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Clinical Reviews

# THE USE OF CEPHALOSPORINS IN PENICILLIN-ALLERGIC PATIENTS: A LITERATURE REVIEW

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☐ **Abstract—Background: The practice of avoiding cephalosporin administration to penicillin-allergic patients persists despite the low rate of cross reactions between both groups of antibiotics. Objective: The purpose of this literature review is to evaluate the published evidence regarding the commonly held belief that patients with a history of an allergic reaction to penicillin have a significantly increased risk of an allergic reaction to cephalosporins. Materials and Methods: Articles were identified through a computerized search of MEDLINE from 1950 to the present using the search terms "penicillin$," "cephalosporin$," "allerg$," "hypersensitivity," and "cross-react$." All articles were reviewed, and additional sources cited in them were added to the literature review. Results: Penicillins have a cross allergy with first-generation cephalosporins (odds ratio 4.8; confidence interval 3.7–6.2) and a negligible cross allergy with second-generation cephalosporins (odds ratio 1.1; confidence interval 0.6–2.1). Laboratory and cohort studies confirm that the R1 side chain is responsible for this cross reactivity. Overall cross reactivity between penicillins and cephalosporins is lower than previously reported, though there is a strong association between amoxicillin and ampicillin with first- and second-generation cephalosporins that share a similar R1 side chain. Conclusions: Although a myth persists that approximately 10% of patients with a history of penicillin allergy will have an allergic reaction if given a cephalosporin, the overall cross-reactivity rate is approximately 1% when using first-generation cephalosporins or cephalosporins with similar R1 side chains. However, a single study reported the prevalence of cross reactivity with cefadroxil as high as 27%. For penicillin-allergic patients, the use of third- or fourth-generation cephalosporins or cephalosporins with dissimilar side chains than the offending penicillin carries a negligible risk of cross allergy.** 

☐ **Keywords—penicillin; cephalosporin; allergic reaction**

## INTRODUCTION

Classic teaching is that patients with a history of an allergy to penicillin have a 10% risk of an adverse reaction if they are given a cephalosporin (1,2). Early studies in the 1960s and 1970s reported cross-reactivity rates of 8–18% (3,4). Articles published by Petz and Dash during this period are the main source of the pervasive belief in the 10% risk theory (5,6). The notion that such high cross reactivity exists translates to clinical practice as the complete avoidance of cephalosporins in penicillin-allergic patients, even when a cephalosporin is indicated as first-line treatment.

When treating a penicillin-allergic patient with an infection for which a cephalosporin is first-line treatment, it is necessary to consider the risks and benefits of using a cephalosporin as well as of avoiding the drug.

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Avoidance may lead to administration of an antibiotic that is less effective or associated with a greater risk for development of pathogen resistance and side effects. Understanding the true risk of adverse events resulting from cephalosporin use in penicillin-allergic patients is critical to providing the highest quality of care.

In this article, we review published information on the cross reactivity of penicillin and cephalosporins to determine if classic teachings are justified.

## MATERIALS AND METHODS

A literature search of MEDLINE (from 1950 to the present) was performed and limited to studies published in English. The search terms "penicillin$," "cephalosporin$," "allerg$," "hypersensitivity," and "cross-react$" were used ("$" indicates truncation, allowing for various endings). The terms were combined in the following search algorithm: "Penicillin$" AND "Cephalosporin$" AND ("Allerg$ as keyword" OR "Hypersensitivity, immediate or Drug hypersensitivity or Hypersensitivity, delayed or Hypersensitivity as subject heading or Hypersensitivity as keyword" OR "Cross reactions as subject heading OR cross react$ as keyword"). The titles and abstracts of the articles were screened, and articles determined to be appropriate for this review, based on their suspected relevance to the clinical question, were collected.

The search yielded 406 articles (Figure 1). Their abstracts and titles were assessed and reviewed by three of the authors. Fifty-five articles were deemed relevant to this review. To be selected, articles needed to specifically address the cross reactivity of cephalosporins in patients with a history of a penicillin allergy or, in laboratory studies, the cross reactivity of cephalosporins with penicillin antibodies. Examination of the reference lists led us to 12 additional articles, giving a total of 67. The set included two meta-analyses, 14 cohort studies (11 prospective and 3 retrospective), two surveys, and nine in vitro studies—a total of 27 articles that were included in this review (Table 1). The remaining 40 articles (reviews, letters to the editor, and background chemistry reports) were used as reference material but were not deemed applicable to the clinical question.

