

Allergy to β -lactams: A survey of current practices

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Many issues related to the diagnosis and management of β -lactam drug allergy still await definitive recommendations. To determine how practicing allergists deal with some of these dilemmas, a questionnaire was mailed to 3500 physician members and fellows of the American Academy of Allergy and Immunology. It was also sent to each of the allergy training program directors in the United States to determine what is currently taught to fellows in training. Benzylpenicilloyl-polylysine (Pre-Pen) and fresh penicillin G are used for skin testing by more than 86% of both respondent groups, whereas minor determinant mixtures are used by only 40%. Epicutaneous followed by intradermal injection was the skin test technique used by 86% of these allergists. More than 90% said they would skin test in cases of reaction history of urticaria, whereas only 1.5% would test in cases of family history of penicillin allergy. Practicing allergists and program directors differed slightly when queried about cephalosporin cross-reactivity. Program directors were more cautious in their use of cephalosporins with patients allergic to penicillin. Program directors were also more likely to repeat skin testing before future penicillin courses than were practicing allergists. Clearly, some individual approaches to the diagnosis and management of β -lactam allergy are practiced. Development of practice guidelines by our professional organizations may be useful. (J ALLERGY CLIN IMMUNOL 1994;94:725-31.)

Key words: Adverse reactions, allergist, cephalosporin, penicillin, skin testing, survey

The diagnostic evaluation of suspected β -lactam antibiotic hypersensitivity is a common clinical dilemma in the practice of allergy. Although more is known about the diagnostic evaluation of penicillin allergy than about most other drugs, many issues remain unresolved in the currently available literature.

Within our own allergy department, many lively exchanges have occurred when diagnosis of β -lactam hypersensitivity is discussed. The varieties of opinion expressed by the 10 allergists within our teaching program caused us to wonder how di-

Abbreviations used

AAAI:	American Academy of Allergy and Immunology
MDM:	Minor determinant mixture
PD:	Program director
ST:	Skin test

verse the diagnostic approaches to β -lactam hypersensitivity are among U.S. allergists. To discover the opinions of other allergists, we developed a survey for practicing allergists in the United States and Puerto Rico, asking opinions about the following issues:

1. Penicillin skin test (ST) materials used.
2. ST techniques.
3. History for which ST is performed
4. Time period for which ST results are considered valid
5. Use of cephalosporins in individuals allergic to penicillin.
6. Use of penicillins in individuals allergic to cephalosporins.

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TABLE I. Survey results

Questions	AAAI answering		AAAI group (yes)		Program directors (yes)
	No.	%	No.	%	%
<i>ST material(s)</i>					
Pre-Penicillin	1479	99.5	1366	92.4	91
Penicillin G			1280	86.5	87
MDM			592	40	44
Aged penicillin			77	5.2	
Individual minor determinants			14	<1	
Other specific implicated penicillin			34	2.2	
Ampicillin, nafcillin, ticarcillin, etc.			35	2.4	
<i>ST technique(s)</i>					
Prick followed by intradermal	1474	99.1	1265	85.8	92
Prick alone			30	2.0	3
Intradermal alone			74	5.0	5
RAST alone			8	<1	
Oral challenge alone			4	<1	
Multitest			2	<1	
Ocular challenge			2	<1	
Patch test			2	<1	
Intradermal alone unless history of severe reaction			12	<1	
<i>ST for what history?</i>					
Family history of penicillin allergy	1475	99.2	24	1.6	3
Unknown childhood reaction			894	60.6	65
Unknown distant adult reaction			914	62	75
Maculopapular rash			858	58.2	56
Urticaria			1328	90	98
Anaphylaxis			1290	87.5	97
<i>ST predictive for:</i>					
Immediate administration	1374	92.4	444	32.3	36
Within 24 hrs			216	15.7	10
Within 48 hrs			104	7.6	10
Within 72 hrs			78	5.7	16
Within 96 hrs			35	2.5	3
1 week to 1 year (various)			25	1.7	
No time limits			472	34.4	21
<i>Penicillin caused hives; would you give the patient without the following ST</i>					
First generation cephalosporin	1467	98.7	388	26.4	15
Second generation cephalosporin			526	35.9	21
Third generation cephalosporin			716	48.3	26
Monobactam (e.g., aztreonam)			863	58.8	55
Do not know about monobactams			117	8	

AAAI surveys mailed: 3500. Surveys returned: 1575 (45% return). Surveys answered: 1487 (42.5%). PD surveys returned: 73%.

