

A survey of antibiotic prescribing and knowledge of penicillin allergy

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Background: Cephalosporins can cause allergic reactions in patients with penicillin (PCN) allergy. Physicians' prescribing habits for patients with PCN allergy can vary.

Objectives: 1) Survey community and academic physicians, students, residents, and allergists on their tendencies to prescribe cephalosporins and/or perform PCN skin testing in patients with different histories of PCN allergy. 2) Evaluate PCN allergy knowledge in these groups.

Methods: A questionnaire consisting of four case scenarios and five true/false questions on PCN allergy was distributed at various conferences and by mailings.

Results: Three hundred seventy-eight completed surveys were analyzed. Given a patient with a history of rash with PCN, an equal number of allergists and nonallergists (36%) prescribed cephalosporins, although there was a difference between pediatricians (56%) and internists (22%). Given a history of PCN anaphylaxis, no allergists but 11% of nonallergists prescribed a cephalosporin. Skin testing was infrequently requested by nonallergists. The correct response rate for the true/false questions was 89% for allergists, community (63%) and academic (67%) physicians, pediatricians (61%), internists (67%), residents (68%), and students (68%). Pediatric residents had the highest (74%) and community pediatricians the lowest (59%) correct response rate.

Conclusions: There is marked variation in prescribing cephalosporins and in requesting PCN skin testing in patients with varied histories of PCN allergy. The survey results indicate a need for increased PCN allergy education.

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INTRODUCTION

Penicillin (PCN) was discovered by Fleming in 1928.^{1,2} Cephalosporin C was isolated in 1953.² PCNs are the most frequently prescribed antibiotics and most common cause of allergic drug reactions in the United States.³ PCN-allergic patients may also be allergic to cephalosporins. Although physicians routinely avoid prescribing PCN to patients with a history of PCN allergy, the approach to prescribing cephalosporins to these patients is less

clear. Ten percent of inpatients and outpatients claim to have "PCN allergy."^{3,4} However, numerous studies have shown patient history is a poor indicator of the true presence of PCN allergy, and >80% of patients who claim to be PCN-allergic have negative PCN skin tests.^{4–9} Conversely, patients with a history of PCN allergy and positive skin tests have a >50% chance of an allergic reaction if given PCN.³ Fortunately, the incidence of PCN anaphylaxis is rare (0.01 to 0.05%).³ Although practice parameters were recently published on management of drug hypersensitivity, the degree of PCN-cephalosporin cross-reactivity, role of cephalosporin skin testing, and role of skin testing a PCN-allergic patient before prescribing a cephalosporin remain controversial.³ Surveys of physicians including allergists have evaluated antibiotic prescribing ten-

dencies given various histories of PCN allergy.^{10,11}

We surveyed community and academic internists and pediatricians, allergists, students, and residents regarding: 1) tendencies to prescribe cephalosporins given various histories of PCN allergy; 2) tendencies to refer/perform PCN skin testing in these scenarios; and 3) evaluate PCN allergy knowledge using true/false questions. We postulated there would be a wide range of prescribing habits and tendencies to perform PCN skin testing.

METHODS

A questionnaire was designed to address our objectives. Demographic information including level of medical education, physician's field of practice, years in practice, community versus academic practice, and history of completing an allergy rotation was gathered. Four clinical vignettes describing patients with various histories of PCN allergy (Table 1) and five true/false questions to gauge knowledge of PCN allergy (Table 2) were administered.

This questionnaire was disseminated in settings intended to survey a broad spectrum of community and academic internists, pediatricians, and allergists. One author (TCP) distributed and collected the survey at pediatric and internal medicine conferences and department meetings at two academic and two community hospitals. Essentially all surveys distributed by TCP at these meetings were collected. The questionnaire was included with the monthly physician newsletter mailed to staff physicians of the Children's Hospital. The questionnaire was mailed to 48 members of the state allergy society.

