

Immediate Hypersensitivity Reactions to β -Lactam Antibiotics

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In this review the immune reactions to β -lactam antibiotics are discussed. The discussion is limited to the penicillin and cephalosporin families because there is little data available on the potential of the newer nonpenicillin, noncephalosporin β -lactam antibiotics to cause adverse immune reactions. However, the discussion of cross-reactivity between penicillins and cephalosporins gives some idea as to what to expect with these newer agents. This discussion dwells almost exclusively on IgE-mediated (immediate) reactions because these reactions are the most dangerous, are purported to cross-react between β -lactam antibiotics, and because concern about the occurrence of these reactions frequently prevents administration of the drug. Furthermore, we can expect the availability of prospective testing for IgE-mediated reactions in the near future.

Haptens as Antigens

Before allergic reactions to drugs in general or to β -lactam antibiotics specifically are discussed, the difference between a hapten and a complete antigen must be understood. Complete antigens are molecules of sufficient size to independently elicit an immune response, e.g., the antigens in bee venom or horse serum. Haptens are low-molecular-weight compounds that are too small to stimulate the immune system on their own [1]. Haptens must bind to a carrier molecule, usually a normal host protein, in order to be immunogenic. Most antibiotics, including the β -lactams, fall into the category of haptens. Either the parent drug or drug metabolites are capable of binding to tissue proteins with subsequent stimulation of an immune response. Although the various metabolites may be structurally similar, the antibody response may be limited to a specific metabolite.

In this discussion the term penicillin will be used in a broad generic sense to mean β -lactam antibiotics containing a β -lactam ring and a thiazolidine ring. When the unaltered penicillin molecule

is referred to as a specific determinant, the abbreviation PCN is used.

Most of the penicillin bound to tissue protein ($\sim 95\%$) is in the penicilloyl form (figure 1) [2, 3]. The penicilloyl determinant is called the major determinant; this does not mean it is of greater importance or that allergic reactions to penicilloyl are of greater severity. A number of other penicillin derivatives, including native penicillin itself, are bound to tissue ($\sim 5\%$ of total); these other metabolites are collectively called the minor determinants [4, 5]. By studying patients with immediate reactions to penicillin, Levine and colleagues [6] identified the penicillin products to which these patients had skin-sensitizing (IgE) antibodies. IgE antibodies were found that were directed toward the major determinant, penicilloyl (PO) and the three minor determinants, penicillin (PCN), penicilloate (PC) and penilloate (PI). Others have confirmed these results [7]. The relative importance of each of these forms in immediate hypersensitivity reactions, as well as the effect of various side-chain substitutions in the specificity of the immune response, are discussed below.

There is a vague notion that contaminants in penicillin preparations were the cause of many allergic reactions seen in the past. These contaminants consist of high-molecular-weight forms of penicillin, probably in the PO form, bound to protein materials from the fermentation/production procedure [8]. The amount of these compounds in present-day materials is small compared with that in drug preparations of the past. How-

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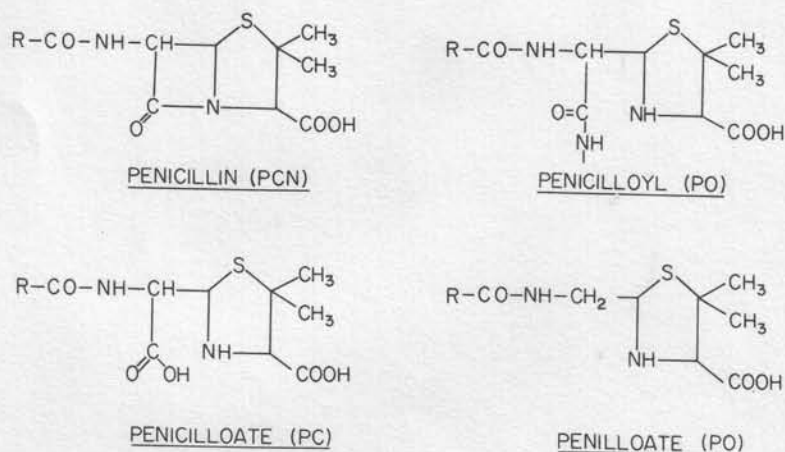


Figure 1. Structures of important penicillin determinants.

ever, Ahlstedt and Kristofferson [9-11] have evidence that even small quantities of these materials may increase the immunogenicity of penicillin. It is doubtful that complete removal of all such protein-bound penicillin contaminants would completely abolish the problem as penicillin haptens could still bind to host proteins *in vivo*.