The 27 articles were evaluated for their level of evidence and methodology by at least two of the authors, using the literature review guidelines published by the American Academy of Emergency Medicine (Tables 2, 3). If there was disagreement in the scoring, a third author reviewed the article. The major articles are summarized in Table 4.

## RESULTS

Laboratory studies performed in the 1960s and 1970s demonstrated immunologic cross reactivity between

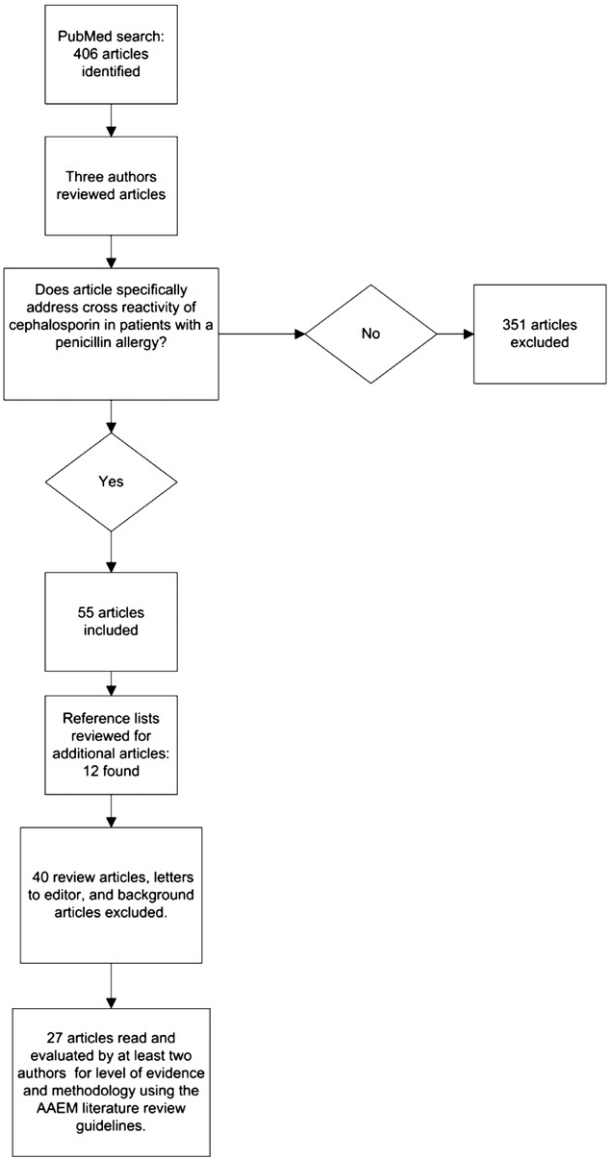



**Figure 1. Process for article selection. AAEM, American Academy of Emergency Medicine.**

penicillins and cephalosporins, specifically to the R1 side chain off the β-lactam ring (7–10). These studies show very little cross reactivity between the β-lactam rings themselves (reaction to the β-lactam rings was one of the original explanations for the link between penicillin and cephalosporin allergies). More recent laboratory studies and several cohort studies confirm the role of the R1 side chain in the cross reactivity (11– 17). Patients with an allergy to a specific cephalosporin also demonstrate cross reactivity to penicillin and other cephalosporins, as evidenced by an elevated immunoglobulin E (IgE) response when challenged (18).

Assem and Vickers challenged 24 penicillin-allergic patients with cephaloridine. Three (12.5%) of them had an adverse reaction (7). This study may be flawed in