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Table 1. Case Scenarios of PCN Allergy in the Survey

Case 1: A healthy patient comes into your office with sinusitis/bronchitis. The patient does not appear in sepsis. The patient has a history of a macular-papular rash from penicillin within the last 10 years. You consider a cephalosporin to treat the infection. Would you:

Case 2: The same patient as in question 2 now states that he had chest and throat tightness with penicillin. You again consider a cephalosporin. Would you:

Case 3: The same patient as in question 2 now gives a history of having penicillin-induced hemolytic anemia. You again consider a cephalosporin. Would you:

Each of the 3 cases above was followed by the following choices:

- a. Prescribe penicillin.
- b. Prescribe cephalosporin.
- c. Prescribe another medication:
quinolone _____ macrolide _____
doxycycline _____ TMP/SMX _____
other _____
- d. Refer patient to an allergist for penicillin/cephalosporin skin testing.
- e. Administer the first dose of cephalosporin in the office and observe for 20 minutes.

Case 4: You have a patient in the hospital with sepsis. Blood cultures grow a bacteria that is only sensitive to penicillin and cephalosporins. The patient has a past history of "PCN allergy"—no additional information is available. Would you:

- a. Prescribe IV penicillin.
- b. Prescribe IV cephalosporin.
- c. Obtain allergy consult for penicillin/cephalosporin skin testing.
- d. Obtain infectious disease consultation.

RESULTS

Three hundred seventy-eight surveys were analyzed. The number of respondents and percentage of the total by subgroup are listed in Table 3. The return response rate was 83% of allergists, 47% of internal medicine residents, and 39% of pediatric residents. Compared with all pediatricians and internists in the metropolitan area, this survey represents 56 and 40% response, respectively, realizing that not

Table 2. PCN Allergy True/False Questions

1. If successful, penicillin desensitization is lifelong.
2. A patient with a cephalosporin allergy can be desensitized to cephalosporins.
3. Penicillin allergy is lifelong ("once allergic, always allergic").
4. There are standardized skin tests for penicillin.
5. There are standardized skin tests for cephalosporins.

all physicians were polled. For case vignettes 1 to 4 (Table 1), choices *b* and *e* were combined to yield the total number of physicians prescribing a cephalosporin. Nearly all respondents answered every question. If responders chose more than one option, each response was included in the analysis. Forty-two percent of nonallergist physicians had completed an allergy rotation, including more pediatricians (54%) than internists (36%). The average years in practice was 15 years for nonallergist physicians and 16.4 years for allergists, suggesting considerable clinical experience for both groups.

Case 1: History of Non-Urticarial Rash with PCN

In this case, physicians prescribing a cephalosporin ranged from 22% of internists to 56% of pediatricians with allergist and students intermediate (Fig 1, 2a). The percentage of nonallergist physicians (excluding students and residents) was identical (36%) to the percentage of allergists. There was minimal difference between community (37%) and academic (33%) physicians when specialties were combined. More pediatric residents (74%) than medicine residents (23%) prescribed a cephalosporin. Neither allergists nor internists, but a small percentage of pediatricians prescribed PCN (Fig 2a). Only 2% of internists, 5% of pediatricians, and 8% of allergists considered PCN skin testing. Overall, 61% of all responders chose an alternative antibiotic. Macrolides were the most popular choice (53%), followed by trimethoprim-sulfamethoxazole (TMP/SMX) (41%), doxycycline (10%), and quinolones (7%). Among allergists,

47% chose a macrolide, 28% chose TMP/SMX, and 16% chose doxycycline (data not shown). Several physicians chose more than one alternative antibiotic.

Case 2: History of Systemic Reaction after PCN

In this case, no allergists but 11% of nonallergist physicians prescribed a cephalosporin (Fig 2b). Differences were again noted between pediatricians (19%) and internists (7%). Cephalosporins were most frequently prescribed by community pediatricians (21%) and least prescribed by community internists (6%). Only 5% of pediatric and 3% of medicine residents prescribed cephalosporins. Academic and community physician results were similar (Fig 1). No respondents prescribed PCN. Referrals for PCN skin testing were requested by 21% of pediatricians, no internists, and only 13% of allergists indicated that they would skin test (Fig 2b). The majority of respondents (88%), including allergists (92%), chose an alternative antibiotic. The most popular choice among non-allergists was a macrolide antibiotic (57%), followed by TMP/SMX (35%), doxycycline (7%), and quinolones (6%). Allergists made similar choices. Several physicians chose more than one alternative antibiotic.

