

# Cross-Reactivity and Tolerability of Cephalosporins in Patients with Immediate Hypersensitivity to Penicillins

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**Background:** In patients with documented IgE-mediated hypersensitivity to penicillins, data on sensitization to cephalosporins vary. Administering cephalosporins to such patients is often deferred because of the risk for cross-reactivity.

**Objective:** To assess the cross-reactivity with cephalosporins and its potential determinants in patients with documented penicillin allergy.

**Design:** Prospective study in patients without clinical indications for cephalosporin treatment.

**Setting:** Italy.

**Patients:** 128 consecutive patients who sustained anaphylactic shock ( $n = 81$ ) or urticaria ( $n = 47$ ) and had positive results on skin tests for at least 1 of the penicillin reagents tested.

**Measurements:** All patients were skin tested with cephalothin, cefamandole, cefuroxime, ceftazidime, ceftriaxone, and cefotaxime. Patients with negative results for the last 4 cephalosporins were challenged with cefuroxime axetil and ceftriaxone.

**Results:** 14 patients (10.9% [95% CI, 6.1% to 17.7%]) had

positive results on skin tests for cephalosporins, mostly for cephalothin or cefamandole. Skin test results for the minor determinant mixture were positive in 10 of 14 patients (71.4%) with cross-reactivity and 44 of 114 patients (38.6%) without cross-reactivity (odds ratio, 3.90 [CI, 1.17 to 13.40];  $P = 0.0189$ ). All 101 patients with negative results on skin tests for cefuroxime, ceftazidime, ceftriaxone, and cefotaxime tolerated cefuroxime axetil and ceftriaxone (tolerability rate, 100% [CI, 96.4% to 100%]).

**Limitations:** Challenges were not followed by full therapeutic courses. Twenty-two patients declined challenges; positive responses in those patients would have decreased the tolerability rate to 82.1% (CI, 74.2% to 88.4%).

**Conclusions:** These data confirm the advisability of avoiding cephalosporin treatment in patients with positive results on skin tests for penicillin. In patients who especially require cephalosporin treatment, we recommend skin tests with cephalosporins before assessing the tolerability of the cephalosporin with a graded challenge.

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Penicillins and cephalosporins are the most widely used antibiotics for treating common infections (1, 2). The former are the most common causes of drug-induced, IgE-mediated hypersensitivity and the most studied so far (3–13). Like penicillin, cephalosporin may cause allergic reactions, especially IgE-mediated reactions (6, 9). They are 2 classes of  $\beta$ -lactam antibiotics with differences in both their core and side-chain structures.

In patients with documented IgE-mediated hypersensitivity to penicillins, the data on sensitization to cephalosporins—diagnosed on the basis of positive responses to challenges carried out without performing prophylactic skin tests with the cephalosporin—vary (5, 14–18). The most recent review estimated a 4.4% rate of positivity (9).

Therefore, certain confusion exists about administering cephalosporins in patients who are allergic to penicillins, which may lead to either under- or overestimating the risk involved. In both cases, negative consequences may result. Recently, Pumphrey and Davis (19) reported that 6 of 12 fatal anaphylactic reactions to antibiotics occurred after the first dose of cephalosporin treatment. In 3 of the 6 reactions, patients were known to be allergic to amoxicillin and 1 patient was allergic to benzylpenicillin. On the other hand, because of the fear of cross-reactivity, the most common therapeutic approach to patients who are allergic to penicillin is to select antibiotics that do not contain a  $\beta$ -lactam ring, such as macrolides, quinolones, trimetho-

prim-sulfamethoxazole, or vancomycin (20–22). However, reduced effectiveness, increased antimicrobial resistance (particularly to vancomycin), and higher costs are major drawbacks of this choice (9).