Allergy to Penicillin

Penicillin is one of the least toxic antibiotics known, because it affects the cell walls of prokaryotic organisms and has virtually no effect on eukaryotic cells [12]. Doses of ≥ 80 g/day have been tolerated by humans without adverse effect. However, penicillin derivatives show a high level of immunogenicity in humans. It is reported that 1%-8% of courses of treatment with penicillin drugs result in some adverse effect or allergic reaction [13, 14]. About two (0.2%) of each 10,000 courses of treatment result in an immediate serious reaction while approximately one (0.001%) of 100,000 courses of treatment results in a fatal reaction [14].

The penicillins are found ubiquitously in the environment, probably as a result of agricultural, industrial, and medical contamination [14, 15]. Various studies report that from 70% to >90% of people who deny any medicinal exposure to penicillin have low, but detectable, levels of IgM antibodies primarily against the PO determinant [6]. About 10% of newborns have similar IgM antibodies [16], which presumably were synthesized *in utero* since IgM, in contrast to IgG, does not cross the placenta [17]. Thus, it is not surprising to en-

counter patients who deny prior history of exposure to the drug and yet experience an allergic reaction to their first documented penicillin therapy. Therefore, it can be assumed that all persons are at potential risk since anyone can produce an immune response to penicillin. Although early reports suggested that individuals with atopy (a hereditary predisposition to allergic rhinitis, asthma, or atopic dermatitis) were at increased risk of a penicillin reaction, later studies have not agreed [18, 19].

Classification of Allergies

It is useful to classify reactions to penicillin by their immunologic mechanisms because the immune basis for these reactions provides a rational basis for diagnostic maneuvers. The various types of drug reactions and the immune mechanism associated with each are summarized in table 1. A complete discussion of the various clinical syndromes is beyond the scope of this article, but comprehensive reviews are available [2, 20, 21].

Type I reactions. Type I reactions result from the presence of preformed IgE antibody to antigenic determinants of penicillin. Production of IgE antibody results from prior antigenic stimulation by the drug or by a cross-reacting compound. The prior exposure may have been completely unknown and uneventful, and the IgE response may persist for years after its initiation, although it tends to diminish over time [14, 22]. The IgE binds to tissue mast cells; upon reintroduction of the antigen (penicillin determinant), the IgE on the mast cells is cross linked, a factor resulting in

Table 1. Classification of reactions to penicillin.

Type of reaction and immune mechanism	Clinical syndrome
I. IgE antibody	Anaphylaxis Laryngeal edema Early onset of urticaria (<72 hr)
II. Cytotoxic antibody	Hemolytic anemia
III. Antigen-antibody complexes	Serum sickness
IV. Delayed hypersensitivity	Contact dermatitis
Idiopathic	Maculopapular drug eruptions Nephritis Late onset of urticaria Fever Eosinophilia

the release of various mast-cell mediators, i.e., histamine, eosinophilic chemotactic factor, bradykinin activator, the slow-reacting substance of anaphylaxis (leukotriene C and D), and others. Thus, the clinical picture of anaphylaxis results.

Fear of IgE-mediated reactions to penicillin is common among physicians. It is again emphasized that only ~0.02% of courses of penicillin treatment are associated with a serious IgE-mediated allergic response. Also, the history of "allergy" to penicillin is often invalid. A survey at UCLA showed that 16% of inpatients have a history of allergy to penicillin, but only 8% of those with a positive history had positive skin tests for penicillin allergy. Without prospective, reliable skin testing, most patients with a positive history receive other antibiotics that may be less effective, potentially more toxic, and more expensive. The number of true IgE-positive persons within a cohort of patients who say they are allergic to penicillin varies from 5% to 30%, depending primarily on the criteria used to classify the patients as having a positive history of allergy [23-27].