Case 3: History of PCN-Induced Hemolytic Anemia

This question was intended to evaluate knowledge that PCN-induced hemolytic anemia is not immunoglobulin (Ig)E-mediated and, therefore, PCN skin testing is not indicated. No allergists performed skin testing, but skin testing was ordered more frequently by pediatricians than internists (Fig 2c). Community and academic physicians (11%) had similar tendencies to refer for skin testing. No respondents prescribed PCN. The choices of alternative antibiotics mirrored those for cases 1 and 2. Although hemolytic anemia is not IgE-mediated, few non-allergists (11%) and allergists (13%) prescribed a cephalosporin.

Case 4: Sepsis with Vague History of PCN Allergy

This case evaluated if physicians pursued PCN skin testing or cephalosporins in a hospitalized, severely ill patient with a vague history of PCN allergy. Many respondents chose more than one option (Fig 2d). Two physicians prescribed intravenous PCN. Intravenous cephalosporins were prescribed by 35% of internists, 44% of pediatricians, 45% of students and residents, but only 8% of allergists. PCN skin testing was ordered by 90% of allergists, but only by 38% of nonallergist physicians and 32% of students and residents. Infectious disease consultation was obtained by 15% of allergists and 31% of nonallergist physicians. Pediatricians were more likely than internists to order PCN skin testing (43 vs 36%), but less likely to obtain an infectious disease consultation (25 vs 36%).

True/False Questions

These questions were designed to evaluate knowledge of PCN allergy. Correct response rates are shown in Figure 3. For question 1, all allergists answered a correct response of false. Internists had the next highest correct response rate (80%), followed by pediatricians (72%), and students and residents (72%). Question 2 was correctly answered true by 92% of allergists, 62% of students and residents, 56% of internists, and 43% of pediatricians. A correct response of false in question 3 was recorded by 80% of allergists, followed by 70% of students and residents, 56% of pediatricians, and 52% of internists. A correct response of true for question 4 was recorded by 82% of allergists, 80% of students and residents, 65% of internists, and 62% of pediatricians. Question 5 was correctly answered false by 95% of allergists, 79% of internists, 71% of pediatricians, and 56% of students and residents.

The overall correct response rate was 90% for allergists and 67% for nonallergists. Pediatric residents had the highest correct response rate of 74%, whereas community pediatri-

Table 3. Total Survey Respondents by Physician Groups

Practitioner type	Number	Percent
Community pediatricians	74	19.6
Academic pediatricians	21	5.6
Allergists	40	10.6
Community internists	104	27.5
Academic internists	41	10.8
Pediatric residents	19	5.0
Internal medicine residents	43	11.4
Medical students (junior/senior)	27	7.1
Miscellaneous*	9	2.4
Total	378	100

* Physician assistants, nurse practitioners, or specialty fellows-in-training.

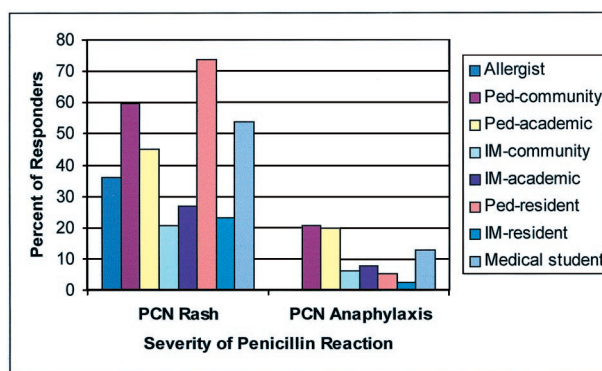


Figure 1. Choice of cephalosporin in patients with a history of rash with PCN compared with systemic symptoms with PCN by various physician groups.

cians had the lowest at 59%. Internists (67%) did slightly better than pediatricians (61%). Academic and community physicians had similar correct response rates (67 vs 63%). Physicians who had completed an allergy rotation did minimally better than those who had not had a rotation (69 vs 65%).