In any case, there is still no consensus on the management of patients with histories of penicillin allergy who require a cephalosporin (9, 12, 21–23). Skin tests are usually recommended to determine whether a patient has IgE antibodies to penicillins (11, 23, 24). Cephalosporins are given to patients with negative results on skin tests, while patients with positive results either are not treated with cephalosporin (9, 24) or—if an alternate drug cannot be used—are desensitized (11, 23).

Histories and penicillin skin test results do not reliably predict the probability of allergic reactions to cephalosporins in patients with histories of penicillin allergy (11).

We conducted this prospective study to evaluate the use of cephalosporins in patients with documented penicillin allergy who especially require cephalosporin treatment. A large group of well-characterized, penicillin-allergic patients was evaluated by skin tests with different cephalosporins to assess the cross-reactivity and its potential determinants. Moreover, patients with negative results on cephalosporin skin tests were challenged to ascertain whether negative results could reliably indicate cephalosporin tolerability.

## METHODS

### Patient Selection

Patients were recruited prospectively from a large outpatient population with a history of immediate reactions to at least 1 penicillin. This sample was evaluated between January 1995 and June 2003 in the allergy units of Complesso Integrato Columbus, Rome, Italy, and Oasi Maria Santissima, Troina, Italy. The inclusion criterion required positive results on skin tests for 1 or more penicillin reagents (penicilloyl-polylysine, minor determinant mixture, and benzylpenicillin), 1 or more semi-synthetic penicillins (ampicillin, amoxicillin, and piperacillin), or both. An indication for cephalosporin treatment was not an inclusion criterion. We evaluated sensitization to cephalosporins by using skin tests with first-generation (cephalothin), second-generation (cefamandole and cefuroxime), and third-generation (ceftazidime, ceftriaxone, and cefotaxime) cephalosporins. In case of negative results for cefuroxime, ceftriaxone, ceftazidime, or cefotaxime, the former 2 cephalosporins were administered to consenting patients. The exclusion criteria were pregnancy; use of  $\beta$ -blockers; and severe cardiovascular, renal, or respiratory compromise. Before the study, all patients received information about possible risks for skin and challenge tests, and each patient or the parents of patients younger than 18 years of age gave written informed consent. The respective institutional review boards approved the protocol.

### Skin Tests

Because 12 different reagents were assessed, the skin testing was performed on 3 different days to reduce the risk for systemic reactions, which were reported in a similar protocol (25).

On the first day, prick and intradermal tests were carried out by using penicilloyl-polylysine (Allergopharma, Reinbek, Germany, distributed by Merck, Sharpe & Dohme SpA, Milan, Italy), minor determinant mixture (benzylpenicillin and sodium benzylpenicilloate [Allergopharma]), and benzylpenicillin (Pharmacia, Milan, Italy). The final concentrations were  $5 \times 10^{-5}$  mmol/L,  $2 \times 10^{-2}$  mmol/L, and 10 000 IU/mL (benzylpenicillin was diluted in normal saline), respectively. A 1:10 dilution in normal saline of the penicilloyl-polylysine final solution was initially used. When results were negative, testing was repeated with the undiluted solution. A 1:1000 dilution, 1:10 dilution in normal saline, and undiluted solution of minor determinant mixture were used. Benzylpenicillin was administered at concentrations of 0.1, 100, and 10 000 IU/mL.

Ampicillin (Amplital, Pharmacia), amoxicillin (Smith-Kline Beecham, Milan, Italy), and piperacillin (Avocin, Wyeth-Lederle SpA, Aprilia, Italy) were all used on the second day at concentrations of 1 mg/mL and 20 mg/mL after dilution in normal saline.

Cephalothin (Keflin, Lilly, Sesto Fiorentino, Italy), cefamandole (Mandokef, Lilly), cefuroxime (Curoxim, Glaxo Wellcome, Verona, Italy), ceftazidime (Glazidim, Glaxo

### Context

The usefulness of cephalosporin skin tests is not well-defined in patients with a history of penicillin allergy.