**Table 1. List of Articles Reviewed**

| Authors, Year of Publication, Reference Number | Type | Grade | Ranking |
|---|---|---|---|
| Pichichero & Casey, 2007 (2) | Meta-analysis | A | Outstanding |
| Anne & Reisman, 1995 (29) | Meta-analysis | A | Good |
| Antunez et al., 2006 (43) | Cohort | C | Adequate |
| Atanaskovic-Markovic et al., 2005 (44) | Cohort | C | Poor |
| Romano et al., 2004 (21) | Cohort | C | Adequate |
| Novalbos et al., 2001 (22) | Cohort | C | Good |
| Romano et al., 2000 (18) | Cohort | C | Adequate |
| Miranda et al., 1996 (17) | Cohort | C | Adequate |
| Audicana et al., 1994 (13) | Cohort | C | Good |
| Blanca et al., 1989 (14) | Cohort | C | Good |
| Beam & Spooner, 1984 (23) | Cohort | C | Good |
| Solensky et al., 2002 (24) | Cohort | C | Good |
| Thoburn et al., 1966 (3) | Cohort | C | Poor |
| Park et al., 2006 (45) | Cohort | C | Good |
| Daulat et al., 2004 (26) | Retro cohort | D | Poor |
| Goodman et al., 2001 (27) | Retro cohort | D | Adequate |
| Apter et al., 2006 (28) | Retro cohort | D | Adequate–Poor |
| Fonacier et al., 2005 (20) | Survey | D | Adequate–Poor |
| Solensky et al., 2000 (30) | Survey | E | Good |
| Arndt & Garratty, 2002 (12) | Laboratory | E | Adequate |
| Mauri-Hellweg et al., 1996 (16) | Laboratory | E | Adequate |
| Dhar & Kulkarni, 1994 (46) | Laboratory | E | Adequate |
| Katsutani & Shionoya, 1993 (15) | Laboratory | E | Adequate |
| Tsuchiya et al., 1979 (10) | Laboratory | E | Adequate |
| Mine et al., 1970 (9) | Laboratory | E | Adequate |
| Batchelor et al., 1966 (8) | Laboratory | E | Adequate–Poor |
| Assem & Vickers, 1974 (47) | Laboratory | E | Poor |
| Girard, 1968 (34) | Laboratory | E | Poor |

that the penicillin and cephaloridine were obtained from the same manufacturer, which increases the risk of cross contamination of the two medications and the chance that they were manufactured in the same *Acremonium* fungus.

Two studies specifically addressed the reaction rate of penicillin-allergic patients to cefamandole (second generation), which is no longer available in the United States. Blanca et al. challenged 19 patients with a confirmed penicillin allergy with cephaloridine (first generation) and cefamandole (second generation) (14). Two patients (10.5%) had an adverse reaction to cefamandole; no reactions were noted with cephaloridine (14). Miranda et al. challenged 21 patients confirmed to be allergic to amoxicillin by skin testing to cefadroxil (first generation) and cefamandole. No reactions were seen to cefamandole, but 8 patients (38%) had a reaction to cefadroxil (17). The combined adverse reaction rate for cefamandole is 0.05% (2).

**Table 2. Literature Review Guidelines: Level of Evidence**

| | |
|---|---|
| Grade A | Randomized clinical trials or meta-analyses (multiple clinical trials) or randomized clinical trials (smaller trials) directly addressing the review issue |
| Grade B | Randomized clinical trials or meta-analyses (multiple clinical trials) or randomized clinical trials (smaller trials) indirectly addressing the review issue |
| Grade C | Prospective, controlled, non-randomized, cohort studies |
| Grade D | Retrospective, non-randomized, cohort or case-control studies |
| Grade E | Case series, animal/model scientific investigations, theoretic analyses, or case reports |
| Grade F | Rational conjecture, extrapolations, unreferenced opinion in literature, or common practice |

Sastre et al. specifically addressed cross reactions in patients with an allergy to amoxicillin and cefadroxil (19). The authors confirmed a penicillin allergy in 76 (13%) of the 576 patients with a reported history of penicillin allergy. The 16 patients who were specifically allergic to amoxicillin were challenged with cefadroxil. Two of them (12.5%) had an immediate allergic event (19).

Fonacier and associates sought to quantify the true risk of an allergic reaction to cephalosporins in patients with a documented penicillin allergy (20). The investigators sent a survey to 186 patients who had a history of penicillin allergy and received a cephalosporin during a hospital stay. Eighty-three patients responded, yielding a response rate of 44%. Seven of the 83 patients reported an allergic reaction (8.4%): 2 of the 44 who received a first-generation cephalosporin, 3 of the 10 who received a second-generation cephalosporin, and 2 of the 19 who received a third-generation cephalosporin. None of the patients who received a fourth-generation cephalosporin had a reaction. Limitations of this study are recall bias

**Table 3. Literature Review Guidelines: Methodology**

| Ranking | Design Consideration Present | Methodology Consideration Present | Both Considerations Present |
|---|---|---|---|
| Outstanding | Appropriate | Appropriate | Yes, both present |
| Good | Appropriate | Appropriate | No (either present) |
| Adequate | Adequate with possible bias | Adequate | No (either present) |
| Poor | Limited or biased | Limited | No (either present) |
| Unsatisfactory | Questionable/none | Questionable/none | No (either present) |

and the small sample size. Patients who had a reaction are more likely to respond, so true cross-reactivity rates in the larger group are likely to be lower.