Type II reactions. The hemolytic anemia associated with high doses of penicillin results from the production of high titers of IgG antibody to the PO determinant [28]. During treatment, the drug is passively absorbed to the membrane of red blood cells and thereby focuses antibody to this site (type II reaction). This IgG then activates complement, which leads to accelerated clearance of the coated red cells in the reticuloendothelial system. Thus, this reaction requires non-IgE, anti-

penicillin antibodies. A complete discussion is found in the article by Bang et al. elsewhere in this issue [29].

Type III reactions. One of the leading present-day causes of the serum sickness syndrome (type III reaction) is an allergic reaction to penicillin. Serum sickness results from the formation of immune complexes between IgM and IgG antibodies and soluble penicillin antigens—probably PO. These complexes lodge preferentially in sites such as skin and kidney, activate complement, and produce the clinical picture that we recognize as serum sickness [30]. In contrast with type II reactions, the site of injury is not directed by the antibody but is a reflection of the nonspecific lodging of the immune complexes. Again, the presence of IgG and IgM antipenicillin antibodies is necessary, but not sufficient, for the production of penicillin-induced serum sickness. Other factors are the amount and route of administration of antigen, the affinity and class of antibody present, and the size and solubility of the complexes formed.

Type IV reactions. Contact dermatitis in response to penicillins, similar to poison ivy reactions, is an example of a type IV reaction. A type IV reaction requires thymus-derived lymphocytes that react with drug that is bound to host tissues. There is no involvement of humoral immunity. The topical use of penicillin has been abandoned and hence, contact dermatitis is rarely seen. However, occasional cases are encountered in pharmacists, nurses, and other individuals who have occasion to handle penicillins. The diagnosis is confirmed by assessing delayed hypersensitivity with patch tests.

Idiopathic reactions. One category of adverse reactions to penicillin is idiopathic. Although various abnormal immune responses are reported [31], no specific immune mechanism has been identified. The most common allergic-type reaction to a β -lactam antibiotic is a maculopapular drug eruption and fever. This idiopathic reaction occurs in 1%-4% of treatment courses. It is important to recognize that pretreatment skin tests for IgE antibody (or other immune parameters relating to penicillin) do not provide evidence for or against the development of any of the idiopathic reactions listed. It is necessary to emphasize to both physicians and patients that skin testing

prognosticates only the likelihood of immediate type I (IgE-mediated) reactions. An unusual idiopathic (and probably nonimmune) reaction to penicillins is the pseudo-anaphylactic reaction observed after im [32, 33] or inadvertant iv administration of procaine penicillin [34]. These reactions are caused by a combination of toxic and embolic phenomena and should not be confused with true IgE-mediated anaphylaxis.

Skin Testing

The presence of IgE antibody, and only IgE antibody, to penicillin antigenic determinants is detected by epicutaneous (prick or scratch) and intracutaneous (intradermal) skin testing techniques. Detailed procedure for this form of testing can be found in standard texts [35]. Results from skin testing are available after 30 min, a factor that is helpful clinically when rapid decisions must be made. The radioallergosorbant, or RAST, test is the *in vitro* analogue of immediate hypersensitivity skin tests. RAST tests require at ≥ 24 hr to perform, and reproducible coupling of all the minor determinants (PCN, PC, PI) in correct immunogenic form to solid-phase supports has not been accomplished.

Retrospective studies. A number of studies have assessed the association of immediate penicillin reactions with the results of skin tests that used the major determinant, PO, and the minor determinants, PC, PI, and PCN. Circulating IgG and IgM anti-PO antibodies have also been studied. Retrospective analyses showed that 8% of patients who had recently finished a course of penicillin therapy had skin tests that were positive to PO, while only one of 103 patients had a skin test positive to minor determinant antigens [6]. Three percent of patients with no recent history of penicillin therapy had skin tests positive to the major determinant. All of these patients also had IgM, or IgM and IgG, antibodies to PO. In contrast, all patients with anaphylactic, accelerated, or urticarial reactions had skin tests that were positive to PO and/or minor determinants as well as IgM and IgM/IgG antibodies to the PO. All those with anaphylactic reactions had IgE directed against the minor determinants. Forty percent of patients with accelerated reactions had positive skin tests with a minor determinant. Only

9% of patients who developed urticaria reacted to the minor determinants. Yet, 10% of the patients with a positive skin test had had no reaction upon exposure to drug.

