

Adverse Drug Reactions to Cephalosporins in Hospitalized Patients with a History of Penicillin Allergy

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ABSTRACT

Estimates on the cross-reactivity between cephalosporin and penicillin range from 1 to 16%. Patients with a history of penicillin allergy usually receive less optimal and more costly alternatives even if cephalosporins are a more viable alternative. One hundred eighty-six patients admitted to Winthrop University Hospital in a 7.5-month period, who reported penicillin allergy and received cephalosporin, were sent surveys. Eighty-three patients completed the survey and their charts were reviewed. Seven of 83 patients (8.4%) from a larger group of 186 penicillin-allergic patients developed a reaction to a cephalosporin. The exact 95% confidence interval is 3.5–16.6%. Six of seven (85.7%) penicillin-allergic patients who reacted to cephalosporin reported a definite history of an immediate reaction to penicillin, including hives. Only 1 of 62 (1.6%) patients who reported that their penicillin reaction was delayed, probable, or unknown had a cephalosporin reaction ($p < 0.001$). Thirty percent (3 of 10 patients) of penicillin-allergic patients, who received a second-generation cephalosporin, had a reaction, whereas 5.5% (4 of 73 patients) of those patients given only a first-, third-, and fourth-generation cephalosporin reacted ($p < 0.04$). None of those patients who received a fourth-generation cephalosporin reacted. Four of 15 (26.7%)

patients who received a cephalosporin with an amino benzyl ring developed a reaction, as compared with 3 of 68 (4.4%) patients who received a cephalosporin without the ring ($p < 0.02$). Four patients with severe cephalosporin reactions had a rash, shortness of breath, difficulty swallowing, lightheadedness, and anaphylaxis. Patients who recall a definite history of an immediate type of penicillin allergy are more likely to develop a cephalosporin reaction compared with patients who reported a delayed, a probable, or an unknown penicillin reaction. Penicillin-allergic patients who receive second-generation cephalosporins, especially those with an amino benzyl side chain, are more likely to develop a reaction to cephalosporin. Although the incidence of reactions to cephalosporin in penicillin-allergic patients is low, those patients who reacted had more severe manifestations including anaphylaxis. Thus, continued caution regarding administration of cephalosporin, especially those with amino benzyl side chains, to patients who have a definite history of an immediate reaction to penicillin is advised. (Allergy and Asthma Proc 26:135–141, 2005)

Many patients report a history of penicillin allergy on admission to the hospital. *In vitro* cross-reactivity between penicillin and cephalosporin is reported to be as high as 40–75%.¹ However, the true incidence of clinical cross-reactivity between penicillin and cephalosporin has not been accurately determined, with estimates ranging from 1 to 16%. Petz reported that 8.1% of patients with a history of penicillin allergy had reactions to various cephalosporins, as compared with 1.9% of patients without such a history.² Kelkar and Li, in a review of cephalosporin allergy, suggested that the risk of an allergic reaction to a cephalosporin in patients with a history of allergy to penicillin may be up to eight times as high as the risk in those

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with no history of allergy to penicillin.³ Anne and Reisman reported a low 1–2% cephalosporin reactivity in penicillin-allergic patients identified by history and positive penicillin skin test.⁴ Another report cautioned on the indiscriminate use of cephalosporin in penicillin-allergic patients reporting that 6 of 12 fatal antibiotic anaphylaxis cases in the United Kingdom followed the first course of cephalosporin, and 3 of 6 of these patients were known to be allergic to amoxicillin and 1 patient was allergic to penicillin.⁵ Because of previous reports of cross-sensitivity between penicillin and cephalosporins, many physicians tend to prescribe less optimal and more costly antibiotics for patients with a history of penicillin allergy even if cephalosporins were a viable alternative. To date, there is no specific immunoglobulin E skin or radioallergosorbent tests to help diagnose true cephalosporin allergy. It has been argued that neither penicillin nor nonirritating doses of cephalosporin skin tests can identify potential cephalosporin reactions.⁴

The objectives of this study were to (1) evaluate the incidence of adverse drug reactions to cephalosporin antibiotics in patients admitted to the hospital with a history of penicillin allergy and (2) determine if the history of a penicillin allergy will help predict the risk of occurrence of adverse reactions to a cephalosporin, without skin testing to penicillin or cephalosporin.