In a cohort study by Romano and colleagues, 128 penicillin-allergic patients (those who sustained anaphylactic shock or urticaria) underwent skin testing with cephalosporins (cephalotin, cefamandole, cefuroxime, ceftazidime, ceftriaxone, and cefotaxime) (21). Fourteen (10.9%) had a positive reaction, mostly to the first-generation cephalosporin, cephalothin. All of the patients with negative skin tests tolerated challenges with cefuroxime (second generation) and ceftriaxone (third generation).

Novalbos et al. challenged penicillin-allergic (confirmed by positive skin test or provocation test) patients with cephalosporins (cephazoline, cefuroxime, and ceftriaxone) that had side chains dissimilar from the one in the penicillin that caused the reaction (22). All of the patients tolerated therapeutic doses without adverse effects.

The study by Beam and Spooner questioned the reliability of a reported history of penicillin allergy (23). Only 2 of the 20 patients who gave a history of a type 1 hypersensitivity reaction to penicillin actually had a positive skin test. Similar results were reported by Solensky et al., who performed skin testing on 58 patients with a history of an IgE-mediated allergic response to penicillin (24). Fifty-three had a negative skin test and were then challenged with three 10-day courses of oral penicillin. Among the 46 patients who completed the protocol, there was no increased risk of resensitization. Of the 7 patients who dropped out of the study, none was known to have experienced an allergic reaction.

A cohort observational study of patients receiving cephalothin (first generation) found that 7 of 54 patients had an adverse reaction (i.e., rash [n = 3], urticaria [n = 2], or anaphylaxis [n = 2]). Five of these patients reported a history of a penicillin allergy, though only 3 had a positive penicillin skin test. Interestingly, 2 of the 7 had a positive skin test to cephalothin, and one patient had positive skin tests to both cephalothin and penicillin—this patient's adverse reaction was reported as anaphylaxis that occurred within 30 s after receiving the cephalothin (3).

In a 6-year cohort observation study, Macy and Burchette followed 249 patients and documented the number of adverse reactions they experienced after receiving antibiotics. Of the 83 patients who were confirmed to be penicillin allergic, 42 were given a cephalosporin, and one in that group had an adverse event. The reaction was attributed to cefixime (third generation). Interestingly, the authors found that the reaction rate in penicillin-allergic patients was actually lower with cephalosporins than with non-$\beta$-lactams ($p = 0.005$). Cephalosporins were also associated with fewer adverse reactions, independent of penicillin skin test results ($p = 0.005$) (25).

Finally, three large retrospective cohort studies confirm that the cross-reactivity rate between penicillin and cephalosporins is very low. From the records of 606 patients who had a history of penicillin allergy and who received cephalosporins during their hospital stay, Daulat et al. found that 1 (0.17%) patient had an adverse reaction (26). These investigators recorded a total of 16 adverse reactions to cephalosporins out of the 27,230 charts they reviewed, yielding an overall adverse reaction rate to cephalosporins of 0.07%. These numbers may be biased by pharmacists who reviewed the orders and recommended alternative therapies and by incomplete coding of patients' medical records (26). Goodman et al. reviewed the charts of 2933 patients who received prophylactic cefazolin (a first-generation cephalosporin) before surgery (27). Of the 300 patients with a documented allergy to penicillin, 1 (0.3348%) had an adverse reaction to the cefazolin. The largest retrospective review was by Apter et al., who reviewed the records of 534,810 patients who received penicillin followed by a cephalosporin within 60 days (28). Of the 3920 patients who reported a reaction to penicillin, 43 (1.09%) had a reaction to a cephalosporin. Among the 530,890 patients who did not report a reaction to penicillin, 581 (0.11%) had a reaction to a cephalosporin. These three studies represent a total of 45 adverse events in 4826 documented penicillin-allergic patients, for a composite cross-reaction rate with cephalosporins of 0.93%.

