

The acceptability of a four-part protocol for penicillin allergy testing by practicing allergists

Alyson B. Simpson, M.D.,*# Andrew W. Murphy, M.D.,*#§ and Ejaz Yousef, M.D.*#

ABSTRACT

Currently, there is no standard protocol to test for penicillin (PCN) allergy since PrePen (manufactured benzylpenicilloyl polylysine; AllerQuest, West Hartford, CT) was discontinued in 2004. Our article reviews allergist's opinions on a protocol to test for PCN allergy in patients without a history of a life-threatening reaction. This study was performed to determine whether fellows of the American Academy of Allergy, Asthma, and Immunology (AAAAI) would use a two-challenge PCN allergy protocol to test for PCN allergy while skin testing to the major determinant, benzylpenicilloyl polylysine, is unavailable. A questionnaire regarding PCN allergy and application of a four-step protocol was sent to 1210 allergists and immunologists. Of the 654 respondents, 324 (49.5%) believed that the protocol was practical in a busy, outpatient allergy practice and 64 (9.8%) wanted more information. One hundred ninety-four (29.7%) did not think it was practical. Two hundred ninety-five respondents (45.1%) then went on to respond that they would apply the protocol in an outpatient practice and 117 (17.9%) were undecided and wanted more information. One hundred thirty-five respondents (20.6%) would not apply the protocol in their practice. Of those who were undecided or did not think it was practical, 58 (8.9%) were awaiting PrePen, 33 (5%) wanted to see a larger protocol, 24 (3.7%) wanted more detail on the challenge, and 14 (2.1%) felt more comfortable desensitizing the patient. Forty-five percent of the fellows of the AAAAI would apply the proposed protocol to test for PCN allergy. Sixty-two percent said they may apply the protocol if a larger study was performed.

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Key words: Allergy, benzylpenicilloyl polylysine, beta-lactam, major determinant, minor determinant, oral challenge, penicillin, RAST, skin test

Allergy to β -lactam antibiotics is the most commonly reported medication allergy.^{1–3} Approximately 10% of the U.S. population self-report a history of penicillin (PCN) allergy, but only 10% of these patients have a true IgE-mediated allergy.^{1–3} Several studies have indicated that 80% of the population labeled as PCN allergic are not and can safely receive PCN.^{4–6} Consequently, patients with a history of PCN allergy are treated with alternative antibiotics that are not first-line, are more expensive, and are of a broader spectrum than is needed. Thus, alternative antibiotics may increase the possibility of developing drug-resistant strains of bacteria and may have a more unfavorable side-effect profile.

Patients with a concerning history for allergy to PCN are evaluated by taking a thorough history, performing an appropriate physical examination

and, if indicated, PCN skin testing and/or challenge. Skin test reagents for PCN were developed after the physiology of PCN metabolism was elucidated and were based on the two components that PCN forms. Ninety-five percent of PCN degrades into the penicilloyl moiety, the major antigenic determinant, and the remaining portion of PCN degrades into the minor antigenic determinants, most importantly, penicilloate and penilloate.⁵ The practice parameters recommend skin testing with both the major and the minor determinants. Acceptable reagents include PCN G, PrePen (penicilloyl polylysine; AllerQuest, West Hartford, CT), and, if available, the minor determinant mixture.⁵ Some studies suggest testing to both minor and major determinants because 20% of patients with documented anaphylaxis may not show reactivity to the major determinant, and other studies have shown similar rates of positives when testing only with PCN G and PrePen.^{3,5} Negative skin-prick test and intradermal test results to PCN G and PrePen or PCN G, PrePen, and the minor determinant mixture suggest that the patient may safely receive PCN after tolerating a test dose and then receiving a full dose.

In 2004, manufacturing of PrePen was discontinued when Hollister Stier, LLC, sold the product. A new U.S. company (AllerQuest, Plainville, CT) has

From the *Division of Allergy and Immunology, Alfred I. duPont Hospital for Children, Nemours Children's Clinic, Wilmington, Delaware, #Division of Allergy, Thomas Jefferson University, Philadelphia, Pennsylvania, and §Asthma, Allergy, and Clinical Immunology of Chester County, West Chester, Pennsylvania

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Address correspondence and reprint requests to Ejaz Yousef, M.D., Division of Allergy and Immunology, Alfred I. duPont Hospital for Children, 1600 Rockland Road, Wilmington, DE