METHODS

Patients with a history of penicillin allergy admitted to the Winthrop University Hospital, a 591-bed comprehensive medical facility and a major teaching affiliate of the State University of New York of Stony Brook from September 1, 1997 to April 15, 1998 were included in the study. Delay in reporting the results was because of multiple factors including collection of data by mail, chart review, and author schedule. The patients who reported penicillin allergy and were given cephalosporin during their hospitalization were identified from the pharmacy records. The decision to give cephalosporin was solely the decision of the admitting physician. All hospital records were reviewed to verify the history of penicillin allergy, the type of cephalosporin received, and any reported adverse reaction to cephalosporin. These patients were sent a survey or were interviewed by a physician during their hospital stay regarding their penicillin allergy. Patients were asked to determine if their penicillin allergy was a definite occurrence, a probable history, or unknown. If patients recollected their reaction as a definite occurrence, questions were asked to determine if the reactions occurred within hours of the penicillin intake and manifested as urticaria, asthma, or anaphylaxis; or within days and manifested as maculopapular rash or eczema. Two physicians evaluated the responses independently. No allergy subspecialty consultation or skin tests to penicillin or cephalosporin were done.

Definition of the Penicillin Allergy

- A. Definite reaction. The patient was sure of the occurrence of a reaction to penicillin
 1. Immediate. Reaction to penicillin occurred within 24 hours of drug intake and manifestations included urticaria, rhinitis, asthma, conjunctivitis, or anaphylaxis (highly suggestive of an immunoglobulin E-mediated reaction)
 2. Delayed. Reaction to penicillin occurred >24 hours after drug intake and within up to 1 week after stopping therapy and manifested as a maculopapular rash
 - B. Probable reaction. The patient recalled a reaction but was unsure of details such as the onset of the reaction or its manifestations
 - C. Unknown. The patient was informed of having a penicillin allergy but had no personal recollection of the incident, the timing, or the clinical manifestations
- The diagnosis and severity of the cephalosporin reaction was confirmed by chart review, patient interview, and/or response to the questionnaire.

Definition of the Cephalosporin Reaction

- A. Mild. Medication stopped, no treatment given, and reaction subsided
- B. Moderate. Medication stopped, treatment given, and reaction subsided with no residual effects
- C. Severe. Medication stopped, treatment given, increased length of hospital stay because of the reaction, and life-threatening reaction or permanent disability

STATISTICAL ANALYSIS

The completed surveys were mailed back by the patient in a self-addressed, stamped envelope or submitted by the physician who conducted the interview. The patients' charts were reviewed. The collected information was entered manually using the EXCEL program. The subsequent spreadsheet was converted to an SAS (Statistical Analysis System) data set. Fisher's exact test was used for all 2 [mult] 2 tables as well as for larger tables.

Data were presented mostly as frequencies or percentages and Fisher's exact test was used to determine statistically significant differences between proportions. Differences were considered statistically significant if the value of $p < 0.05$. All analyses including those to obtain exact 95% confidence bounds for reaction rates were run using SAS 6.12 for Windows 95 (SAS Institute, Cary, NC). In questions with missing data, percentages were computed based on the total number of patients supplying a nonmissing response.

RESULTS

Of 19,407 admissions, between September 1, 1997 and April 15, 1998, 2026 patients (10.4%) reported a penicillin allergy on admission and 186 (9.2%) of these

TABLE I

Adverse Reaction to Cephalosporins in Penicillin-Allergic Patients Based on the Penicillin Allergy History			
History of Penicillin Allergy	(-) Cephalosporin Reaction	(+) Cephalosporin Reaction	Total
Definite history of an immediate reaction	15	6 (28.6%)	21
Delayed, probable, or unknown			
Delayed (4)	61	1 (1.6%)	62
Probable (1)			
Unknown (56)			
Total	76	7	83

Fisher's exact test: $p < 0.001$.