7. Concerns about the resensitization risk after negative ST results are obtained before or 6 weeks after penicillin therapy.

Although the allergy literature during the last two decades has suggested answers to some of these issues, differences of opinion still exist. Furthermore, although minor determinant mix-

tures (MDMs) for ST are diagnostically helpful agents,¹ they are not yet commercially available. We wondered what allergists faced with this non-availability are doing to adequately evaluate complaints of penicillin hypersensitivity. Finally, we wanted to know whether there were differences between what is currently taught in allergy fellow-

TABLE 1—cont'd

Questions	AAAI answering		AAAI group (yes)		Program directors (yes)
	No.	%	No.	%	%
<i>Patient allergic to penicillin; before giving a cephalosporin would you:</i>					
Do no ST at all	1465	98.5	431	29.4	13
ST for penicillins only			220	15	12
ST for penicillins plus cephalosporins			529	36.1	62
ST for cephalosporins only			153	10.4	10
Other			127	8.7	
<i>Patient allergic to penicillin; ST negative for penicillin and a cephalosporin, too; would you now:</i>					
Give cephalosporin without delay	1403	94.4	493	35.1	34
Desensitize to cephalosporin			247	17.6	24
Not give the cephalosporin			101	7.2	7
Not applicable (would not test with both)			380	27.1	19
Test dose with the cephalosporin			78	5.6	
Progressive challenge with the cephalosporin			32	2.3	
Other			71	5.1	
<i>ST patient allergic to cephalosporin before giving penicillin?</i>					
No	1415	95.2	497	35.1	19
Only if the penicillin and cephalosporin share side chain			147	10.3	5
Yes			771	54.5	76
<i>With what history would you repeat ST before future courses of penicillin?</i>					
Unknown childhood reaction	1384	93.1	146	10.5	22
Unknown distant adult reaction			169	12.2	20
Maculopapular rash reaction			199	14.4	18
Urticarial reaction			576	41.6	63
History of anaphylaxis			933	67.4	80
<i>If negative ST 6 weeks after penicillin course?</i>					
Unknown childhood reaction	1379	92.7	113	8.2	15
Unknown distant adult reaction			120	8.7	13
Maculopapular rash reaction			131	9.5	17
Urticarial reaction			323	23.4	40
History of anaphylaxis			650	47.1	67

ship programs and the approaches to these issues taken by practicing allergists. This report summarizes our findings.

METHODS

A nine-question survey was developed and mailed to 3500 members and fellows of the American Academy of Allergy and Immunology (AAAI) and to the program directors (PDs) of all accredited allergy-immunology fellowship programs in the United States. A stamped, addressed return envelope was included with each survey. No financial incentive was offered. Mailing labels for the 3500 AAAI members were purchased

directly from the AAAI after the organization reviewed the survey and its purpose. Returned surveys were reviewed and answers were hand tabulated by two of the authors (G. M. W., W. A. N.). No demographic information was collected from respondents.

RESULTS

Of the 3500 surveys mailed to members of the AAAI, 1575 were returned (45%), with 1487 (42.5%) at least 50% answered. Eighty-eight surveys (2.5%) were returned unanswered for various reasons: wrong address, member deceased, member no longer in practice, member in basic

research only. The answered return rate for PDs was 73%.

Results of the survey are summarized in Table 1. In general, PDs and the 1487 respondents among the larger AAAI group differed little in their approach to surveyed issues.