E-mail address: eyousef@nemours.org

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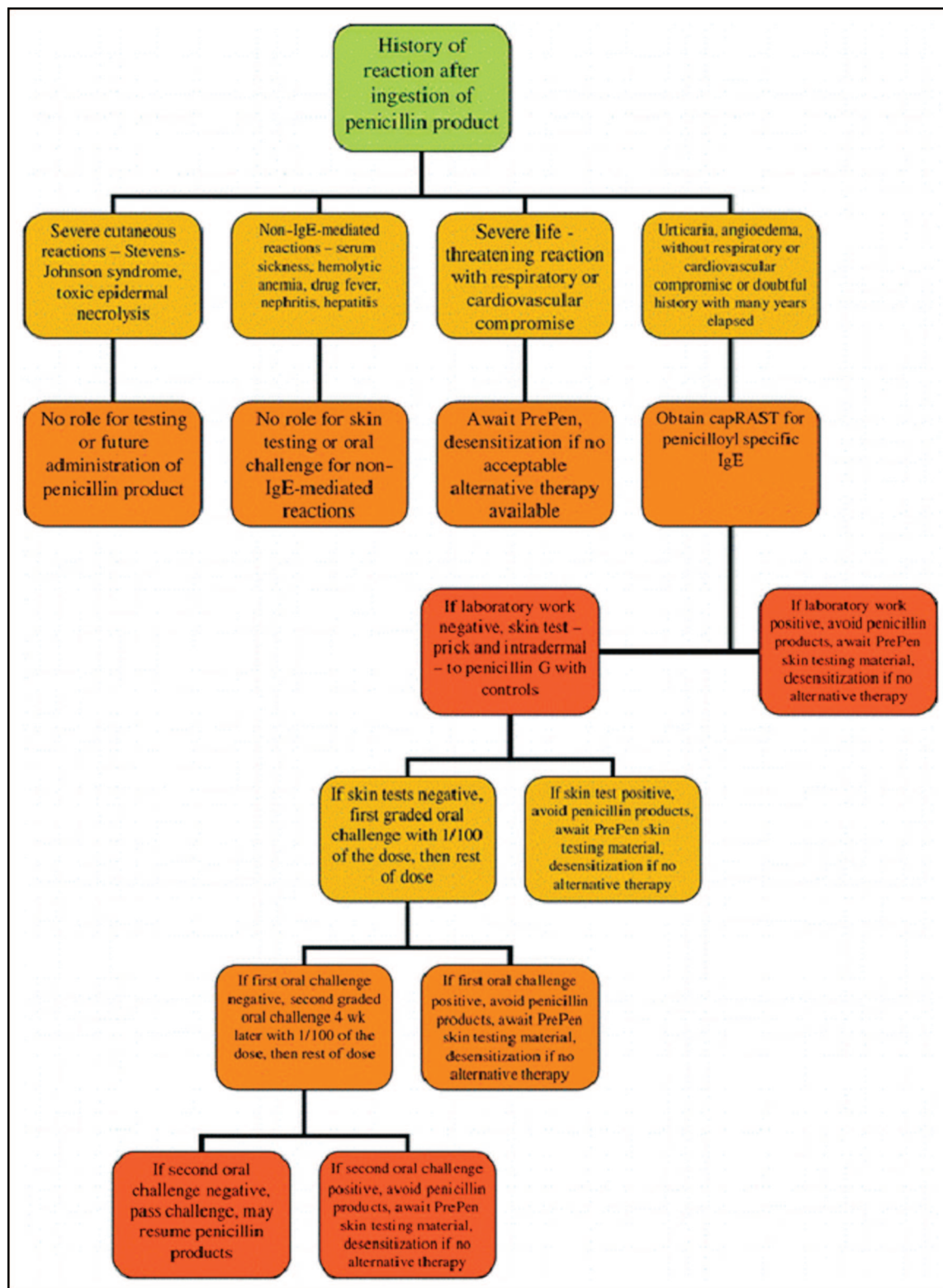


Figure 1. Two-challenge protocol to test for penicillin allergy. (Used with permission from Ref. 8.)

purchased the patent rights to produce PrePen, and this should be available in 2008 for skin testing.⁷ This severely limits allergists' ability to evaluate patients with potential PCN allergy.² We have proposed a

protocol to evaluate patients with a non-life-threatening reaction to PCN in an outpatient allergy practice (Fig. 1).⁸ To help determine whether this protocol is both practical and applicable to an outpatient

FRUSTRATED WITH PENICILLIN ALLERGY PATIENTS?

Dear Physician:

Recently, our letter to the editor was published in the November 2006 issue of the *Annals of Allergy, Asthma, and Immunology* entitled "Two-Challenge Approach to Evaluation of Penicillin in the Absence of Skin Testing Reagents". We are soliciting your opinion regarding this letter and the protocol it proposes for the evaluation of patients presenting with possible PCN allergy. Please take a few moments to read the enclosed letter, complete this survey, and return it to us promptly in the enclosed self-addressed, postage-paid envelope.

