with penicillins and among cephalosporins. Specifically, subjects with positive skin tests to penicillin reagents and/or responsible cephalosporins other than cephalothin, cefamandole, ceftazidime, ceftriaxone, cefuroxime and cefotaxime were also tested with the latter 6. Those positive to penicillin reagents and/or one or more of the aforesaid 6 cephalosporins were also tested with the others in this group. On the basis of skin-test and CAP-FEIA results, considered routine tests, we classified our 76 patients into 5 groups: group A (3 patients), positive only to penicillin reagents; B (17), positive to both cephalosporin and penicillin reagents; C (24), positive to more than one cephalosporin; D (21), positive only to the responsible cephalosporin; E (11), negative to skin tests and the CAP-FEIA, including 5 sepharose-RIA positive.

From this series of 76 cases, we evaluated cross-reactivity among cephalosporins in a subset of 55 patients, who had reacted against a single cephalosporin, by performing skin tests with 6 cephalosporins (cephalothin, cefamandole, ceftazidime, ceftriaxone, cefuroxime, and cefotaxime) as well as the culprit one, if the latter was not one of the 6 (personal unpublished data). A highly significant cross-reactivity was found between cefotaxime and ceftriaxone ($P = 0.0009$, odds ratio: 7.0, 95% confidence interval: 2.1-23.5), but not between these 2 cephalosporins and ceftazidime ($P = 0.6637$ and $P = 0.9017$, respectively) (Fig. (4)). This suggests an IgE recognition mainly related to identity, and not to similarity, of the R₁ side chain of the 3 molecules (Fig. (2)). On the other hand, we found no significant cross-reactivity

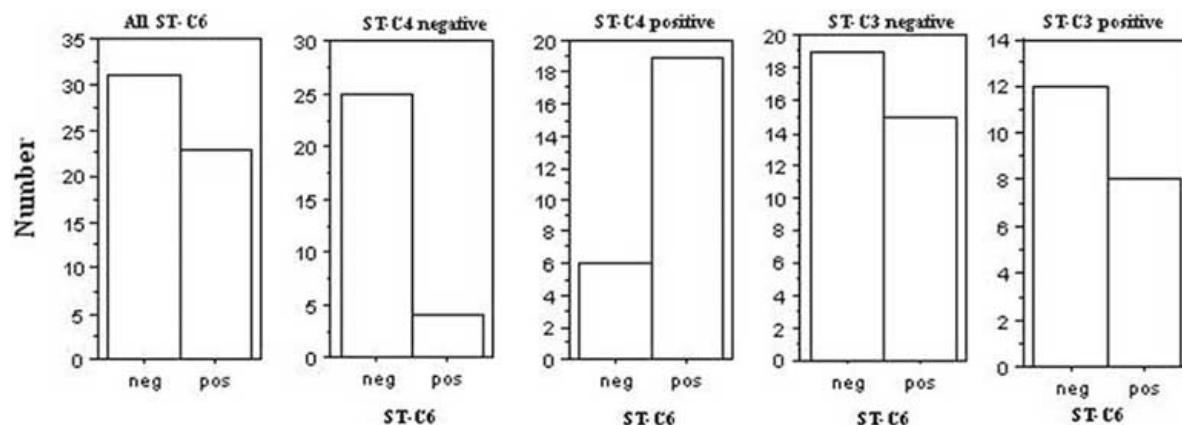


Fig. (4). Skin-test (ST) cross-reactivity among cefotaxime, ceftriaxone, and ceftazidime in 55 patients who had suffered an immediate reaction to a cephalosporin and who were prospectively recruited in Italy.*

*These patients belonged to our previously published series [19] and were tested with 6 cephalosporins (cephalothin, cefamandole, ceftazidime, ceftriaxone, cefuroxime, and cefotaxime) as well as the culprit one, if the latter was not one of the 6 (personal unpublished data).

Abbreviations: Ceftazidime (C3), Ceftriaxone (C4) and Cefotaxime (C6).

between cefotaxime and cephalothin, despite identical R_2 side chains. This suggests that cross-reactivity is more frequently related to R_1 than to R_2 side-chain recognition.