### Contribution

These investigators performed cephalosporin skin tests of 128 patients with a history of documented penicillin allergy. About 11% of patients had positive skin test results. Patients with negative skin test results tolerated subsequent challenge doses of cephalosporin without an allergic reaction.

### Implications

Since 10% of patients with documented penicillin allergy also had positive results on skin tests for cephalosporin, physicians should avoid using cephalosporins in such patients unless they have tested these patients for cephalosporin allergy.

—The Editors

Wellcome), cefotaxime (Zariviz, Aventis, Milan), and ceftriaxone (Rocefin, Roche, Milan, Italy) at a concentration of 2 mg/mL in 0.9% sodium chloride were used on the third day.

All of these reagents—prepared fresh with the intravenous form under sterile conditions daily—were initially tested on volar forearm skin by the prick method. Reactions were considered positive when a wheal larger than 3 mm in diameter with surrounding erythema was present 20 minutes later. When prick test results were negative, 0.02 mL of the reagent solution was injected intradermally on volar forearm skin. Readings were made 20 minutes after injections. Results were considered positive when wheals larger than 5 mm accompanied by erythema developed. Positive controls for prick tests were done with histamine at 10 mg/mL. Normal saline was used as a negative control. The concentration used for cephalosporins was nonirritant in a control group of 40 healthy patients, as we previously described (26).

### In Vitro Tests

Assays (UniCAP specific IgE, Pharmacia, Milan, Italy) were performed, according to the manufacturer's instructions, for specific IgE antibodies to penicilloyl G, penicilloyl V, ampicilloyl, and amoxicilloyl. A positive result (that is, detectable specific IgE antibodies) was defined as a value of 0.35 kIU/L or greater. Blood samples were obtained when patients were evaluated and sera were kept at  $-20^{\circ}\text{C}$  until assayed.

### Cephalosporin Test Dosing

Challenges with cefuroxime axetil (500 mg orally) and ceftriaxone (1 g intramuscularly) were also administered (each on a different day) in patients with negative results on skin testing for cefuroxime, ceftriaxone, ceftazidime, or

cefotaxime. We administered an initial dose of one hundredth of the therapeutic dose. In patients with negative results, we administered a dose of one tenth of the therapeutic dose 1 hour later. If the result was again negative, we administered a full dose after another hour.

Each patient was carefully monitored during test dosing, and complete equipment for cardiopulmonary resuscitation was immediately available.

Patients with positive results on skin tests for cefuroxime and ceftriaxone were not challenged because such positivity indicates sensitization. Those with positive results for cefotaxime or ceftazidime were also not challenged because our previous observations (27) indicated a risk for cross-reactions related to structural similarities in the aforesaid cephalosporins.

### Statistical Analysis

Data were prospectively collected and analyzed by using Statview 5 software for Windows (SAS Institute, Inc., Cary, North Carolina).

Our goal was to assess the cross-reactivity with cephalosporins and its potential determinants in patients with documented penicillin allergy. The frequency of positive skin test results is given as a percentage and exact 95% CI (28). We compared the group of patients who were cross-reactive with those who were not. Age is reported as the means ( $\pm$ SD), and the time interval between the last adverse reaction and testing was reported as the median and

range. These continuous variables were compared by using a Mann–Whitney U-test. Categorical data are given as numbers of cases and percentages, and they were compared by using a chi-square test. A *P* value of 0.05 or less indicates statistical significance. The odds ratio of categorical determinants was determined only in determinants that corresponded to at least 10 outcomes per independent variable and were found to be statistically significantly associated with cross-reactivity.

### Role of the Funding Source

The Ministry for University, Scientific and Technological Research (MURST), Rome, Italy, and Ministry for National Education, Research and Technology (MENRT), Paris, France, provided 60% and 40% of funding, respectively. The MURST funding was used for performing the skin testing and challenges, and the MENRT funding was used for the biological and statistical analyses. The funding sources had no role in the decision to submit the manuscript for publication.