DISCUSSION

We demonstrated that physicians are more likely to prescribe cephalosporins in the setting of a history of rash with PCN compared with a systemic reaction to PCN. Over one-third of allergists and >50% of pediatricians prescribed a cephalosporin in those with a history of rash. This is in contrast to no allergists, <7% of internists or residents, but >18% of pediatricians who prescribed a cephalosporin, given a history of systemic reaction to PCN. Cephalosporins were prescribed by more pediatricians than internists or allergists. Solensky et al¹⁰

also demonstrated cephalosporins were prescribed more often given a vague history of PCN allergy. Thus, physicians have increased concern regarding PCN-cephalosporin cross-reactivity given a history of PCN anaphylaxis than a non-urticarial rash. Allergists and internists seem more conservative than pediatricians in our survey.

Our survey differed from the study by Solensky et al¹⁰ in the choice of alternative antibiotics. We discovered macrolide class of antibiotics were the alternative drug of choice for allergists and pediatricians. Internists preferred TMP/SMX. We listed "macrolide" as an alternative antibiotic class instead of "erythromycin," as in the Solensky et al¹⁰ survey. Also, doxycycline was chosen by >10% of internists and allergists in our survey, but it was not listed as a choice in the other study. In our study, <7% of internists, allergists, and pediatricians selected a quinolone, but it was a frequent choice in

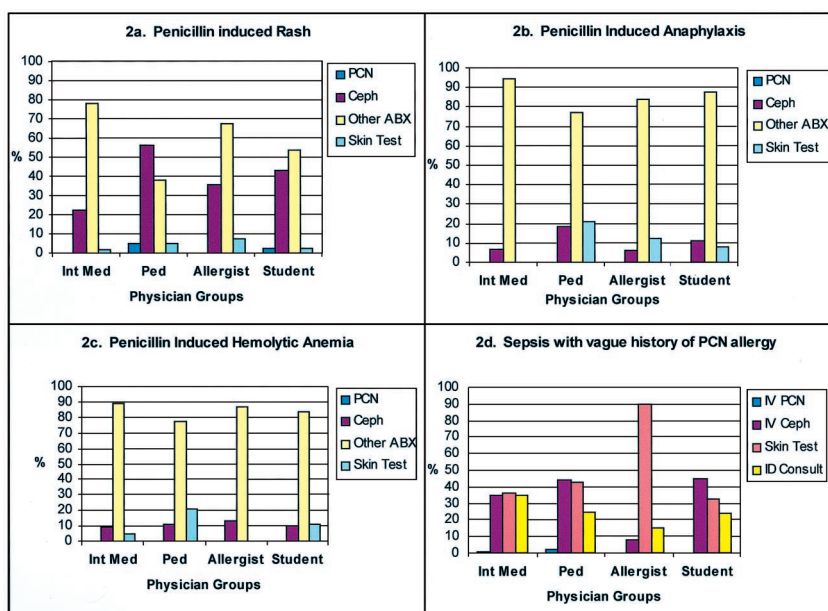


Figure 2. Antibiotic choices in a patient with various histories of PCN reaction (n = 378).

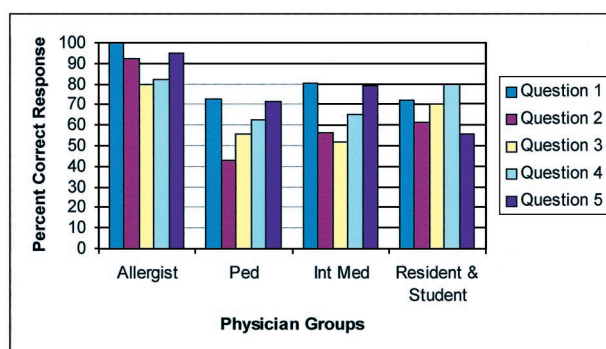


Figure 3. Correct responses to true/false questions by physician group.

the Solensky et al study (up to 44%).¹⁰ Vancomycin was chosen frequently in the other study (up to 63%) but was not an alternative listed in our survey. These differences may reflect regional prescribing habits or the specialties of the physicians polled. We demonstrated a similar percentage (20%) of community and academic physicians who chose cephalosporins, whereas community physicians were more likely to choose cephalosporins in the Solensky et al study.¹⁰ Community physicians favored macrolides and academic physicians preferred TMP/SMX as alternatives. Community physicians were 8-fold more

likely to choose doxycycline. These differences could reflect different formularies available to community and academic physicians.