With regard to *in vitro* tests, the cefaclor sepharose-RIA produced the highest rate of positive results in the patients who had reacted to cefamandole, as well as in the patients of groups A and B. This suggests an IgE recognition mainly related to the benzyl side chain of cefaclor, which is present in benzylpenicillin as well as in cefamandole and cefaclor. Therefore, the cefaclor sepharose-RIA could be a useful tool – in addition to skin tests – for assessing cross-reactivity between penicillins and cephalosporins. For this reason, we added it systematically to the sepharose-RIA performed with the culprit cephalosporin. Using these reagents, the rate of positive detection of IgE was found to be 74.3%.

We performed sepharose-RIA with the 6 cephalosporins used in skin testing – cephalothin, cefamandole, cefuroxime, cefotaxime, ceftriaxone and ceftazidime – in a subset of 24 patients from our series [19] in order to investigate the *in vitro* cross-reactivity related to R_1 and/or R_2 similarity or identity (personal unpublished data). There were 5 (20.8%), 3 (12.5%), 9 (37.5%), 7 (29.2%), 3 (12.5%) and 8 (33.3%) positive sepharose-RIA to cephalothin, cefamandole, cefuroxime, cefotaxime, ceftriaxone and ceftazidime, respectively. We considered the sera with sepharose-RIA positivity to either ceftazidime, ceftriaxone and cefotaxime and determined the rate of positivity observed with the other 5 cephalosporins. The results, presented in Fig. (5), show a clear cross-reactivity between ceftriaxone and cefotaxime (Kruskal Wallis test, $P = 0.0005$), which corresponds to the identity of their R_1 side chains, and between these 2 cephalosporins and ceftazidime ($P = 0.0073$ and $P = 0.0276$, respectively), which corresponds to a similarity of R_1 side chains (Fig. (2)). In our study [19], therefore, cross-reactivity was observed *in vitro* among the molecules sharing either

similar or identical side chains, while in skin tests it was observed only among molecules having identical side chains. Thus, skin testing is a more specific approach than *in vitro* assays for investigating cross-reactivity among cephalosporins.

We have previously determined the binding affinity of specific IgE to small chemical compounds such as muscle relaxant drugs and radio contrast media, using a Dixon plot of hapten inhibition of IgE binding to the sepharose-RIA solid reactive phase [58]. Using this method, we found a dissociation constant (K_d) varying from μM to nM scale for muscle relaxant-IgE binding, suggesting a wide range from medium to high affinity. On the other hand, a low affinity, on the order of mM , was recorded for radio contrast media. From a mechanistic point of view, these findings suggest that a μM - nM scale range and a nM scale of concentration, respectively, of the muscle relaxants and radio contrast media assessed are needed to bind IgE (Table 1). We applied this method to determine the binding affinity of specific IgE to the culprit drug in 3 patients who had suffered an anaphylactic shock to amoxicillin, cefadroxil and ceftriaxone, respectively. The K_d was 54 nM for amoxicillin, 17 for cefadroxil, and 18 for ceftriaxone, indicating a high affinity. This suggests that a low *in situ* concentration of cephalosporin is needed to produce the IgE binding to the drug (Table 1).

4. Cross-Reactivity to Cephalosporins in Subjects with IgE-Mediated Hypersensitivity to Penicillins or Other Betalactams

The data regarding allergic cross-reactivity to cephalosporins – demonstrated by skin-test positivity to the cephalosporin concerned – in samples of more than 20 patients with immediate hypersensitivity to penicillins diagnosed on the basis of skin-test, specific-IgE-assay, and/or challenge positivity are not consistent [49, 66-70]. In fact, such cross-

reactivity varies between 0% [69] and 46% [67]. We must consider, however, that some of these studies were carried out before 1980, using first-generation cephalosporins such as cephalothin and cephaloridine, whose side chains are very similar to that of benzylpenicillin, to which most patients had