Definite, patient was sure of the occurrence of a reaction; immediate, reaction within 24 hours of drug intake and manifested as urticaria, rhinitis, asthma, conjunctivitis, or anaphylaxis; delayed, reaction occurred >24 hours after drug intake and manifested as a maculopapular rash; probable, patient recalls the reaction but not details; unknown, patient has no personal recollection of the reaction.

patients received cephalosporins. Surveys were completed and charts were reviewed in 83 of these patients and then statistical analysis was done. The mean age of the participants was 51.7 years with a range of 2–88 years. The study included 61 female (73.5%) and 22 male (26.5%) patients.

Fifty-seven of 83 (68.7%) patients did not recall the event leading to the diagnosis of penicillin allergy. Twenty-one (25.3%) patients reported a definite history of immediate reaction to penicillin. Patients reported symptoms including hives, shortness of breath, nausea, vomiting, diarrhea, light-headedness, difficulty swallowing, and tongue and mouth swelling. The onset of their reaction was within 24 hours after a penicillin dose and reaction resolved a few hours after penicillin discontinuation. Four (4.8%) patients whose onset was delayed had a definite history of penicillin reaction (>24 hours after drug intake). They manifested as maculopapular rash or blisters occurring after many doses of penicillin and resolving in a few days or weeks after penicillin discontinuation. One (1.2%) patient recalled a probable reaction of nausea and diarrhea without a rash. Patients categorized the severity of their penicillin reaction as mild (9.6%), moderate (3.6%), severe (9.6%), or unknown (77.1%).

Seven of the 83 (8.4%) patients with a history of a penicillin allergy were given a cephalosporin and developed an adverse drug reaction to the cephalosporin. The exact 95% confidence interval is 3.5–16.6%. There were four severe reactions and one moderate, one mild, and one unknown reaction to cephalosporin.

The occurrence of adverse drug reactions to cephalosporins seemed to be related to the nature of the penicillin allergy. Six of the seven (85.7%) penicillin-allergic patients who had a reaction to cephalosporin recalled a definite history of an immediate reaction to penicillin, which included hives. Of the 21 patients who recalled a definite history of an immediate reaction to penicillin, 6 (28.6%) patients had a reaction to cephalosporin. Of the 62 patients

TABLE II

Severity of Penicillin Allergy and Occurrence of Cephalosporin Reaction		
Penicillin Reaction Severity	Penicillin Reaction	Cephalosporin Reaction
Mild	8	3
Moderate	3	0
Severe	8	3
Unknown	64	1
Total	83	7

Mild, medication stopped, no treatment given, and reaction subsided; moderate, medication stopped, treatment given, and reaction subsided with no residual effects; severe, medication stopped, treatment given, increased length of hospital stay because of the reaction, and life-threatening reaction, or permanent disability; unknown, patient unable to recollect.

whose reaction to penicillin was delayed, probable, or unknown, only one patients reacted to cephalosporin (1.6%; $p < 0.001$; Table I).

The severity of the previous penicillin allergy, if known, did not seem to be associated with the occurrence of a cephalosporin reaction. Three of eight patients who reported mild penicillin allergy and another three of eight patients with severe penicillin allergy had a reaction to cephalosporin (Table II).

Six of the seven patients who reacted to cephalosporin had the last penicillin reaction occurring >10 years before the cephalosporin administration (range, 11–44 years). Eleven of 83 (13.3%) patients with reported penicillin allergy had other drug hypersensitivities including to sulfonamides, ciprofloxacin, erythromycin, codeine, and triple antibiotic cream. Five of the seven penicillin-allergic patients who reacted to cephalosporin had a history of an allergy to other medications.