### RESULTS

We examined 128 adults (90 women, 38 men; mean age [ $\pm$ SD], 45.3  $\pm$  16.7 years) with histories of immediate reactions to penicillins. Our work-up was performed with intervals ranging from 1 to 420 months (median, 7 months)

Table 1. Characteristics of Study Group according to Challenge Test Assessment

| Clinical Characteristics                   | Challenge Test            |                        |                          |                      |
|--|---------------------------|------------------------|--------------------------|----------------------|
|  | All Patients<br>(n = 128) | Performed<br>(n = 101) | Not Performed<br>(n = 5) | Declined<br>(n = 22) |
| Mean age $\pm$ SD, y                       | 45.5 $\pm$ 16.7           | 45.2 $\pm$ 16.8        | 46.4 $\pm$ 18.9          | 46.7 $\pm$ 16.2      |
| Men, n (%)                                 | 38 (29.7)                 | 31 (26.0)              | 2 (40.0)                 | 5 (22.7)             |
| Median time interval (range), mo*          | 7 (2–47)                  | 7 (2–36)               | 2 (1–7)                  | 27 (2–132)           |
| Family history, n (%)                      | 42 (32.8)                 | 36 (35.6)              | 0                        | 6 (27.3)             |
| Personal history, n (%)                    | 28 (21.8)                 | 22 (21.7)              | 1 (20.0)                 | 5 (22.7)             |
| Culprit penicillins, n (%)                 |                           |                        |                          |                      |
| Aminopenicillins                           | 103 (80.5)                | 80 (79.3)              | 5 (100.0)                | 18 (81.8)            |
| Benzylpenicillin                           | 12 (9.4)                  | 9 (80.9)               | 0                        | 3 (13.6)             |
| Benzathine-penicillin                      | 7 (5.5)                   | 6 (5.9)                | 0                        | 1 (4.5)              |
| Piperacillin                               | 6 (4.7)                   | 6 (5.9)                | 0                        | 0                    |
| Manifestations, n (%)                      |                           |                        |                          |                      |
| Urticaria                                  | 24 (18.3)                 | 19 (18.9)              | 2 (40.0)                 | 3 (13.6)             |
| Angioedema or urticaria                    | 23 (7.9)                  | 20 (19.8)              | 0                        | 3 (13.6)             |
| Anaphylactic shock                         | 81 (63.3)                 | 62 (61.4)              | 3 (60.0)                 | 16 (72.7)            |
| Positive skin test results, n (%)          |                           |                        |                          |                      |
| Penicilloyl-polylysine                     | 45 (35.2)                 | 37 (36.6)              | 3 (60.0)                 | 5 (22.7)             |
| Minor determinant mixture                  | 54 (42.2)                 | 40 (39.6)              | 3 (60.0)                 | 11 (50.0)            |
| Benzylpenicillin                           | 56 (43.7)                 | 42 (41.5)              | 2 (40.0)                 | 12 (54.5)            |
| Ampicillin                                 | 73 (57.0)                 | 55 (54.4)              | 3 (60.0)                 | 15 (68.2)            |
| Amoxicillin                                | 72 (56.2)                 | 55 (54.4)              | 3 (60.0)                 | 14 (63.6)            |
| Piperacillin                               | 32 (25.0)                 | 26 (25.7)              | 2 (40.0)                 | 4 (18.2)             |
| Positive specific IgE assay results, n (%) |                           |                        |                          |                      |
| Penicilloyl G                              | 42 (32.8)                 | 33 (32.6)              | 3 (60.0)                 | 6 (27.3)             |
| Penicilloyl V                              | 43 (33.6)                 | 34 (33.6)              | 3 (60.0)                 | 6 (27.3)             |
| Ampicilloyl                                | 41 (32.0)                 | 32 (31.7)              | 3 (60.0)                 | 6 (27.3)             |
| Amoxicilloyl†                              | 32 (25.0)                 | 26 (25.7)              | 3 (60.0)                 | 3 (13.6)             |

\* Time elapsed between last adverse reaction and current allergologic examination.