The meta-analyses by Pichichero and Casey, and Anne and Reisman show that a cross allergy of penicillin with first-generation cephalosporins (odds ratio 4.8, confidence interval 3.7–6.2) does exist (2,29). The estimated incidence is 1% to 10%. Their data show a negligible cross allergy of second-generation cephalosporins (odds ratio 1.1, confidence interval 0.6–2.1) with penicillin.

Solensky et al. addressed physicians' willingness to administer a cephalosporin to patients with penicillin

**Table 4. Summary of Pertinent Articles**

| First Author, Year of Publication, Reference Number | Confirmed True Penicillin Allergy* | Number of Patients with Alleged or Confirmed Allergy† | Number of Reactions to a Cephalosporin | Notes |
|---|---|---|---|---|
| Apter, 2006 (28) | No | 3920 | 43 (1%) | Retrospective study of 534,810 patients who received a prescription for penicillin followed by cephalosporin; 3920 reported an allergic event to penicillin, and 43 of them also reported a reaction to a cephalosporin. |
| Assem, 1974 (7) | Yes | 24 | 3 (12.5%) | Twenty-four penicillin-allergic patients were challenged with cephaloridine. Three had a reaction. Penicillin and cephaloridine were obtained from the same manufacturer. |
| Audicana, 1994 (13) | Yes | 12 | 0 | Penicillin-allergic patients were challenged with cephalexin and ceftazidime. No reactions were noted. |
| Blanca, 1989 (14) | Yes | 19 | 2 (10.5%) | Penicillin-allergic patients were challenged with cefamandole and cephaloridine. Two had a reaction to cefamandole. |
| Dault (26) | No | 606 | 1 (0.16%) | Retrospective review of 23,270 hospital records. One reaction was noted in a patient with a penicillin allergy and 15 in patients who did not have a penicillin allergy. |
| Fonacier, 2005 (20) | No | 83 | 7 (8.4%) | Surveys were sent to 186 patients with a history of penicillin allergy who received a cephalosporin; 83 completed the survey; 7 self-reported an allergic reaction to a cephalosporin. Four patients reacted to a first-generation and 3 to a second-generation cephalosporin. No reactions to any third-generation cephalosporins were documented. |
| Girard, 1968 (34) | Yes | 23 | 2 (8.7) | Penicillin-allergic patients were challenged with cephaloridine. |
| Goodman, 2001 (27) | No | 300 | 1 (0.33%) | Penicillin-allergic patients were given cefazolin for surgery. |
| Macy, 2002 (25) | Yes | 83 | 7 (8.4%) | Followed a total of 249 patients (83 with confirmed penicillin allergy) over 6 years and documented the number of reactions to any antibiotic. The adverse reaction rate for those with a known penicillin allergy was 8.4%, and 4.2% for those without a known allergy. The difference was not statistically different ($p = 0.31$). |
| Miranda, 1996 (17) | Yes | 21 | 8 (38%) | Patients were challenged with cefadroxil and cefamandole after being confirmed allergic to amoxicillin. Eight patients had a reaction to cefadroxil. No reactions to cefamandole were noted. |
| Novalbos, 2001 (22) | Yes | 41 | 0 | Penicillin-allergic patients were challenged with cefazolin, cefuroxime, and ceftriaxone; no reactions were noted. |
| Park, 2006 (45) | Yes | 11 | 0 | Trial of 999 people with a history of penicillin allergy who agreed to undergo skin testing. Fifty-three (5.3%) had a confirmed or equivocal skin test. Eleven of these patients received a $\beta$-lactam antibiotic, with no adverse reaction. Of the 946 patients who had a negative skin test, 5 (0.5%) had an adverse reaction to a $\beta$-lactam. |
| Romano, 2004 (21) | Yes | 75/128 | 0 | Penicillin-allergic patients were challenged with cephalothin and cefamandole. No reactions were seen in the 75 patients with negative skin tests to cephalosporins. Five patients were not challenged due to a positive skin test for a cephalosporin, and 22 refused challenge. |
| Sastre, 1996 (19) | Yes | 16 | 2 (12.5%) | 576 patients with a suspected history of penicillin allergy; 76 (13%) were confirmed allergic to a penicillin, and 16 were allergic specifically to amoxicillin. The 16 allergic to amoxicillin were challenged with cefadroxil; 2 had an allergic reaction. |
| Saxon, 1987 (38) | Yes | 62 | 1 (1.6%) | Penicillin-allergic patients were challenged with unknown cephalosporins. One reaction was noted. |