1) Area of practice:

Pediatric Allergy Adult Allergy Both Private Practice Academic Practice

2) Are you board certified in Allergy?

Yes No

4) How many years in practice?

1-5 6-10 10-20 over 20

5) Do you deal with drug allergic patients? If YES, proceed to Q6. If NO, proceed to Q11.

6) What is your current approach towards possible PCN-allergic patients in the absence of testing reagents (Major and minor determinants)?

- a) No action
- b) Oral/IV challenges (Depending on history).
- c) Desensitization (Depending on history).

7) For non-PCN antibiotics (i.e. cephalosporins), what is your current approach?

- a) No action
- b) Use a non-irritating concentration for skin testing.
- c) Oral/IV challenges (Depending on history).
- d) Desensitization (Depending on history).

8) Please rate this article on the scale of 1-4

- (1) Complete dissatisfaction
- (2) Some dissatisfaction
- (3) Satisfaction
- (4) Complete Satisfaction

9) Is this protocol practical for a busy clinical practice?

10) Would you use the findings of this letter to the editor in your clinical practice?

11) Do you have any other suggestions or alternate approach regarding this issue?

Thank you for your time.

Figure 2. Questionnaire sent out to fellows of the American Academy of Allergy, Asthma, and Immunology.

allergy practice, we sent out a questionnaire to fellows of the American Academy of Allergy, Asthma, and Immunology (AAAAI) regarding their current approach to PCN and cephalosporin allergy and the role that this protocol⁸ would have in evaluating drug-allergic patients in a busy, outpatient allergy practice. Our goal was to determine how many allergists would apply the proposed protocol if a prospective trial was performed and to show the impact PrePen had in testing for PCN allergy in patients with a history of an adverse reaction to PCN.

METHODS

The Division of Allergy mailed out a questionnaire to allergists and immunologists on a certified mailing list from the AAAAI regarding his or her approach to PCN allergy and the potential use of our protocol in an outpatient allergy practice (Fig. 1). The survey allowed us to assess whether our protocol was accepted in the allergy and immunology community. It also allowed us to link which demographic factors and experiences affected a favorable or unfavorable response. The ques-

tionnaire (Fig. 2) included demographic information: area and type of practice, board certification and years of experience, the physician's approach to PCN and cephalosporin allergy, and whether he or she thought the proposed protocol (Fig. 1) would be practical and applicable to an outpatient allergy practice. We included a copy of a published letter, "Two-Challenge Approach to Evaluation of Penicillin Allergy in the Absence of Skin Testing Reagents"⁸ (Fig. 1), providing the allergists with an overview of the protocol and a case report attempting to use the protocol. Briefly, the protocol included (1) radioallergosorbent test (RAST) IgE testing to penicilloyl-specific IgE, and, if negative, (2) skin and intradermal testing to PCN G, and, if negative, (3) PCN challenge with 1%, 9%, and 90% of the age- and weight-appropriate PCN dose given in 20-minute intervals, and then (4) repeating the PCN challenge 4 weeks later to show that the patient is not resensitized. The mailings included a prestamped return envelope. We did not have to send out second letters or incentives because we received such a strong response.

Study Variables

The answers were coded by different variables on a spreadsheet (Microsoft Excel 2000, Redmond, WA). Patient population was categorized into 0 = pediatric, 1 = adult, 2 = both, and 3 = no response; type of practice was categorized into 0 = private, 1 = academic, 2 = both, 3 = government/military, and 4 = no response; board certified was categorized into 0 = no, 1 = yes, and 2 = no response; and see drug-allergic patients, 0 = no and 1 = yes. The answer to current approach to PCN allergy was separated into 4 variables categorized as (1) no action (0 = no, 1 = yes, and 2 = no response), (2) oral/i.v. challenge (0 = no, 1 = yes, and 2 = no response), (3) desensitization (0 = no, 1 = yes, and 2 = no response), and (4) wrote in an alternative response (0 = no, 1 = yes, and 2 = no response). The answer to current approach to cephalosporin allergy was also divided into 4 variables categorized as (1) no action (0 = no, 1 = yes, and 2 = no response), (2) use of skin test (0 = no, 1 = yes, and 2 = no response), (3) oral/i.v. challenge (0 = no, 1 = yes, and 2 = no response), and (4) desensitize (0 = no, 1 = yes, and 2 = no response). Scale of article was recorded under the variables of 0 = dissatisfaction, 1 = some dissatisfaction, 2 = satisfaction, 3 = complete satisfaction, and 4 = no response. The answers to (1) whether an allergist felt the protocol was practical and (2) whether they would apply the protocol were divided into 0 = no, 1 = yes, 2 = maybe, and 3 = no response. The suggestions were divided into binary variables for "no second dose" (0 = no and yes), "need a larger protocol" (0 = no and yes), "need more information on the challenge"