† *P* = 0.0244 between patients who did not undergo challenges and those who declined challenges.

**Table 2. Summary of Results of Cephalosporin Skin Tests and Challenges**

| Skin Test Results                     | Eligible for Challenge |                    | Not Eligible for Challenge | Total |
|---------------------------------------|------------------------|--------------------|----------------------------|-------|
|                                       | Received Challenge     | Declined Challenge |                            |       |
|                                       | ←-----n----->          |                    |                            |       |
| Positive for at least 1 cephalosporin | 7                      | 2                  | 5                          | 14    |
| Negative for all cephalosporins       | 94                     | 20                 | 0                          | 114   |

after the most recent adverse reaction. No case met any exclusion criterion.

A total of 103 patients reported adverse reactions to aminopenicillins (amoxicillin, ampicillin, and bacampicillin), 12 patients reported adverse reactions to benzylpenicillin, 7 patients reported adverse reactions to benzathine penicillin, and 6 patients reported adverse reactions to piperacillin. **Table 1** presents the clinical manifestations, classified according to their severity as anaphylactic shock and urticaria with or without angioedema. All patients had positive results on skin tests for at least 1 of the penicillin reagents tested. **Table 2** summarizes the results of cephalosporin skin testing. Fourteen of 128 patients (10.9% [95% CI, 6.1% to 17.7%]) displayed positive responses to skin tests for cephalosporins. Nine patients had positive results for cephalothin, cefamandole, or both, while 5 patients presented different patterns of skin test positivity.

Fifty-one of the patients who underwent in vitro assays (39.8% [CI, 31.3% to 48.3%]) had positive results. All but 6 patients had specific IgE antibodies to penicilloyl G, penicilloyl V, or both.

Among the 128 patients, 114 patients had negative results on skin tests for all the cephalosporins tested. Of these, 94 patients agreed to challenges with cefuroxime axetil and ceftriaxone and 20 patients declined challenges. Nine of the 128 patients had positive results on skin tests for cephalothin, cefamandole, or both. Of these, 7 patients accepted challenges and 2 patients declined challenges. The remaining 5 patients were not challenged because they had positive results for at least 1 of the following: cefuroxime, ceftazidime, ceftriaxone, or cefotaxime (**Table 2**).

All 101 patients who underwent challenges tolerated oral cefuroxime axetil and intramuscular ceftriaxone. We found no statistically significant difference in sex, age, time interval between the last adverse reaction and allergologic examination, clinical manifestations of penicillin allergy, and skin tests and specific IgE assays for penicillin reagents between patients who underwent challenge tests and those who either declined challenges or were not challenged because of cephalosporin skin test positivity. A higher rate of positive results on IgE assays for amoxicillin was among patients with positive results on cephalosporin skin tests who were not challenged, as compared with those who declined challenges (**Table 1**). In addition, the frequency of these characteristics did not statistically significantly differ between patients with either positive or negative results on skin tests for cephalosporins; the exception was skin test

positivity to the minor determinant mixture, which occurred in 10 of 14 (71.4% [CI, 47.7% to 95.1%]) patients and 44 of 114 (38.6% [CI, 29.7% to 47.5%]) patients with and without cross-reactivity, respectively ( $P = 0.0189$ ) (**Table 3**). The estimated odds ratio of skin test positivity to the minor determinant mixture for cross-reacting to at least 1 cephalosporin was 3.90 (CI, 1.17 to 13.40).