Prospective studies. More recent prospective studies reveal a number of interesting findings [23, 24]. As clinicians have long suspected, the history of so-called penicillin allergy was an extremely unreliable indicator of positive skin tests, as only one in 10 of such patients had positive skin tests. Patients who were skin-test negative to both major and minor determinants essentially had no risk of anaphylactic reactions. This experience has been confirmed in other prospective studies [25-27], as well as in our experience at UCLA with >300 patients. Thus, skin-test negative patients appear to be appropriate candidates for treatment with penicillin. Our usual procedure in these history-positive, skin-test negative patients is to administer full therapeutic doses of penicillin, although some investigators have suggested giving a prior test dose of 8,000 units, or 5 mg.

There is little prospective data on patients with positive skin tests who were subsequently given penicillin. In the studies of Levine and Zolov [23, 24], no patients were given penicillin who had positive skin tests to both the major and minor antigen preparations. Eight patients with isolated positive skin tests to the major antigens and three with isolated positive tests to the minor antigens were treated with penicillin. Five of the eight patients with positive tests to major antigen had accelerated urticarial reactions. Two of the patients with positive tests to minor antigen had accelerated flush reactions, and the other one had immediate urticaria. These reactions occurred in spite of a gradual desensitization protocol of administration of penicillin and antihistamine. This high rate of reactions to penicillin in skin-test positive patients has been confirmed in other studies [26, 36].

Thus, the retrospective data indicated that 10% of patients with a positive skin test had had no clinical reaction to penicillin. On the other hand, in prospective studies, >50% of patients with a positive skin test prior to penicillin therapy subsequently reacted to the drug. One potential explanation is that the skin-test-positive, treatment-negative patients in the retrospective study comprise $\leq 40\%$ of those people in the prospective

study who were skin-test-positive but treatment-negative. This interpretation would require that >10% of patients given penicillin have an IgE-mediated reaction. Hence, this explanation is untenable. A more likely explanation is that some skin-test-positive patients who were discovered retrospectively represent individuals who made IgE antipenicillin antibodies in response to recently completed courses of penicillin treatment. Indeed, the development of antipenicillin IgE during penicillin therapy has been documented [23]. Similarly, individuals who are not allergic to grass can produce a short-lived, IgE-anti-grass-antibody response when deliberately immunized [37]. Most of the antibody responses to penicillin probably do not persist for long periods of time [22]. This limited life-span of the IgE response probably accounts for the fact that positive skin-test reactions are most common in patients who have recently received penicillin [14, 26]. Those patients in whom IgE antibody production to penicillin determinants persists are the individuals recognized in prospective studies as those at risk.

In summary, the prospective determination of production of IgE antibody to penicillin antigen is a reliable predictor of IgE-mediated reactions. The fact that a patient has previously received penicillin without incident does not guarantee the safety of a subsequent course, especially if it occurs soon after the previous treatment. Furthermore, patients who have a history of prior reactions to penicillin who are found to be skin test-negative and receive the drug without problem, should not be told they no longer have to worry about penicillin allergy. This group of individuals is likely to contain a significant number of patients who previously had made IgE to penicillin, but in whom the level of this IgE had fallen to a nondetectable level. However, these people may synthesize IgE antibody following clinical administration of penicillin, or unrecognized environmental exposure, and they may be at risk in the future. Such patients should receive repeated skin testing prior to any subsequent administration of penicillin derivatives. They should not be reassured that they can receive penicillins in the future without precaution. Indeed, in the past two years we have observed three patients with positive histories who were skin-test negative, received penicillin without incident, and then were found to be skin-test posi-

tive after retesting prior to a subsequently proposed course of penicillin therapy.