| | | | | |
|---|---|---|---|---|
| Solley, 1982 (48) | Yes | 27 | 0 | Performed penicillin skin testing on 778 patients with a history of penicillin allergy; 108 (14%) had a positive skin test. Among the 27 patients who had a positive skin test and received a cephalosporin, there were no reactions. The skin test was for penicillin, ampicillin, and methicillin. |
| Thoburn, 1966 (3) | Yes | 11 | 2 (18.2%) | 51 patients who were receiving cephalothin were observed; 7 patients who experienced an allergic reaction to cephalothin underwent skin testing. Three of the 7 patients had a positive skin test to cephalothin, and 2 had a positive skin test to penicillin. One patient had a positive skin test for both penicillin and cephalothin. |

* Study confirmed that the patient was allergic to penicillin by either skin testing or radioallergosorbent testing, or both.
† Number of patients with confirmed penicillin allergy in studies that did confirmation testing; otherwise, number of people who had reported penicillin allergy.

allergy (30). For patients with a vague penicillin allergy, 58% and 59% of physician responders would choose a cephalosporin to treat mild or moderate disease, respectively, and 40% would choose vancomycin. For patients with a convincing penicillin-allergy history and severe disease, 55% of physicians would choose erythromycin, 44% would prescribe a quinolone for oral use, and 63% would choose vancomycin. The study is limited by a 16% response rate.

## DISCUSSION

Our literature review indicates that the cross reactivity between penicillins and cephalosporins is overestimated and much lower than reported in early studies. The high cross reactivity found in the early studies probably was caused, at least in part, by contamination of the study drugs with penicillin during the manufacturing process. Before the 1980s, pharmaceutical companies used *Acremonium* (formally called *Cephalosporium*) to create both penicillins and cephalosporins (31). Furthermore, the authors of the early studies loosely defined "allergy" and did not account for the fact that penicillin-allergic patients have an increased risk of adverse reactions to *any* medication (2).

True penicillin allergies are less common than reported. Only IgE-mediated immunologic responses (manifested as bronchospasm, angioedema, a pruritic rash, urticaria, or hypotension) are likely to result in anaphylaxis (representing a true allergy). Several studies in this review confirm a very low rate of positive skin and radioallergosorbent tests (a blood test used to determine if a person is allergic to a specific substance) in those with a reported penicillin allergy (14,23). This is further supported by the work of Surtee et al., who studied 132 patients with a purported history of penicillin allergy (32). The allergy was confirmed by radioallergosorbent test in only 4 (3.03%) of the 132 patients. The remaining 128 patients were given a single dose of oral penicillin and experienced no allergic reaction. The amassed data indicate that the true incidence of an allergy to penicillin in patients believed to have such allergy is < 10% (1). An international survey finds the incidence of anaphylaxis after administration of penicillins to be 0.015–0.004%, with a fatality rate of 0.02–0.0015% (33).

The early in vitro studies did not clearly distinguish cross reaction of IgM or IgG antibodies to cephalosporin antibodies from a true cross allergy (7,34). A true allergic response is an IgE-mediated hypersensitivity reaction. IgG- and IgM-mediated responses are not allergic responses and are known to develop in most patients who receive penicillin (35). IgG and IgM antibodies may cross react with cephalosporin antigens in in vitro tests, but this does not represent an allergic cross reaction (8,29,36–38).