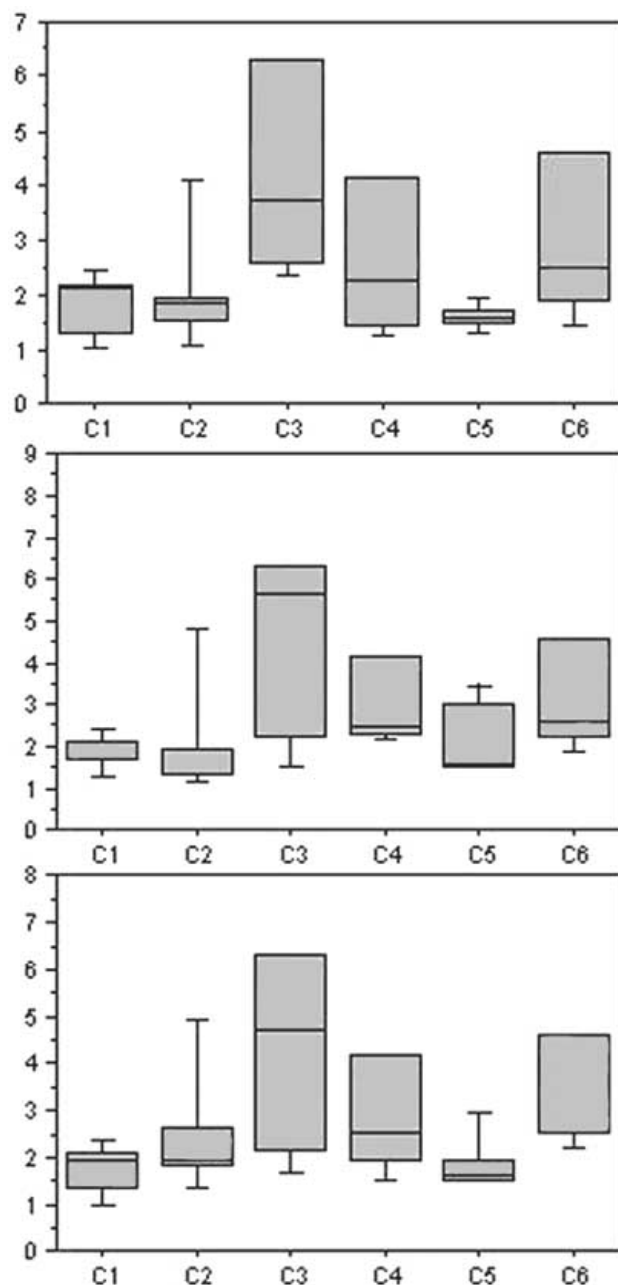


Fig. (5). *In vitro* cross-reactivity evaluated by IgE sepharose-RIA among ceftazidime (top), ceftriaxone (medium) and cefotaxime (bottom) in a subset of 24 patients from our series [19] in order to investigate the *in vitro* cross-reactivity related to R₁ and/or R₂ similarity or identity (personal unpublished data). Other cephalosporins tested were cephalothin, cefamandole and cefuroxime. Y-axis: patient vs control ratio.

Abbreviations: Cephalothin (C1), Cefamandole (C2), Ceftazidime (C3), Ceftriaxone (C4), Cefuroxime (C5) and Cefotaxime (C6).

previously reacted [66, 67]. Moreover, some early first-generation cephalosporins were contaminated with trace amounts of benzylpenicillin [71].

Even considering only more recent studies – in which most patients had previously reacted to amoxicillin and very few to benzylpenicillin – the range of cross-reactivity is between 0% [69] and 14.7% [49]. Such variability most likely depends on the fact that different cephalosporins were used to evaluate cross-reactivity. The study by Audicana *et al.* [49] showed cross-reactivity with cephalexin in 5 out of 34 subjects, and none at all with ceftazidime. The recent study by Novalbos *et al.* [69] showed a lack of allergenic cross-reactivity to 3 cephalosporins (cefazolin, cefuroxime, and ceftriaxone) among 41 patients allergic to penicillins. Such subjects, diagnosed by positive skin tests and/or provocation tests, were challenged with the aforementioned cephalosporins without any reaction. Therefore, the latter 2 studies demonstrated indirectly the importance of side-chain determinants, showing a lack of allergenic cross-reactivity to cephalosporins – such as ceftazidime, cefazolin, cefuroxime, and ceftriaxone – that do not share the same side chain with the culprit penicillin among patients allergic to penicillins [49, 69]. However, in the previously cited study by our group [70] – which evaluated 128 patients with documented IgE-mediated hypersensitivity to penicillins – the rate of cross-reactivity to the cephalosporins assessed by skin tests (cephalothin, cefamandole, cefuroxime, ceftazidime, ceftriaxone and cefotaxime) was 10.9% (14 out of 128 patients). Unlike Novalbos *et al.* [69], we found that 5 (3.9%) out of our 128 subjects presented skin-test positivity to cefuroxime, ceftriaxone, ceftazidime, or cefotaxime, which do not share the same side chain with penicillins. Our results demonstrated, therefore, that the risk of cross-reactivity is not related only to the structural similarities between the side-chain determinants of penicillins and cephalosporins [27, 54].