Retrospective and prospective studies indicate that patients with positive skin tests to PO are at >50% risk of an IgE-mediated reaction. The reactions are generally accelerated or urticarial reactions although anaphylaxis has occurred. Presently, we do not recommend using penicillins in this group of patients because of the high risk involved and the availability of alternative drugs. Patients with positive skin tests to minor determinants have a >75% chance of experiencing an anaphylactic reaction and, therefore, should not receive treatment if this is at all avoidable. If the decision is to treat with penicillin a patient with a positive skin test to a major or minor determinant, therapy should take place in an intensive care unit with the capability of treating anaphylaxis.

Desensitization. If penicillin must be given, it is customary to prescribe a schedule of gradually increasing dosage of penicillin, iv or im, following premedication with antihistamines and steroids [24]. This procedure is likened to the production of controlled anaphylaxis with gradual depletion of all IgE antibody to penicillin. There is only one preliminary, unconfirmed, retrospective study of the efficacy of oral desensitization [38]. After any desensitization regimen, patients are considered at risk and are retested prior to readministration of the drug. The mechanism of inhibition by desensitization is probably gradual antigenic saturation of both free and mast cell-bound IgE antipenicillin antibody. Once administration of antigen is stopped, free antibody will likely reappear with subsequent binding to mast cells and clinical re-sensitization.

Who to skin test? Only history-positive patients are usually tested because of time and financial considerations. When appropriate penicillin antigens become readily available to the general medical community, it may be appropriate to prospectively skin test all patients, regardless of their history of allergy. One study tested all patients who were to receive penicillin in an inpatient service [25]. The authors found that three history-negative individuals were skin test-positive to PO, and they were not treated. No IgE-mediated reactions occurred during the study, a frequency that was significantly less than that during a prior period on the same service [25]. The use of such pro-

spective testing for all hospital inpatients who are about to receive penicillin, as well as for outpatients in settings such as emergency departments and venereal disease clinics, may ultimately prove cost effective.

Patients should receive skin tests within 48 hr of potential use of penicillin. Patients who do not require penicillin in that time frame should not be tested as it is misleading to assure such patients that they will not be sensitive at some future time.

Penicillin antigens for skin testing. The battery

of penicillin antigens in use at UCLA is shown in figure 2. It is important to include negative (diluent) and positive (histamine) controls to ensure reliable interpretation. The recommended antigens are PO, PCN, PC, and PI [7, 22, 24]. Cross-reactivity occurs between the PC and PI antigens, but rarely do patients show a positive test to only one of the two. Of all the people who have reactions, 90% react to PO or PCN, 70% respond to PO, and the remaining 10% react only to PC or PI. Thus, only 90% of persons with potential re-

**UCLA AFFILIATED CLINICAL IMMUNOLOGY-ALLERGY
PENICILLIN STUDY**

Hospital: UCLA _____ HGH _____ Wadsworth _____
 Patients's name: _____ Age: _____ Sex: Male _____ Female _____
 Hospital number: _____
 Reason to give penicillin: _____

History of previous reaction to penicillin: No _____ Yes _____ (explain) _____

Skin tests:

Date: _____ Performed by: _____

	Prick*		I.D.*	
	Erythema	Wheal	Erythema	Wheal
1. Penicilloyl-polylysine (PO)				
2. Penicillin (PCN)				
3. Penicilloate (PC)				
4. Penilloate (PI)				
B. Buffer control				
H. Histamine control				

Penicillin given: Yes _____ No _____

Dose _____

Route _____

Reactions _____

* Measure largest diameter in mm.

Figure 2. Protocol form for penicillin immediate hypersensitivity skin testing. I.D. = intradermal.

actions are found by testing with PO and PCN. Similarly, the American Academy of Allergy skin tested with only PCN and PO and found that 3% of skin test-negative patients subsequently had an allergic reaction [26]. A report from the Mayo Clinic described 10% fewer reactions when only PCN and PO were used [36]. Juhlin et al. [7] also showed that 17% of potential reactions are missed by testing with PO and PCN alone.