Both surveys demonstrated that a few physicians prescribed PCN to patients with a PCN allergy history. Solensky et al found 2 to 6% of physicians prescribed PCN with a vague history of PCN allergy.¹⁰ We noted 5% of pediatricians, but no internists or allergists, prescribed PCN with a history of PCN rash. Fortunately, in the case of PCN anaphylaxis, no physicians prescribed PCN, and only one responder in the Solensky et al survey gave PCN with a "convincing history"

of PCN allergy. In our survey, no physicians prescribed PCN with a history of PCN-induced hemolytic anemia or anaphylaxis, but 1% of nonallergists prescribed PCN to the patient with sepsis and a vague history. We believe prescribing PCN to patients with a previous history of even vague PCN allergy without PCN skin testing exposes the patient to an unnecessary risk of a drug reaction, an opinion shared by others.^{3,9,10,12,13} The use of a suitable alternative antibiotic may be appropriate rather than expose the patient to unnecessary risk.

Skin Testing

In evaluating PCN skin testing by primary care physicians and allergists in different clinical scenarios, <8% of physicians, including allergists, pursued PCN skin testing with a PCN rash history. With PCN anaphylaxis, no internists, 21% of pediatricians, and only 13% of allergists pursued PCN testing. Our study supports the belief that prescribing an alternative antibiotic is more convenient than pursuing PCN skin testing. In the case of PCN anaphylaxis, >90% of all physicians chose an alternative antibiotic. Allergists would need to educate primary care physicians when PCN skin testing is clinically indicated and outline the risks, benefits, and limitations of this type of testing. Fortunately, PCN skin testing has reaction rates of 0.3%–1.1%.^{3–5,9,13}

The low incidences of PCN skin testing by allergists in cases 1 and 2 are in striking contrast to rates published in a survey of American Academy of Allergy and Immunology members and US allergy training program directors. More than 50% of Academy members and program directors reported that they would perform skin testing in a patient identical to case 1. In addition, >85% of Academy members and nearly all training program directors would perform skin testing with a history of PCN anaphylaxis identical to case 2.¹¹ Allergists in our survey may have presumed skin testing was contraindicated given a history of PCN anaphylaxis, or they may have

preferred desensitization without previous skin testing.

In case 4, nearly 90% of allergists performed PCN skin testing, in contrast to <45% of internists or pediatricians. Some physicians obtained an infectious disease consultation, and it is unknown if those consultants would request an allergy evaluation and subsequent PCN skin testing. Thus, among the allergists responding to the survey, few performed PCN skin testing before prescribing a cephalosporin in the outpatient cases, but nearly all performed testing in the seriously ill patient with a vague history of PCN allergy. Nonallergist physicians rarely referred patients for PCN skin testing, especially in the outpatient scenarios.

PCN skin testing is not predictive of non-IgE-mediated drug reactions such as serum sickness or cytopenias.³ In case 3, some internists and pediatricians requested PCN skin testing. This probably reflects a deficiency in understanding the immunologic mechanism of drug-induced hemolytic anemia. Increased education on the immune mechanisms of drug allergy could prevent unnecessary referrals for skin testing in cases of non-IgE-mediated reactions.

The results of the true/false questions raises several issues regarding the working knowledge of practicing physicians. PCN allergy is not lifelong. Positive PCN skin tests decrease by 10% annually after a PCN-allergic reaction,¹⁴ and 78% of PCN-allergic patients have negative skin tests after 10 years of avoidance.¹⁵ Also, a study revealing 52% of PCN-allergic patients and 92% of amoxicillin-allergic patients had negative skin testing after 5 years demonstrated that the type of PCN may affect duration of sensitivity.^{14,16} Resensitization can occur after loss of skin test reactivity,^{4-6,8,9,17} especially after use of intravenous β -lactams.¹⁸