On the other hand, data concerning cross-reactivity between penicillins and cephalosporins may differ significantly, even considering studies that evaluated such cross-reactivity by administering cephalosporins with identical side chains to those of penicillins to which patients were sensitive. In 2 studies [68, 72], patients with immediate hypersensitivity to amoxicillin were administered cefadroxil, which shares the same side chain containing an aminogroup. The percentage of patients (8 of 21, 38.1%) who reacted to cefadroxil in the study by Miranda *et al.* [68] was higher than that (2 of 16, 12.5%) in the one by Sastre *et al.* [72]. In the former study, inhibition studies indicated that the side chain contributed significantly to inhibition.

It is difficult to determine whether some subjects develop a response to cephalosporins because of cross-reactivity with penicillins or because of coexisting sensitivities. Patients allergic to benzylpenicillin who have never been administered cephalosporins may have demonstrable antibodies specific to the benzyl side chain, indicating a cross-sensitivity [54, 73, 74]. However, there is some evidence [75] that co-existing sensitivities may occur.

Finally, as far as betalactams other than penicillins are concerned, a case of sensitization to aztreonam with cross-reactivity to ceftazidime (a third-generation cephalosporin,

Table 1. Affinity and Specificity of Drug-IgE Binding Determined by Dixon Plot

Drug	Dissociation constant (Kd)	Binding affinity	Binding specificity
NMBD	1.5 nM-6 μ M	medium-high	yes
Amoxicillin	54 nM	high	yes
Ceftriaxone	18 nM	high	yes
Cefadroxil	17 nM	high	yes
ICM	1.5 mM	low	non-specific?

NMBD = Neuro Muscular Blocking Agents.

ICM = Iodinated Contrast Media.

Table 2. Rate of Cephalosporin Adverse Reactions in Penicillin Allergic-Patients According to Whether or Not They Had Been Previously Assessed with Cephalosporin Skin Tests (Adapted from [19])

	Number of subjects	Skin testing		Challenge		
		Penicillin reagents	Cephalosporin(s)	Administered cephalosporin(s)	Administration route(s)	Number of reactions (%)
Assem and Vickers [67]	3	BP, BPO	NP	CR	IM	3 (100)
Solley <i>et al.</i> [77]	27	BP, AM, ME	NP	NS	NS	0
Saxon <i>et al.</i> [3]	62	NS	NP	NS	NS	1 (1.6)
Blanca <i>et al.</i> [78]	16	BPO, BP, AM, AX	NP	CM	IM	2 (10.5)
Shepherd and Burton [79]	9	BPO, BP	NP	NS	NS	0
Macy [80]	28	BPO, BP, AX, PN, PC	NP	NS	Oral	1 (3.6)
Total	145					7 (4.8)
Warrington <i>et al.</i> [89]	3	BPO, MDM, AM, CO, ME	CL	NS	NS	0
Audicana <i>et al.</i> [49]	29	BPO, MDM, AM, AX	CH, CZ	CH, CZ	CH: Oral, CZ: IV	0
Novalbos <i>et al.</i> [69]	41	BPO, MDM, BP, AX	CA, CU, CT	CA, CU, CT	IM	0
Romano <i>et al.</i> [70]	101	BPO, MDM, BP, AM, AX, PP	CL, CM, CZ, CU, CT, CX	CU, CT	CU: Oral, CT: IM	0
Total	174					0

BP = Benzylpenicillin; BPO = Benzylpenicilloyl; MDM = Minor determinant mixture; PN = Penilloate; PC = Penicilloate; PP = Piperacillin; ME = Methicillin; CO = Cloxacillin; AM = Ampicillin; AX = Amoxicillin; CL = Cephalothin; CM = Cefamandole; CZ = Ceftazidime; CU = Cefuroxime; CT = Ceftriaxone; CX = Cefotaxime; CA = Cefazolin; CH = Cephalixin; CR = Cephaloridine; NP = Not performed; NS = Not specified; IM = Intramuscular; IV = Intravenous.

which shares the same side-chain with aztreonam) diagnosed by skin tests has been reported [76].