(0 = no and yes), "just use an alternative antibiotic" (0 = no and yes), "get PrePen back on the market/make PrePen" (0 = no and 1 = yes), "use an alternative protocol" (0 = no and 1 = yes), "skip RAST testing" (0 = no and 1 = yes), "need formal approval before they would carry out the protocol" (0 = no and 1 = yes), "think the protocol is unsafe/uncomfortable to perform in the office" (0 = no and 1 = yes), and "would desensitize the patient" (0 = no and 1 = yes). All of the answers were separated into specific variables and the answers to each question were coded under one response. The suggestions were organized into categories based on the topic they addressed even if the same idea was worded slightly differently. There could have been more allergists who would have agreed with the suggestion if given a list from which they could choose rather than having to write in their own thoughts.

Statistical Analysis

The answers were later transposed into SPSS (SPSS, Inc., Chicago, IL) to assess frequency and percentages. Pearson's chi-square analysis was then used to examine which factors affected whether an allergist felt (1) that the protocol was practical and (2) that the protocol was applicable. We included binary variables to some of the questions so that we could apply the information to Pearson's chi-square analysis. A value of $p < 0.05$ was considered significant and all values of $p \geq 0.000$.

RESULTS

A total of 1290 questionnaires were mailed; responses were received for 654 respondents (50.6%). Of those who responded, 562 (85.9%) take care of both children and adults (Table 1). Two hundred eleven respondents (32.2%) were in practice for <10 years, and 439 (67.1%) were in practice for >10 years. Three hundred and nine respondents (47.2%) were in private practice, 89 (13.6%) were in academic practice, and 238 (36.4%) did not respond to the question (Table 1). Five hundred and eighty-eight respondents (89.9%) were board certified, and 634 (96.9%) see drug-allergic patients.

Of the respondents who treat PCN allergy, 304 (46.5%) do oral and i.v. challenges based on history, 320 (48.9%) use desensitization based on history, 21 (3.2%) have their own protocol (wrote in their own response), and 189 (28.9%) do no action depending on history. Forty-seven respondents (7.2%) had two approaches to testing, and 12 (1.8%) had three approaches to testing for PCN allergy (Table 1). Of the respondents who treat cephalosporin allergy, 171 (26.1%) use skin testing, 267 (40.8%) do oral and i.v. challenges based on history, 278 (42.5%) desensitize based on history, and 194 (29.7%) do nothing. One

Table 1 Answer to survey questions

Question	No. (%)	Question	No. (%)
Area of practice		Approach to patients with a reaction to cephalosporin	
Pediatrics	31 (4.7)	No action	194 (29.7)
Adults	41 (6.3)	Skin testing	171 (26.1)
Pediatrics and adults	562 (85.9)	Oral/ i.v. challenge	267 (40.8)
No response	20 (3.1)	Desensitization	278 (42.5)
Type of practice		No response	25 (3.8)
Private	309 (47.2)	Level of satisfaction with proposed protocol.	
Academic	89 (13.6)	Complete dissatisfaction	25 (3.8)
Private and academic	15 (2.3)	Some dissatisfaction	195 (29.8)
Government/military	3 (0.5)	Satisfaction	362 (55.4)
No response	238 (36.4)	Complete satisfaction	43 (6.6)
Board certification		No response	29 (4.5)
Yes	588 (89.9)	Protocol is practical for a busy, outpatient practice	
No	61 (9.3)	Yes	324 (49.5)
No response	5 (0.8)	Maybe	64 (9.8)
Years of experience		No	194 (29.7)
1–5 yr	128 (19.6)	No response	72 (11)
6–10 yr	83 (12.7)	Applicable to practice	
10–20 yr	196 (30)	Yes	295 (45.1)
>20 yr	243 (37.2)	Maybe	117 (17.9)
No response	4 (0.7)	No	135 (20.6)
See drug-allergic patients		No response	107 (16.4)
No	17 (2.6)	Suggestions	
Yes	634 (96.9)	Awaiting PrePen	58 (8.9)
No response	3 (0.5)	No second challenge	41 (6.3)
Approach to patients with a reaction to penicillin		Larger study	33 (5)
No action	189 (28.9)	More information method	24 (3.7)
Oral/i.v. challenge	304 (46.5)	Need formal approval	23 (3.5)
Desensitization	320 (48.9)	Uncomfortable/unsafe	21 (3.2)
Wrote in own protocol	21 (3.2)	Desensitization	14 (2.1)
No response	28 (4.3)	Use alternative antibiotic	11 (1.7)
		Skin RAST	12 (1.8)
		Use alternative protocol	6 (0.9)

i.v. = intravenous; RAST = radioallergosorbent test.

hundred thirty-two respondents (20.2%) had two approaches to testing, and 73 (11.2%) had three approaches to testing for cephalosporin allergy (Table 1).