TABLE III

Cephalosporin (First Course) Used in Penicillin-Allergic Patients

First generation	
Cefadroxyl (Duricef)	1
Cephalexin (Keflex)	11
Cefazolin (Ancef)	37
Total	49 (51%)
Second generation	
Cefuroxime (Ceftin)	4
Cefaclor (Ceclor)	3
Total	7 (9.4%)
Third generation	
Cefixime (Suprax)	2
Ceftazidime (Fortaz)	2
Ceftriaxone (Rocephin)	17
Total	21 (25.3%)
Fourth generation	
Cefepime (Maxipime)	6
Total	6 (7.2%)

Ten of the patients received more than one course of cephalosporin. In eight of these patients, the second course of cephalosporin was from a different-generation cephalosporin and they were not included in the following analysis of the reaction rate to different generations of cephalosporins. The two patients who received another course of cephalosporin from the same generation were included in this analysis. Table III summarizes the different cephalosporins administered in the first course of antibiotic to the patients included in our study. Two of 44 penicillin-allergic patients who received first-generation cephalosporins had an adverse reaction to cephalosporins (4.6%). Three of six penicillin-allergic (50%) patients who received second-generation cephalosporins had an adverse reaction. Two of 19 penicillin-allergic patients who received third-generation cephalosporins had an adverse reaction (10.5%). None of the six patients who received fourth-generation cephalosporins had an adverse drug reaction (Table IV).

Patients were grouped into those patients who never received a second-generation cephalosporin during their hospital stay compared with those patients who did. Patients who received a second-generation cephalosporin had a higher reaction rate of 30% (3 of 10 patients) whereas the reaction rate for patients on first-, third-, and fourth-generation cephalosporins was 5.5% (4 of 73 patients; $p < 0.04$; Table V).

Review of the structures of the cephalosporin associated with adverse reactions showed that two patients had a reaction to cephalexin and two patients had a reaction to cefaclor. Both cephalosporins have the amino benzyl ring (Fig. 1). There was one reaction to cefuroxime, one reaction to cefixime, and one reaction to ceftriaxone. Thus, 4 of 15 (26.7%) of patients who received a cephalosporin with the amino benzyl side chain had an adverse reaction compared

TABLE IV

Reaction to Different Generations of Cephalosporins

Generation	Total	Cephalosporin Reaction	Reaction Rate (%)
First	44	2	4.6
Second	6	3	50
Third	19	2	10.5
Fourth	6	0	0
Total	75	7	0

Fisher's exact test, $p = 0.023$.

Seventy-three patients received one cephalosporin; 10 patients received two cephalosporins; 2 patients received second drug of the same generation; 8 patients received two different generations of cephalosporins (not included in this evaluation).

with 3 of 68 (4.4%) of patients who received a cephalosporin with no amino benzyl ring ($p < 0.02$; Table VI).

All the reactions reported had dermatologic manifestations and four patients with severe cephalosporin reactions had associated systemic manifestations, including shortness of breath, difficulty swallowing, nausea, lightheadedness, and anaphylaxis. Three of these patients received a second-generation cephalosporin, and one patient received a first-generation cephalosporin. Two patients who reacted to a cephalosporin had hives with no associated systemic manifestations and another patient had a nonspecific rash (Table VII).

DISCUSSION

Ten percent of admissions to Winthrop University Hospital during the 7.5-month study period reported a history of penicillin allergy. Only 9.2% of these reported penicillin-allergic patients received a cephalosporin.

Of our patients who reported a history of penicillin allergy and were given a cephalosporin, 8.4% developed a reaction to cephalosporin. This incidence is similar to studies reported on patients with a history of penicillin allergy (5.4–16.5%) compared with patients with no history of penicillin allergy (1–2.5%).⁶ However, this reaction rate was higher than recently published reports on patients with a positive skin test to penicillin.^{4,7} This difference may be because of the inability of the current penicillin or cephalosporin skin tests to identify side-chain-specific reactivity.^{8–15}

Information about prior penicillin allergy was useful in assessing the risk of reacting to a cephalosporin. Patients who recalled a definite history of an immediate reaction to penicillin were more likely to have a reaction to cephalosporin compared with patients whose reactions were delayed, probable, or unknown. This may be reflective of an immunologically mediated, type I immediate hypersensitivity.