Cephalosporin Cross-Reactivity

PCN/cephalosporin cross-reactivity is controversial and central to our survey. Early in vitro studies demonstrated cross-reactivity rates of 40 to 75%.¹⁹⁻²¹ A 1978 retrospective review reported 8.1% of patients with a history of PCN

allergy had cephalosporin reactions.²² Most reactions were to cephalothin, which has a side chain that resembles a side chain on benzyl PCN.^{2,3} Also, early first-generation cephalosporins contained trace amounts of PCN, which could have resulted in overestimation of the cross-reactivity.^{1,2} No PCN contamination has been documented since 1980.³ Whereas several studies report PCN/cephalosporin cross-reactivity rates of 0 to 5%,^{1,5,7,8,17} one documented a rate of 10.5%.²³

A review of cross reactivity and postmarketing studies of second- and third-generation cephalosporins revealed no increase in allergic reactions in those patients with a history of PCN allergy.² Because PCN skin testing did not identify history-positive patients who subsequently had a cephalosporin reaction, the authors concluded PCN skin tests are not indicated before administering cephalosporins to these patients and that PCN-cephalosporin cross reactivity is overestimated. Patients with a history of PCN allergy are three times more likely to have an adverse reaction to any additional antibiotic (including cephalosporins).¹ Mendelson¹² estimates only 2% of patients with a PCN allergy history and positive PCN skin tests will have a reaction to a second- or third-generation cephalosporin within 24 hours. However, he recommends skin testing to PCN and a non-irritating concentration (3 mg/mL) of the cephalosporin before cephalosporin administration.^{3,12,14} Cephalosporin skin testing is considered experimental because of unknown haptenic determinants and the practice parameters recommend cautious graded cephalosporin challenge if the skin test is negative.^{3,14}

The practice parameters state there is no consensus on the management of PCN-allergic patients who require a cephalosporin. If a patient is given a second- or third-generation cephalosporin without PCN skin testing, the authors estimate reaction rates <1%, although fatal anaphylaxis has occurred. If PCN skin testing is negative, <1% of patients will have a mild reaction to the cephalosporin within 24

hours.³ Fortunately, cephalosporin anaphylaxis is rare (<0.02%).²

True/False Questions

The overall correct response rates were 90% for allergists and only two-thirds for nonallergists. Most nonallergist physicians knew PCN desensitization is not lifelong and standardized cephalosporin skin tests do not exist. However, many were unfamiliar with cephalosporin desensitization or spontaneous resolution of PCN allergy. Also, >30% of pediatricians and internists were unaware of the existence of standardized PCN skin tests. It is unclear why 20% of allergists felt PCN allergy was lifelong, unless they interpreted the question to ask if PCN allergy might be lifelong in some patients. Based on allergists' comments, those who answered false believed this question asked whether all PCN testing extracts are standardized, including minor determinants.

The correct response rates of nonallergists revealed interesting trends. Overall, residents and students did as well as physicians, and they did better on questions 3, 4, and 5. Pediatric residents had the highest correct rate, and community pediatricians had the lowest. Academic pediatricians scored higher than community pediatricians, but results for academic and community internists were similar. Unfortunately, completing an allergy rotation had minimal impact on the correct response rate.

CONCLUSION

Our survey revealed variation among physician groups in prescribing cephalosporins in different scenarios of PCN allergy. We believe the results of our survey are complementary to previous surveys of physicians¹⁰ and allergists.¹¹ This survey included pediatricians, internists, allergists, medical students, and residents. Because our survey did not include family practice physicians, surgeons, or obstetrician/gynecologists, the conclusions can not be generalized to these physician groups. The approach to PCN skin testing by allergists surveyed differs from recommendations of the pub-

lished practice parameters suggesting significant underutilization. Additional studies are needed to formulate consensus statements on PCN and cephalosporin allergy.

This is the first survey that evaluated PCN allergy knowledge, and the results indicate further education is needed to address PCN/cephalosporin allergy. It can be concluded that improved education on PCN allergy is needed, focusing on natural history, role of PCN/cephalosporin skin testing, and indications for desensitization. Allergists should take the lead in providing this education.

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