A majority (62%) of the respondents were satisfied with the article included in the survey⁷ (Table 1). A significant number of respondents (49.5%) believed that the two-part protocol was practical in a busy, outpatient allergy practice. Two hundred ninety-five (45.1%) responded that the protocol was applicable to an outpatient practice, 117 respondents (17.9%) were undecided and wanted more information, 135 (20.6%) would not apply the protocol in their practice, and 107 (16.4%) did not respond (Table 1). Thirty-three respondents (5%) wanted to see a larger study before they apply the protocol to their practice (Table 1).

We performed a chi-square analysis to assess which demographic variables had a significant effect in de-

termining whether allergists thought our protocol was practical or applicable or both (Tables 2 and 3). Years in practice was a significant demographic variable affecting allergists' opinion of whether they felt the protocol was practical ($p = 0.046$), but it was not a significant variable in determining whether the protocol was applicable ($p = 0.189$). The rest of the demographic variables were not significant in determining whether an allergist felt the protocol was practical or applicable (Tables 2 and 3). We did not include board certification because almost every allergist was board certified and most of the other allergists graduated before boards were required to enter the field.

We then performed a chi-square analysis to assess which approaches to drug allergy affect the allergists' thoughts regarding our proposed protocol. Allergists who currently perform an oral or i.v. challenge were

Table 2 Variables affecting whether the protocol is applicable

Demographic	Not		Applicable		No response		Chi-Square	<i>p</i> Value
	Applicable		Applicable		No response			
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%		
Area of Practice								
Children	9	3.7	12	4.1	10	8.5	10.567	0.103
Adults	21	8.7	14	4.7	6	5.2		
Both	203	83.9	263	89.1	96	82.1		
No response	9	3.7	6	2.0	5	4.3		
Type of practice								
Private	107	44.2	149	55.5	53	45.3	11.314	0.079
Academic	34	14.0	30	10.2	25	21.4		
Both	7	2.9	7	2.4	1	0.0		
No response	94	38.8	109	37.0	38	32.5		
Experience								
1–5 yr	36	14.8	63	21.4	29	24.8	6.142	0.189
6–10 yr	32	13.2	38	12.9	13	11.1		
>10 yr	174	71.9	194	65.8	75	64.1		
Current approach to PCN								
No action								
No	160	66.2	219	74.2	86	73.5	4.668	0.097
Yes	82	33.9	76	25.7	31	26.5		
Desensitize								
No	133	55.0	152	51.5	49	41.9	5.443	0.066
Yes	109	45.0	143	48.5	68	58.1		
Have own protocol								
No	235	97.1	286	96.9	112	95.7	0.528	0.768
Yes	7	2.9	9	3.1	5	4.3		
Oral/i.v. challenge								
No	157	64.9	134	45.4	59	50.4	20.768	0.000
Yes	85	35.1	161	54.6	58	49.6		
Current approach to cephalosporin								
No action								
No	162	66.9	215	72.9	83	70.9	2.272	0.321
Yes	80	33.1	80	27.1	34	29.1		
Skin testing								
Yes	185	76.4	215	72.9	83	70.9	1.501	0.472
No	57	23.6	80	27.1	34	29.1		
Desensitize								
Yes	153	63.8	164	55.6	57	48.7	7.956	0.019
No	87	36.2	131	44.4	69	51.3		
Oral/i.v. challenge								
Yes	168	69.4	154	52.2	65	55.5	17.087	0.000
No	74	31.6	141	48.8	52	44.5		

PCN = penicillin; oral/i.v. = oral or intravenous; $p < 0.05$ = significant chi-square test.

likely to apply our protocol ($p < 0.001$) and found our protocol practical ($p < 0.001$). Those who desensitize their patients, have their own protocol, or do nothing with some PCN allergy patients, were less likely to think our protocol was practical and applicable (Tables 2 and 3). Allergists who were skin testing to cephalosporin and doing oral/i.v. challenges to cephalosporin

were more likely to find the protocol practical ($p = 0.001$) and applicable ($p < 0.001$) (Table 2). Allergists who desensitize patients to cephalosporin were more likely to apply the protocol ($p = 0.019$). Allergists who do nothing with some patients with cephalosporin allergy were unlikely to find the protocol practical or applicable.