These workers confirmed that all positive reactions were predicted by testing with PO, PCN, PC, and PI, while a variety of other penicillin determinants did not further increase the predictability of the test. Thus, the use of PO, PCN, PC, and PI is recommended while the use of only PO and PCN may produce 10%–20% false-negative tests.

The recommended concentrations of determinants— 10^{-2} M for PCN, PC, and PI; and 10^{-6} M for PO—must be used for skin testing. A concentration that is too high risks serious reactions in sensitive individuals [21], while suboptimal amounts will increase the incidence of false-negative results. For patients with a history of life-threatening reactions, a preliminary prick (intraepidermal) test may be performed with a 100-fold dilution of the antigens. These skin test reagents (PO, PCN, PI, PC) are presently under evaluation in a large, prospective, multicenter trial conducted by the National Institutes of Allergy and Infectious Diseases. Hopefully, these studies will provide data sufficient to permit the licensing and commercial availability of these reagents to the medical community in the near future.

Cross-Reactivity

Other Penicillins. What is the predictive value of skin testing with penicillin determinants described for patients for whom a semisynthetic penicillin has been prescribed? This subject was recently reviewed in detail by Dewdney [8]. Antibodies to the different penicillin derivatives of the IgG and IgE classes are known to have different binding affinities and specificities. For most penicillins, the differences are modest, and skin-test cross-reactivity is expected. However, the penicillinase-resistant semisynthetic penicillin (PRSP), which contains an isoxazole group (e.g., oxacillin and cloxacillin) displays decreased cross-reactivity in vitro. In a study of skin testing in 253 patients,

the use of penicillin determinants prepared from PRSP were of no greater value than standard penicillin antigens [27]. Our center has observed no IgE reactions in 120 patients who had negative reactions to skin tests that used standard penicillin G antigens, had a positive history of allergy to PRSP, and subsequently received a PRSP. Further clinical data regarding the predictive value of skin tests in such patients should be forthcoming from the ongoing multicenter trial mentioned earlier.

Cross-reactivity of cephalosporins. The cephalosporins are β -lactam antibiotics that differ in structure from the penicillins by the substitution of a dihydrothiazine ring for the thiazolidine ring of penicillins (figure 3). In a series of thousands of patients, the incidence of putatively immune or allergic adverse reactions was 1%–3% [39]. These large cohort studies are deficient in that most of the diagnoses of an allergic reaction are historical and have not been critically proved. Nonetheless, it is the impression of this author that the overall incidence of adverse immune reactions to cephalosporins is lower than that with penicillins.

IgE-mediated (type I) reactions do occur in response to cephalosporins. This problem and its relationship to penicillin hypersensitivity is discussed in detail below. Antibody-mediated cytotoxic injury (type II) also occurs and gives rise to hemolytic anemia. This occurrence is a rare complication and does not parallel the documented, relatively high incidence of positive Coombs's tests in patients receiving cephalosporins [39]. Illnesses like serum sickness (type III) or contact dermatitis (type IV) caused by cephalosporins, if they occur, must be very rare. The majority of potential hypersensitivity reactions to cephalosporins are maculopapular skin eruptions, fever, and eosinophilia.

Of primary concern is the potential for allergic cross-reactivity in patients who have previously reacted to penicillin. In the mid 1960s a few case reports described patients who had had previous immediate reactions to penicillin and then had anaphylactoid reactions following initial doses of cephalothin [40, 41]. Subsequent in vivo and in vitro animal studies showed parallel increases in levels of induced antibodies to PO and cephalosporin antigens. The induced antibodies were reactive with, or were absorbed by, either antigen [42, 43]. The data demonstrate cross-reactivity be-