5. Administration of Cephalosporins in Patients with IgE-Mediated Hypersensitivity to Penicillins

In patients with documented IgE-mediated hypersensitivity to penicillins, the data regarding a sensitization to cephalosporins – diagnosed on the basis of positive responses to challenges carried out without performing prophylactic skin tests with the cephalosporin concerned – are variable [3, 67, 77-80]; a recent review estimated the rate of positivity at 4.4% [5]. Therefore, a certain confusion still exists concerning the administration of cephalosporins to

patients sensitive to penicillins. Such confusion may cause cross-reactivity to be either under- or overestimated. In both cases, there may be negative consequences, such as fatal anaphylactic reactions in penicillin-allergic patients to whom cephalosporins had been administered [81], or decreased effectiveness and increased antimicrobial resistance due to excessive use of non-beta-lactam antibiotics [5].

In any case, there is still no consensus on the management of patients with histories of penicillin allergy who require a cephalosporin [5, 20, 82-84]. In the United States, it is usually recommended that the patient be skin tested to determine whether he or she has IgE antibodies to penicillins [82, 85, 86]: cephalosporins are given to patients with nega-

tive skin tests, while subjects with positive tests are either not treated with them [5, 86] or – if an alternate drug cannot be used – are desensitized [82, 85]. In the management of such patients, prophylactic skin tests with cephalosporins are not routinely performed [5, 20, 82-86], although some allergists carry out skin tests for both penicillin reagents and the cephalosporin in question before giving cephalosporins to a patient [87, 88].

However, the previously cited study by our group [70], as well as previous ones assessing subjects with IgE-mediated hypersensitivity to penicillins [49, 69, 89], demonstrated that negative results in skin testing with cephalosporins are a useful indicator of tolerability. There were no adverse reactions to cephalosporins in a total of 174 challenged patients with negative skin tests to these betalactams: our 101 patients [70] plus the 73 from the previous smaller series [49, 69, 89]. By contrast, 7 of the 145 (4.8%) penicillin-allergic subjects from all the aforesaid studies [3, 67, 77-80] – who were not administered cephalosporin skin tests – suffered adverse reactions (Table 2). The difference in adverse reactions to cephalosporins between the two groups is statistically significant when considering either only our 101 patients ($P = 0.0251$) or the sum of the 174 patients with negative cephalosporin skin tests ($P = 0.0034$). Such difference in adverse reactions to cephalosporins between the 2 groups supports the advisability of performing skin tests with cephalosporins before their administration to penicillin-allergic patients.

In this study [70], skin-test positivity to the minor determinant mixture was a significant predictor for the risk of a positive skin test to at least one cephalosporin, with an odds ratio estimated at 3.90 (95% confidence interval: 1.17-13.40). Therefore, our data provided substantial clinical support to the conclusion of the Joint Task Force on Practice Parameters [82], which advises avoidance of cephalosporins in penicillin skin-test positive patients and suggests the use of an alternative antibiotic. In patients who especially require cephalosporin treatment, the clinician should perform prophylactic skin tests, and, in case of negative results, a graded challenge with the cephalosporin concerned.

CONCLUSIONS

Skin tests and specific IgE assays, specifically sepharose-RIAs, are sensitive tools in diagnosing immediate hypersensitivity to cephalosporins, but their sensitivity appears to decrease with time.

In selected cases, displaying negative results in both skin tests and IgE assays, cephalosporin hypersensitivity can be diagnosed by a graded challenge with the implicated drug.

Cephalosporin IgE-mediated hypersensitivity may be a temporary condition; therefore, it is advisable to repeat allergologic exams in subjects with negative initial work-ups, including challenges.

ABBREVIATIONS

CAP-FEIA = CAP System FEIA

FEIA = Fluoro Enzymatic Immune Assay

Kd = Dissociation constant
mM = Millimolar
 μ M = Micromolar
nM = Nanomolar
RIA = Radioimmunoassay

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