Table 3 Variables that affect an allergist's decision to find our protocol practical

Demographic	Not Practical		Practical		No response		Chi-Square	<i>p</i> value
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%		
Area of Practice								
Children	16	6.0	14	4.3	1	1.6	4.913	0.555
Adults	17	6.4	19	5.9	5	7.8		
Both	222	83.5	284	87.7	56	88.0		
No response	11	4.1	7	2.2	2	3.1		
Type of practice								
Private	122	45.9	161	50.0	24	40.6	3.571	0.735
Academic	35	13.2	45	13.9	9	14.2		
Both	8	3.0	6	1.9	1	1.6		
No response	101	38.0	112	34.6	28	43.8		
Experience								
<10 years	47	17.7	75	23.1	6	9.4	9.667	0.046
6–10 years	39	14.7	38	11.7	6	9.4		
>10 years	180	67.7	211	65.1	52	81.3		
Approach to PCN								
No action								
No	181	68.0	239	73.8	45	70.3	2.348	0.309
Yes	85	32.0	85	26.2	19	29.7		
Desensitize								
No	147	55.3	158	48.8	29	45.3	3.409	0.182
Yes	119	44.7	166	51.2	35	54.7		
Have own protocol								
No	258	97.0	315	97.2	60	93.8	2.133	0.344
Yes	8	3.0	9	2.8	4	6.2		
Oral/i.v. challenge								
No	168	63.2	146	45.1	36	56.3	19.442	0.000
Yes	98	36.8	178	54.9	28	43.7		
Current approach to cephalosporin								
No action								
No	181	68.0	234	72.2	45	70.3	1.222	0.543
Yes	85	32.0	90	27.8	19	29.7		
Skin testing								
No	214	80.5	230	71.0	39	60.9	12.903	0.002
Yes	52	19.5	94	29.0	25	64.0		
Desensitize								
No	163	61.5	179	55.4	32	50.0	3.781	0.151
Yes	102	39.5	144	44.6	32	50.0		
Oral/i.v. challenge								
No	177	66.5	169	52.2	41	64.1	13.206	0.001
Yes	89	33.5	155	27.8	23	35.9	4.913	

i.v. = intravenous; PCN = penicillin.

Our last chi-square analysis assessed which approaches to treating PCN allergy—no action, desensitization, oral or i.v. challenge, or writing in their own protocol—were significant contributors to the most common suggestions: (1) need PrePen back on the market, (2) need formal approval, (3) need more information on the challenge, or (4) thought the protocol

was uncomfortable or unsafe. Of those who do nothing with some patients with PCN allergy, a significant number wrote in that they were uncomfortable with the protocol or thought it was unsafe (5.8%; $p = 0.016$; Table 4). A significant number of allergists who wrote in their own protocol said PrePen should be back on the market (28.6%; $p = 0.001$). Approach to PCN al-

Table 4 Response to suggestions based on approach to penicillin (PCN)

	<i>p</i> Value	%
Suggestions from no action with PCN allergic patients		
Uncomfortable with the protocol or unsafe	0.016	5.8
Formal approval	0.762	3.2
PrePen/reagent back on the market	0.762	8.5
More information on challenge	0.668	3.2
Suggestions from allergists who perform desensitization		
Uncomfortable with the protocol or unsafe	0.146	2.2
Formal approval	0.167	2.5
PrePen/reagent back on the market	0.122	10.6
More information on challenge	0.348	4.4
Suggestions from allergists who wrote in own protocol		
Uncomfortable with the protocol or unsafe	0.396	0.0
Formal approval	0.753	4.8
PrePen/reagent back on the market	0.001	28.6
More info on the challenge	0.363	0.0
Allergists who perform oral/i.v. testing on PCN-allergic patients		
Uncomfortable with the protocol or unsafe	0.219	2.3
Formal approval	0.472	3.0
PrePen/reagent back on the market	0.100	6.9
More information on the challenge	0.631	3.3

The *p* values represent significance of the Pearson's chi-square test. *p* < 0.05 is significant.

i.v. = intravenous.

lergy was not a significant variable in needing formal approval or wanting more information on the challenge (Table 4).