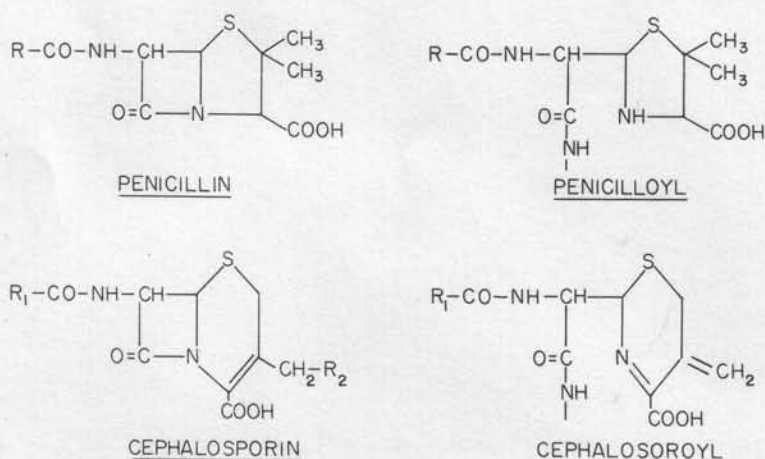


Figure 3. Structures of penicillin and cephalosporin nuclei and penicilloyl and cephalosporoyl derivatives.

tween induced, non-IgE antibodies to penicillin and cephalosporin determinants. However, these findings have not elucidated the clinical relevance of penicillin/cephalosporin allergic cross-reactivity.

These studies, and all subsequent studies, suffer from a lack of knowledge about the immunogenic nature of the cephalosporin determinants. Thus, while a cephalosporoyl moiety may occur in vitro (figure 3), its stability and importance remain to be determined. Furthermore, data from studies on animals suggest that the immune response to cephalosporins is more dependent on the side-chain substituents than is the case for penicillins [8, 44]. Thus, cephalosporins bearing a side chain similar to benzyl penicillin may be more likely to cross-react with penicillin. In laboratory studies of non-IgE antibody, cephalosporins bearing a side chain that is very different from that of benzyl penicillin show less cross-reactivity [45–47]. Whether determinants similar to PI and PC are produced by metabolic breakdown of cephalosporins is unknown but doubtful, as the reaction of cephalosporins with proteins is likely to produce molecules that are dissimilar to the penicillin determinants [8]. The possibility that native cephalosporin could function as antigen and cross-react with the PCN determinant was suggested in a study with one patient [48].

Patients receiving cephalosporins experience elevations in levels of hemagglutinating antibodies that react with penicillins, and, conversely, patients receiving penicillin experience increases in levels of anticephalosporin antibodies [49]. These results from studies with patients are consistent

with the cross-reactivity to PO and some determinant form of cephalothin for non-IgE antibodies found in animals [50–52]. However, non-IgE antibodies appear to be of little clinical import [53].

Confusion about cross-reactivity of penicillin and cephalosporins has occurred because retrospective and prospective clinical studies have assessed patients' reactions to cephalosporins on the basis of on a history of allergy to penicillin. For example, in one study, 8.2% of patients with a history of penicillin allergy had some form of adverse reaction, while 1.7% of history-negative patients had an adverse reaction [54]. Recall that <20% of such history-positive patients probably have IgE hypersensitivity to penicillin. Without the ability to prospectively detect patients with IgE antibody to penicillin and without the ability to distinguish true IgE immunologic reactions from idiopathic or functional problems in patients given cephalosporins, it is impossible to claim increased immune or IgE-mediated reactions to cephalosporins in true penicillin-allergic (IgE) patients [39, 54]. It is known that patients with a history of drug allergy constitute a highly selected group of reactors, which will certainly skew any study. The study by Smith et al. [55] supports this point, as he found a three-fold increase in reported reactions to penicillin in patients with prior reactions to drugs.

Only a few studies have used skin tests as evidence of IgE cross-reactivity or cross-sensitization between penicillins and cephalosporins. All of the studies using cephalosporin skin tests suffer from poor definitions of antigen(s) used and lack of

knowledge about dosage of antigens. There is no accepted form of cephalosporin skin testing, and such testing should be reserved for investigational use only.