## DISCUSSION

Administering cephalosporins to penicillin-allergic patients who might benefit from this treatment is often deferred because of the fear of cross-reactivity (9). In the management of such patients, prophylactic skin tests with cephalosporins are not routinely performed (9, 11, 12, 21–24), although some allergists perform skin tests for both penicillin and the cephalosporin in question before giving cephalosporin to a patient (29, 30). Two important reasons

**Table 3. Characteristics of Study Group according to Results of Cephalosporin Skin Tests**

| Clinical Characteristics                   | Cross-Reactivity |              |
|--|------------------|--------------|
|  | No (n = 114)     | Yes (n = 14) |
| Mean age ± SD, y                           | 45.5 ± 17.1      | 43.1 ± 13.8  |
| Men, n (%)                                 | 32 (28.1)        | 6 (42.8)     |
| Median time interval (range), mo*          | 7 (2–36)         | 8 (2–120)    |
| Family history, n (%)                      | 38 (33.3)        | 4 (28.6)     |
| Personal history, n (%)                    | 24 (21.1)        | 4 (28.6)     |
| Culprit penicillins, n (%)                 |                  |              |
| Aminopenicillins                           | 91 (79.8)        | 12 (85.7)    |
| Benzylpenicillin                           | 10 (8.7)         | 2 (14.3)     |
| Benzathine-penicillin                      | 7 (6.1)          | 0            |
| Piperacillin                               | 6 (5.3)          | 0            |
| Manifestations, n (%)                      |                  |              |
| Urticaria                                  | 22 (19.3)        | 2 (14.3)     |
| Angioedema or urticaria                    | 21 (18.4)        | 2 (14.3)     |
| Anaphylactic shock                         | 71 (62.3)        | 10 (71.4)    |
| Positive skin test results, n (%)          |                  |              |
| Penicilloyl-polylysine                     | 38 (33.3)        | 7 (50.0)     |
| Minor determinant mixture†                 | 44 (38.6)        | 10 (71.4)    |
| Benzylpenicillin                           | 49 (42.9)        | 7 (50.0)     |
| Ampicillin                                 | 65 (57.1)        | 8 (57.1)     |
| Amoxicillin                                | 62 (54.4)        | 10 (71.4)    |
| Piperacillin                               | 26 (28.8)        | 6 (42.8)     |
| Positive specific IgE assay results, n (%) |                  |              |
| Penicilloyl G                              | 38 (33.3)        | 4 (28.6)     |
| Penicilloyl V                              | 38 (33.3)        | 5 (35.7)     |
| Ampicilloyl                                | 37 (32.6)        | 4 (28.6)     |
| Amoxicilloyl                               | 28 (28.7)        | 4 (28.6)     |

\* Time elapsed between last adverse reaction and current allergologic examination.  
†  $P = 0.0189$ .

**Table 4. Rate of Adverse Reactions to Cephalosporin in Penicillin-Allergic Patients according to Previous Assessment with Cephalosporin Skin Tests\***

| Study (Reference)        | Patients, n | Skin Testing  |  | Challenge                           |  |                  |
|--------------------------|-------------|---|--|-------------------------------------|--|------------------|
|                          |             | Penicillin Reagents   | Cephalosporin(s)   | Administered Cephalosporin(s)       | Administration Route                         | Reactions, n (%) |
| Assem and Vickers (14)   | 3           | Benzylpenicillin, benzylpenicilloyl   | NP   | Cephaloridine                       | Intramuscular                                | 3 (100)          |
| Solley et al. (15)       | 27          | Benzylpenicillin, ampicillin, methicillin   | NP   | NS                                  | NS   | 0                |
| Saxon et al. (5)         | 62          | NS  | NP   | NS                                  | NS   | 1 (1.6)          |
| Blanca et al. (16)       | 16          | Benzylpenicilloyl, benzylpenicillin, ampicillin, amoxicillin  | NP   | Cefamandole                         | Intramuscular                                | 2 (10.5)         |
| Shepherd and Burton (17) | 9           | Benzylpenicilloyl, benzylpenicillin   | NP   | NS                                  | NS   | 0                |
| Macy (18)                | 28          | Benzylpenicilloyl, benzylpenicillin, amoxicillin, penicilloate, penicilloate                          | NP   | NS                                  | Oral   | 1 (3.6)          |
| Warrington et al. (43)   | 3           | Benzylpenicilloyl, minor determinant mixture, ampicillin, cloxacillin, methicillin                    | Cephalothin  | NS                                  | NS   | 0                |
| Audicana et al. (34)     | 29          | Benzylpenicilloyl, minor determinant mixture, ampicillin, amoxicillin                                 | Cephalexin, ceftazidime  | Cephalexin, ceftazidime             | Cephalexin: oral; ceftazidime: intravenous   | 0                |
| Novalbos et al. (44)     | 41          | Benzylpenicilloyl, minor determinant mixture, benzylpenicillin, amoxicillin                           | Cefazoline, cefuroxime, ceftriaxone  | Cefazoline, cefuroxime, ceftriaxone | Intramuscular                                | 0                |
| Present study            | 101         | Benzylpenicilloyl, minor determinant mixture, benzylpenicillin, ampicillin, amoxicillin, piperacillin | Cephalothin, cefamandole, ceftazidime, cefuroxime, ceftriaxone, cefotaxime | Cefuroxime, ceftriaxone             | Cefuroxime: oral; ceftriaxone: intramuscular | 0                |