DISCUSSION

Since PrePen was taken off the market in 2004, there has not been an established protocol to treat patients with PCN allergy. In our survey alone, 28.9% of the respondents do nothing for patients with PCN allergy, and 58 (8.9%) are awaiting PrePen. Of those who treat PCN allergy, there is no protocol to follow: 46.5% do oral or i.v. challenges, 48.9% use desensitization based on history, 3.2% have a unique approach or access to PrePen for research purposes, and 9% have more than one approach. Many allergists find it easier to use an alternative broad-spectrum antibiotic or find it safer to desensitize a patient every time it is medically necessary. This creates a financial drain on society and leads to increased antibiotic resistance. Our four-step protocol (Fig. 1) may help to alleviate the frustration allergists and immunologists have and give them a safe, practical way to test for PCN allergy in the office.

We recently applied the four-step protocol⁸ to a 14-year-old girl with a history of recurrent pharyngitis and an adverse reaction to PCN. She had negative RAST results to penicilloyl, negative skin test and intradermal test results to PCN G, and passed her first oral graded amoxicillin challenge. She was rechallenged a month later and developed pruritus of her left leg with some linear raised excoriations likely secondary to a dermatographic response. If she had passed the second oral challenge, we would have cleared her of amoxicillin allergy. By sharing this protocol with the allergy community, we are able to organize all of the suggestions and improve the four-step protocol for future application on prospective patients.

It is noted that there are patients with a negative reaction to benzyl-PCN but respond to the semisynthetic PCN reagents ampicillin, amoxicillin, or cloxacillin. It is controversial whether side-chain-specific reactions to semisynthetic derivatives are clinically significant immunogenic epitopes that can cause an immediate hypersensitivity reaction. Silviu-Dan *et al.* found skin test reactivity to be limited in 47.6% of 121 patients with an allergic reaction to the semisynthetic PCN reagents derived from ampicillin, amoxicillin, or cloxacillin.⁹ These patients had negative skin tests to the major and minor benzyl-PCN derivatives. Miranda *et al.* went on to show that eight patients with an allergic reaction to amoxicillin also reacted to a cephalosporin with the same side-chain, cefadroxil.¹⁰ These studies suggest that the side-chain plays an important role in immunogenicity in a good proportion of patients. The RAST testing to PCN V, amoxicillin, and PCN G have been used in previous studies but the negative predictive values have not been well studied.

ied.^{10–12} Based on the suggestions, we would include skin testing and intradermal testing to amoxicillin and add RAST testing to PCN V, PCN G, and amoxicillin.

In reviewing the suggestions, we felt the need to clarify the necessity of the second challenge 4 weeks later. Dr. Solensky wrote an editorial response¹³ stating that PCN resensitization after treatment with oral PCN is rare^{5,13,14} and suggested that the second challenge is unnecessary. Some (6.3%) of our respondents felt there was no need to rechallenge the patient 4 weeks later. We noted in our original editorial that there was controversy regarding resensitization risk.¹⁵ We agree that patients with a negative skin test to penicilloyl-polylysine do not need to be retested 4 weeks later given the excellent negative predictive value in testing to the major determinant. Because we do not have established negative predictive values for our four-step protocol, we still recommend the two-graded challenges 4 weeks apart to ensure there is no procedure-induced sensitization. Perhaps, in the future, with more established data, this recommendation will change.

There are weaknesses in the protocol, because the combined negative predictive value of RAST to penicilloyl and skin testing to PCN G is not well studied, and the negative predictive value of RAST to penicilloyl alone is listed as 45–95%.¹¹ Although we would prefer to screen patients with skin testing to penicilloyl-polylysine, it is not commercially available at this time. Although Goldberg and Cofino-Cohen published an article suggesting that even patients with a positive history of a non-life-threatening allergic reaction to PCN could have an oral PCN challenge as a diagnostic method when skin testing is not feasible,¹⁶ this study focused on adults with a remote history of allergy who could have naturally outgrown their allergy or may not have had a true allergy. We still need a protocol that allows us to decide which children could safely perform a graded diagnostic challenge in the office while PrePen is not available, even if they had a recent adverse reaction to PCN as the patient previously described. Our protocol will help to select those children with a non-life-threatening reaction to PCN, who are more likely to pass the diagnostic challenge safely even if the reaction to PCN was more recent than the previous study.

We recognize that there are limitations to the survey. Some of the responses could have been influenced by Dr. Solensky's editorial response¹³ and some may have been reluctant to circle more than one approach to PCN allergy. More allergists may have offered suggestions or agreed with the comments of their colleagues if there were options to choose from and more space to respond. A few physicians decided to stop before the last three open-response questions (Fig. 2) and may have responded if there were choices such as yes, no, or maybe. We also had to group suggestions together

based on topic or category even if worded slightly differently.