Thoburn et al. [56] described seven patients who had adverse reactions to cephalosporin, five of whom gave a history of penicillin allergy. These authors state that three-fourths of the patients who reacted had positive PO skin tests, but, in fact, only three of seven did. Furthermore, only four of the seven had reactions which would be classified as IgE-mediated. Of these, only three received skin tests; one reacted to PO, PCN, and cephalothin, while one each only reacted with PO or cephalothin. Girard [57] reported a study of 36 selected patients with skin tests highly positive to PO and PCN who received cephalosporin skin tests. At least two had had immediate reactions to cephalosporin also. Thirty-nine percent had positive skin tests to cephalosporin at a concentration (1 mg/ml) that is not thought to induce non-specific false-positive results. The author could not explain the high rate of positive tests, as only two of 23 of the penicillin-positive patients treated with cephalosporins developed allergic reactions. Pedersen-Bjergaard [58] demonstrated that eight of 13 sera known to contain IgE to penicillin determinants transferred skin sensitivity to individuals subsequently given 1 g of cephalothin iv. However, this author states that the cephalothin may have contained minute quantities of penicillin. Although he argues that the amount of penicillin present would be too small to account for the findings, the rate of cross-reaction was so high (61%) that the results are difficult to explain otherwise. Furthermore, the amount of penicillin in the cephalosporin was never actually quantitated. Unfortunately, similar studies have not been done subsequently; the passive transfer test has been largely abandoned because of the risk of hepatitis involved. Investigations using in vitro antigen-specific IgE binding (RAST) and the inhibition of binding by various drugs have not been reported. Such studies potentially could elucidate this matter of antigenic cross-reactivity between IgE to penicillin determinants and cephalosporins.

Likely to give useful information at a clinical level would be the prospective study of patients with positive skin tests to IgE antipenicillin who are subsequently treated with a cephalosporin.

Such studies would identify the patients possessing IgE antipenicillin who may be at high risk from cephalosporins and then assess the outcome when such patients are treated with a cephalosporin.

Solley et al. [36] reported on 24 patients who were skin test-positive to one or more penicillin determinants and subsequently received a cephalosporin. None of these patients had an immediate-type allergic reaction. Warrington et al. [27] also treated with cephalothin three patients who had positive skin tests to the major and minor penicillin determinants, and none of the patients had any reaction. Likewise, we have now treated with a cephalosporin 10 patients with skin tests positive to penicillin at UCLA and observed no allergic reactions. A breakdown of results of skin tests of our patients and the drug administered are given in table 2. Thus, in these small prospective series, the presence of IgE to penicillin determinants did not appear predictive of IgE-mediated reactions to challenge with cephalosporin. Clearly, this phenomenon should be studied in more patients. If clinical cross-reactivity between cephalosporins and penicillins occurs at the IgE level, it is not frequent (statistically less than one in 20). This fact has been appreciated by many physicians who have continued to use cephalosporins as the drug of choice in patients with histories of adverse reactions to penicillin. The present indication is that cephalosporins are likely to be well tolerated even

Table 2. Results of skin tests in 10 patients with one or more positive test results who had no allergic reaction when treated with a cephalosporin.

Patient no.	Results of skin tests with indicated penicillin determinant*				Cephalosporin received
	PO	PCN	PC	PI	
1	+	+	-	-	Cephalothin
2	-	+	+	+	Cephalexin
3	+	-	-	-	Cefazolin
4	-	+	+	-	Cefoxitin
5	+	-	-	-	Cefamandole
6	+	-	-	-	Cefazolin
7	+	-	-	-	Cephalothin
8	-	+	-	-	Cefoxitin
9	-	-	+	+	Cefazolin
10	+	-	-	-	Cefazolin

* PO = penicilloyl; PCN = penicillin; PC = penicilloate; PI = penilloate; + = positive; and - = negative.

in the patient with documented IgE antibody to penicillin.

The future availability of a battery of penicillin skin-test reagents should allow physicians to identify history-positive patients with a false-positive history for IgE allergy to penicillin and hence allow therapy with penicillins or cephalosporins. Furthermore, the use of such reagents will help resolve the question of whether the presence of IgE antibody to penicillin determinants is associated with an increased incidence of immediate hypersensitivity reactions when the patient subsequently receives cephalosporins.

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Discussion

QUESTION. I have heard one could safely continue penicillin therapy after an anaphylactic reaction to penicillin. Would you comment?

DR. ANDREW SAXON. The $t_{1/2}$ for IgE is three days, so that you would probably be safe for two to three days; however, I would not advise this procedure.