\* NP = not performed; NS = not specified.

for not performing cephalosporin skin tests are the lack of standardization of such tests and some researchers' belief that cephalosporin skin testing is experimental because of unknown hapten determinants (9, 12, 23, 31, 32).

In our experience, however, cephalosporin skin tests at a concentration of 2 mg/mL were reliable and effective for diagnosing immediate hypersensitivity to these  $\beta$ -lactams (26, 27, 33). For this reason, we do not perform challenges with cephalosporins in patients with positive results; authors who did so in single patients elicited immediate urticarial or anaphylactic reactions to the responsible cephalosporins (34–37).

Among our patients, 10.9% displayed skin test positivity to cephalosporins. Positivity to the minor determinant mixture was a statistically significant predictor because the risk for having a positive skin test to at least 1 cephalosporin was increased 4-fold. Nine of 14 patients had positive results on skin tests for cefamandole, cephalothin, or both, which have side-chain structures similar to those of penicillins (8, 38). Specifically, cefamandole, benzylpenicillin, and ampicillin have similar side-chain structures, which are benzyl derivatives (38). Five of 14 patients had skin test positivity to at least 1 of the other cephalosporins tested, which have side-chain structures different from those of penicillins. Our results demonstrate, therefore, that the risk for cross-reactivity is not only related to the structural similarities between the side-chain determinants of penicillins and cephalosporins (8, 38).

The question of whether some patients developed a response to cephalosporins because of cross-reactivity with penicillins or because of coexisting sensitivities is difficult to answer. Patients who are allergic to benzylpenicillin and never received cephalosporins may have demonstrable antibodies specific for the latter, which indicates cross-sensitivity (38–40). However, some evidence (41) suggests that coexisting sensitivities may occur. Such sensitivities may be related to a propensity to several antibiotic reactions. A recent study by Strom and colleagues (42) suggested that the association between hypersensitivity reactions to sulfonamide antibiotics and subsequent allergic reactions to sulfonamide nonantibiotics was due to a predisposition to allergic reactions rather than to cross-reactivity with sulfonamide-based drugs.