TABLE V			
Adverse Reaction to Second-Generation Cephalosporins in Penicillin-Allergic Patients			
	(-) Cephalosporin Reaction	(+) Cephalosporin Reaction	Total
Never received a second-generation cephalosporin	69	4 (5.5%)	73
Received second-generation cephalosporin	7	3 (30%)	10
Total	76	7	83

Fisher's exact test, p < 0.04.

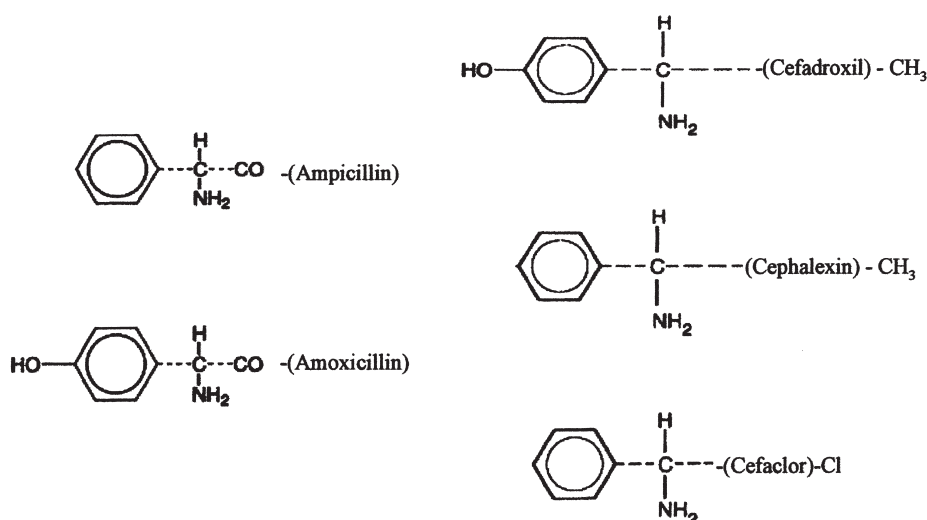


Figure 1. Common amino benzyl ring side chain in ampicillin and cephalosporins: cefadroxil, cephalixin, and cefaclor.

TABLE VI			
Adverse Reaction to Cephalosporins with Amino benzyl Side Chain in Penicillin-Allergic Patients			
Cephalosporin	(-) Cephalosporin Reaction	(+) Cephalosporin Reaction	Total
With amino benzyl side chain (cephalexin, cefaclor, and cefadroxyl)	11	4 (26.7%)	15
No amino benzyl side chain	65	3 (4.4)	68
Total	76	7	83

Fisher's exact test, p < 0.02.

ity to penicillin compared with penicillin intolerance or a type IV delayed hypersensitivity reaction. The severity of the penicillin reaction and the time between the penicillin-allergic reaction and the administration of cephalosporin did not seem to influence the occurrence of an adverse reaction to cephalosporin.

The reaction rates to cephalosporins with an amino benzyl ring (specifically cefuroxime and cefaclor) appeared higher compared with cephalosporin without the amino benzyl ring^{16,17} in penicillin-allergic patients. The higher reaction rate seen in our patients who received a second-generation cephalosporin may be because of the presence of the amino benzyl ring in cefaclor, a preferred drug in our

formulary. Ampicillin and amoxicillin have similar amino benzyl side chains.^{18,19} The importance of side-chain groups and their involvement in many allergies to β -lactam drugs have been reported by Zhao *et al.*²⁰ Side-chain-specific antibodies may predominate in the immune response to cephalosporins.³ Also, as discussed in an article regarding the cross-reactivity of sulfonamide medications, the association of allergic reactions may be because of the predisposition to allergic reactions rather than to cross-reactivity among drugs. These reactions may represent multiple drug sensitivities by unknown mechanisms rather than the immunologic cross-reactivity between penicillin and cephalosporin.²¹