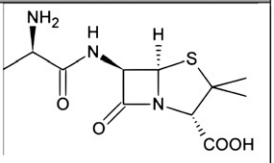
| Penicillin | Cephalosporins That Cross React | Common R1 Side Chain |
|---|---|---|
| Amoxicillin<br>Ampicillin | Cefaclor†<br>Cefadroxil*<br>Cefatrizine*<br>Cefprozil†<br>Cephalexin*<br>Cephradine* |  |



**Figure 2. Penicillin and cephalosporins known to have a risk of allergic cross reaction (17,19,34,37,47,49). These cephalosporins should be avoided in patients who are allergic to penicillin.**
***First generation.**
**†Second generation.**
**Patients who are selectively allergic to amoxicillin or ampicillin should avoid the cephalosporins listed, because they have similar R1-group side chains.**

The structural similarities between penicillins and cephalosporins led to the belief in a high rate of cross reactivity. Penicillins and cephalosporins are both small-molecular-weight compounds with a $\beta$-lactam ring that has various side chains (39). The two groups differ in regard to the constituents and structure of the side chains as well as their degradation pathways (39–41). However, similarities in the side chains does correlate with risk for cross reactivity (2,42). A number of studies indicate that the R1 side chain off the $\beta$-lactam ring rather than the ring itself is the determining factor for the rate of cross reactivity (8,9,11,13–16). In particular, the aminopenicillins, amoxicillin and ampicillin, have the same R-group side chains as several first- and second-generation cephalosporins (Figure 2). The highest observed cross reactivity rate (27%) is with cefadroxil, which has the same R-group side chain as amoxicillin. This statement is based on two studies that documented a total of 10 adverse events in 40 patients (17,19). Based on these data, patients confirmed to be selectively allergic to amoxicillin or ampicillin, but who tolerate penicillin, should not be given cephalosporins with similar R1 side chains.

Skin testing in penicillin-allergic patients cannot reliably predict an allergic response to a cephalosporin (13,29). The meta-analysis by Anne and Reisman, encompassing published reports and post-marketing data from pharmaceutical companies, found that skin testing does not predict allergic response to cephalosporins in penicillin-allergic patients, particularly to compounds with dissimilar side chains (29). However, skin testing may be useful in determining whether a true allergy to penicillin exists (24).

## CONCLUSIONS

There is limited correlation between allergy to a penicillin antibiotic and allergy to a cephalosporin antibiotic. Most cross reactivity between penicillins and cephalosporins stems from whether their R1 side chains are structurally similar. Cross reactivity between penicillins and most second- and all third- and fourth-generation cephalosporins is negligible. The overall cross reactivity between penicillins and cephalosporins in individuals who report a penicillin allergy is approximately 1% and, in those with a confirmed penicillin allergy, 2.55%.

If a patient has had an allergic response to penicillin, it is safe to administer a cephalosporin with a side chain that is structurally dissimilar to that of the penicillin or to administer a third- or fourth- generation cephalosporin. It is also recommended, based on a small number of cases (n = 40), that cefadroxil be avoided in these patients. For patients with a questionable history of penicillin allergy, skin testing predicts a true penicillin allergy but does not reliably predict allergy to cephalosporins, particularly to those with dissimilar side chains.

### *Recommendations*

When patients provide a history of penicillin allergy, further information should be obtained to determine whether an IgE-mediated response (anaphylaxis) occurred. In patients with a documented IgE-mediated response to penicillin, third- and fourth-generation cephalosporins can be used generously. First- and second-generation cephalosporins with R1 side chains similar to that of penicillin (ie, cefaclor, cefadroxil, cefatrizine, cefprozil, cephalexin, and cephradine; Figure 2) should be avoided; first- and second-generation cephalosporins with different R1 side chains can be given. Skin testing is not recommended for determining the safety of administration of cephalosporins to penicillin-allergic patients due to its unreliability.

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## ARTICLE SUMMARY

**1. Why is this topic important?**

An understanding of the prevalence of cephalosporin sensitivity among patients who are allergic to penicillin is important because it affects clinical decisions regarding choice of antibiotics.

**2. What does this review attempt to show?**

This literature review challenges the previously reported 10% prevalence of cross reactivity to penicillins and cephalosporins.

**3. What are the key findings?**

Cross reactivity between penicillins and most second-generation and all third- and fourth-generation cephalosporins is negligible. The overall cross reactivity between penicillins and cephalosporins with similar side chains is approximately 2.5%, and overall cross reactivity between penicillins and all cephalosporins is 1%.

**4. How is patient care impacted?**

Patient care is affected by broadening clinicians' ability to choose the most appropriate first-line antibiotic for a specific infection in a patient who is allergic to penicillin. Avoidance of some medications may lead to administration of a less-effective antibiotic and thus heighten the risk of pathogen resistance.