In the present study, as in previous studies assessing patients who are allergic to penicillins (34, 43, 44), negative results on skin testing for cephalosporins seem to indicate tolerability (Table 4). No adverse reaction to cephalosporins occurred in patients with negative results on cephalosporin skin tests from any of the earlier, smaller studies (34, 43, 44) or our 101 patients, while adverse reactions occurred in patients who did not undergo cephalosporin skin tests from 4 of the 6 previously mentioned studies (5, 14–18). Specifically, the rate of adverse reactions to cephalosporin in the largest study was 1.6% (5) (Table 4). Since we challenged patients with cefuroxime and ceftriaxone, the reliability of cephalosporin skin tests

applies to only these 2 compounds and not to the other 4 cephalosporins skin-tested. Moreover, because we studied these patients for research purposes (rather than because they had a clinical indication for cephalosporin treatment), challenges were not followed by a full therapeutic course. Another important limitation of our study was that 22 patients declined to be challenged. We have compared the characteristics of challenged patients with those of patients who declined to be challenged (Table 1). We found no statistically significant differences and therefore think that the possibility of bias in our results is limited. Ignoring the patients who declined challenge suggests that the rate of cephalosporin tolerability was 100% (CI, 96.4% to 100.0%) (101 of 101 patients challenged). However, the potential effect of these patients on the final estimate of cross-reactivity should be evaluated. For this purpose, we considered various scenarios based on hypothetical results of challenge tests in the 22 patients who declined to be challenged. If 50% of patients who declined had positive results on challenges, the cephalosporin tolerability rate would be 91.6% (CI, 84.6% to 95.5%) (112 of 123 patients). In another scenario, if all 22 patients had positive results on challenges, the rate of cephalosporin tolerability would decrease to 82.1% (CI, 74.2% to 88.4%). Further studies are needed before a definitive conclusion can be drawn.

Finally, our data provide substantial clinical support to the conclusion of the Joint Task Force on Practice Parameters (23), which advises physicians to avoid giving cephalosporins to patients with positive results on penicillin skin tests and suggests using an alternative antibiotic. Taking into account the aforesaid practice measures and the results of our study, the clinician faced with a patient with a documented penicillin allergy and a compelling need for a cephalosporin (cefuroxime or ceftriaxone) has the following 3 clinical options:

1. **Desensitize** without cephalosporin skin testing. *Pros:* This is a careful way to administer antibiotic and is supported by practice measures (23). *Cons:* 1) Brief intensive care unit admission increases resource use; 2) reaching the full strength antibiotic dose is delayed 3.5 to 4 hours (presumably an alternative antibiotic would be used in the interim) (45); and 3) patient keeps label of “cephalosporin allergy.”

2. **Graded challenge** to cephalosporin without cephalosporin skin testing. *Pros:* 1) This approach is safer than administering full dose immediately because a less severe reaction may occur with a smaller dose of cephalosporin; 2) desensitization is not needed in intensive care unit; and 3) reaching the full dose is delayed 2 (instead of 4) hours. *Cons:* 1) There is a 4.4% reaction rate (based on recent review data [9]); 2) there is a **medical–legal risk** if the patient reacts, as practice measures state that “If the (penicillin) skin test is positive, there may be an increased risk of a reaction if the cephalosporin is given and desensitization with the cephalosporin should be performed” (23); 3) during the 2-hour delay in reaching the full dose, presum-

ably an alternative antibiotic may be used (45); and 4) patient keeps label of “cephalosporin allergy.”

3. **Skin test** with cefuroxime or ceftriaxone. If skin test result is negative, proceed to give cefuroxime or ceftriaxone with a graded challenge. *Pros:* 1) None of our 101 patients tested had a reaction; 2) desensitization is not needed in intensive care unit; 3) reaching the full dose is delayed 2 (instead of 4) hours; and 4) a negative result helps establish that a patient may not be allergic to cephalosporin, which can be confirmed later if repeated cephalosporin skin test results are negative (46). *Cons:* 1) There is a medical–legal risk if a reaction occurs in a patient with a negative result on a cephalosporin skin test, considering the practice measures statement (23); and 2) during the 2-hour delay in reaching the full dose, presumably an alternative antibiotic may be used (45).

We believe that the positive considerations of the third clinical option outweigh the negative ones. Even considering the disadvantage of the 2-hour delay, we still recommend a graded challenge until enough patients have been studied, especially in light of some data showing that penicillin skin testing may have suboptimal sensitivity (47).

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