TABLE VII

Clinical Data of Patients with Cephalosporin Reactions

	Reported Penicillin Allergy	Penicillin Severity	Cephalosporin (Generation)	Cephalosporin Reaction
1. 58/F	DI—hives, shortness of breath, lightheaded, Nausea, vomiting after second dose; MD Tx	Severe	Cephalexin (1)	Generalized hives, nausea, vomiting, and diarrhea
2. 46/F	DI—generalized hives; self-Tx	Severe	Cefuroxime (2)	Generalized hives, nausea, lightheaded, and dysphagia
3. 79/F	DI—hives on arms and face; self-Tx	Mild	Cephalexin (1)	Hives on arms
4. 22/F	DI—shortness of breath, throat closing 10–15 min after first dose; MD Tx	Severe	Cefaclor (2)	Shortness of breath and throat closing
5. 23/F	DI—generalized hives and vomiting; No Tx	Mild	Cefaclor (2)	Generalized hives, shortness of breath, lightheaded, dysphagia, and nausea
6. 55/F	DI—hives; MD Tx	Mild	Cefixime (3)	Generalized hives
7. 82/F	Rash	Unknown	Ceftriaxone (3)	Rash

DI = definite history of immediate type reaction; F = female; MD = physician provided; Tx = treatment.

There were no reactions reported to fourth-generation cephalosporins (cefepime) when used in patients with a history of a penicillin allergy. This was consistent with previous reports showing that cross-reactivity between penicillins and cephalosporins seems to be higher for the first- and lower for the fourth-generation cephalosporins. Thus, it may be safer to administer a currently available fourth-generation cephalosporin (cefepime) to penicillin-allergic patients, but more studies need to be done. Patients with a history of penicillin allergy and concomitant sensitivities to other medications had a greater association of reaction to cephalosporin, probably reflecting multiple drug reactors.

Although the incidence of reactions to cephalosporins in penicillin-allergic patients was a low 8.4%, those patients who did react had more severe manifestations including anaphylaxis. Thus, continued caution regarding administration of cephalosporins, especially those with the amino benzyl side chains, to patients with a definite history of an immediate hypersensitivity reaction to penicillin allergies is warranted. The data from this study suggest that it is premature to recommend indiscriminate prescribing of cephalosporins in patients who report penicillin allergy. Additional studies including tests on side-chain reactions of β -lactam antibiotics need to be done.

Limitations inherent to surveys and retrospective studies applied to this study. Only 83 of the 186 patients who reported a history of a penicillin allergy and who were given a cephalosporin had data available, *i.e.*, completed the survey and had a review of their hospital chart. Thus, there may be a selection bias as to increased tendencies of patients who had reactions to respond to the survey. There also is no information regarding the severity of the penicillin allergy on the 1420 patients who did not receive a cephalosporin

and the 103 penicillin-allergic patients who received a cephalosporin but did not respond to the survey. Our pharmacy data only include the presence or absence of penicillin allergy and not the severity of the reaction. Another source of selection bias was physician selection of penicillin-allergic patients who received a cephalosporin. In 91% of the patients who reported a history of penicillin allergy, an alternative antibiotic may have been given. This may reduce sample size and underestimate the reaction rate because many physicians have a tendency not to give cephalosporins to penicillin-allergic patients. In the analysis of different generations of cephalosporins, we were limited by the hospital formulary, which did not include all of the commercially available cephalosporins. No skin tests to penicillin or cephalosporin were done; thus, there was no documentation of the penicillin or cephalosporin allergy. This may not necessarily be a limitation because this study measured the predictive value of the history. Also, we were not able to confirm the presence of ampicillin or amoxicillin hypersensitivity in patients who had a reaction to a cephalosporin with a similar amino benzyl side chain.

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