Given that 59.1% of the respondents would apply the protocol if we had a larger study to establish the negative predictive value of capRAST to penicilloyl and skin testing to PCN G, and even more would accept it if we included skin and intradermal testing to amoxicillin and RAST testing to PCN V and PCN G; the next step will be to perform the four-step protocol in at least 20 patients. Based on the help of our respondents' suggestions, we would like to perform the improved four-step protocol on prospective patients including (1) RAST-specific IgE testing to penicilloyl, PCN G, PCN V, and amoxicillin, and, if negative (2) skin testing and intradermal testing to PCN G and amoxicillin, and, if negative, (3) oral challenge with 1%, 9%, and 90% of the required dose of PCN in 20-minute intervals, and, if negative, (4) repeat the challenge 4 weeks later to show the patient has not been resensitized. Our goal is to safely show that this protocol could standardize our approach to performing diagnostic PCN challenges in patients with a non-life-threatening reaction while PrePen is not available.

Many allergists agree that we need a uniform protocol supported by the Food and Drug Administration, the AAAAI, and the American College of Asthma, Allergy, and Immunology to guide our approach to PCN allergy. They have a vested interest in this topic and are equally frustrated with testing for drug allergy as indicated by the excellent response rate for the survey (654/1210; 50.6%). We have concluded that 45% of the fellows of the AAAAI would apply the four-step allergy protocol in an outpatient, allergy practice. Another 17.9% said they would possibly apply the protocol after it has undergone a prospective trial. The allergy community needs a uniform protocol such as the four-step protocol to standardize its approach to PCN allergy in low-risk patients while PrePen is currently unavailable.

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REFERENCES

1. Thethi AK, and Van Dellen RG. Dilemmas and controversies in penicillin allergy. *Immunol Allergy Clin North Am* 24:445–461, 2004.
2. Solensky R. Drug hypersensitivity. *Med Clin North Am* 90:233–260, 2006.
3. Solensky R. Hypersensitivity reactions to beta-lactam antibiotics. *Clin Rev Allergy Immunol* 24:201–220, 2003.
4. Gadde J, Spence M, Wheeler B, et al. Clinical experience with penicillin skin testing in a large inner-city STD clinic. *JAMA* 270:2456–2463, 1993.

5. Mendelson LM, Ressler C, Rosen JP, and Selcow JE. Routine elective penicillin allergy skin testing in children and adolescents: Study of sensitization. *J Allergy Clin Immunol* 73:76–81, 1984.
6. Sogn DD, Evans R III, Shepherd GM, et al. Results of the National Institute of Allergy and Infectious Diseases Collaborative Clinical Trial to test the predictive value of skin testing with major and minor penicillin derivatives in hospitalized adults. *Arch Intern Med* 152:1025–1032, 1992.
7. Yates A. Management of patients with a history of allergy to beta-lactam antibiotics. *Am J Med* 121:572–576, 2008.
8. Wang HC, and Yousef E. Two-challenge approach to evaluation of penicillin allergy in the absence of skin testing reagents. *Ann Allergy Asthma Immunol* 97:713–715, 2006.
9. Silviu-Dan F, McPhillips S, and Warrington RJ. The frequency of skin reactions to side-chain penicillin determinants. *J Allergy Clin Immunol* 91:694–701, 1993.
10. Miranda A, Blanca M, Vega JM, et al. Cross-reactivity between a penicillin and cephalosporin with the same side chain. *J Allergy Clin Immunol* 98:671–677, 1996.
11. Romano A, Di Fonso M, Papa G, et al. Evaluation of adverse cutaneous reactions to aminopenicillins with emphasis on those manifested by maculopapular rashes. *Allergy* 50:113–118, 1995.
12. Sanz ML, Garcia BE, Prieto I, et al. Specific IgE determination in the diagnosis of beta-lactam allergy. *J Invest Allergol Clin Immunol* 6:89–93, 1996.
13. Solensky R. Evaluation of penicillin allergy without benzylpenicilloyl-polylysine. *Ann Allergy Asthma Immunol* 98:402–403, 2007.
14. Solensky R, Earl HS, and Gruchalla RS. Lack of penicillin re-sensitization in patients with a history of penicillin allergy after receiving repeated penicillin courses. *Arch Intern Med* 162:822–826, 2002.
15. Macy E, Mangat R, and Burchette RJ. Penicillin skin testing in advance of need: Multiyear follow-up in 568 test result-negative subjects exposed to oral penicillins. *J Allergy Clin Immunol* 111:1111–1115, 2003.
16. Goldberg A, and Confino-Cohen R. Skin testing and oral penicillin challenge in patients with a history of remote penicillin allergy. *Ann Allergy Asthma Immunol* 100:37–43, 2008. □

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