The most commonly used ST agents were penicilloyl-poly-L-lysine (92.4% AAAI, 91% PD) and fresh penicillin G (86.5% AAAI, 87% PD). Approximately 40% of each group also used an MDM product. Many of the respondents in larger academic institutions made their own products, whereas some private practitioners obtained MDM from nearby centers. Interestingly, 25 AAAI respondents stated that they refuse to perform penicillin ST until a commercially prepared, Food and Drug Administration-approved MDM product becomes available. "Aged" penicillin G, thought by some to be an MDM substitute, was reportedly used by 5.2% of AAAI respondents. No program directors reported use of "aged" penicillin. Fewer than 2% to 3% of AAAI members responded that they used a specific penicillin derivative when that derivative either had caused a past reaction or was the intended therapeutic agent.

ST techniques used were fairly traditional. About 86% of AAAI respondents and 92% of PDs used prick (epicutaneous) testing, followed with intradermal testing if the prick test result was negative. Two percent of AAAI respondents and 3% of PDs reported use of the prick test alone, whereas 5% of each group reported use of intradermal techniques only. Among the AAAI respondents, small numbers used other diagnostic techniques: eight used RAST alone, four gave an oral penicillin challenge, two used the Multi-Test device (Lincoln Diagnostics, Decatur, Ill.), two performed a conjunctival challenge, and two used patch tests with unspecified agents.

When presented with various hypothetical reaction histories, the two groups were fairly similar in deciding which histories dictated ST. In general, PDs were more apt to perform ST regardless of the history. Both groups rarely tested in the case of a family history of penicillin allergy (1.6% AAAI, 3% PD), whereas most tested when confronted with histories of urticaria (AAAI 90%, PD 98%) and anaphylaxis (AAAI 87.5%, PD 97%). Several AAAI respondents wrote that a strong history of anaphylaxis dissuaded them from ST for fear of inducing another reaction during the ST procedure. Others believed that an anaphylactic history precluded the use of penicillins

entirely and thus made ST an unnecessary expense.

The period for which negative ST results were considered valid was also questioned. The majority in each respondent group (62% AAAI, 72% PD) required administration of the penicillin product less than 72 hours after negative ST results. Half of this majority requested immediate administration, with some giving in-office oral penicillin to their outpatient referrals. Thirty-four percent of AAAI respondents and 21% of PDs gave no time limits.

Issues regarding cephalosporin cross-reactivity were addressed in four questions. The first of these dealt with concerns of penicillins cross-reactivity with different generations of cephalosporins. In general, PDs were more concerned with potential cross-reactions than were members of the AAAI group. Among AAAI respondents, fewer than half would give a cephalosporin of any generation without ST. Only one fourth of PDs directors were willing to administer cephalosporins without ST in this scenario. More AAAI and PD respondents were willing to give a later generation cephalosporin than a first-generation cephalosporin, and a little more than half of each group would give a monobactam without performing penicillin ST. In the AAAI group, 8% of respondents left the question unanswered or specifically mentioned that they did not know enough about monobactams to answer.

The second cephalosporin question asked respondents about their acceptance of cephalosporins as ST agents. This was an area of varied opinion. In the case of a patient known to be sensitive to penicillin, before giving a cephalosporin AAAI respondents would do the following: 29% would perform no ST at all, 15% would ST for penicillin alone, 36% would ST for both penicillin and the involved cephalosporin, 10% would ST for the cephalosporin alone, and 9% would do something else, usually not specified. PDs were more apt to attempt cephalosporin ST. Only 13% would perform no ST, 12% would ST for penicillin alone, 62% would ST for both, and 10% would ST for the cephalosporin alone.

The third cephalosporin question dealt with the faith respondents placed in negative results of cephalosporin ST. If a patient allergic to penicillin had negative ST results for *both* penicillin and the cephalosporin, about 35% of both groups would give the cephalosporin without delay. Majorities in both groups, however, would be more cautious and either desensitize, test dose, or perform a

more rapid, progressive challenge with the cephalosporin.

The last cephalosporin question asked what respondents would do in the case of a patient known to have cephalosporin allergy who was to be given penicillin. Seventy-six percent of PDs would perform penicillin ST before permitting administration of the penicillin. The number with the response was only 55% among the AAAI group. Ten percent of AAAI respondents would ST only if the cephalosporin and penicillin shared similar side chains, whereas 5% of PDs thought the same.

The final two questions raised the issue of resensitization after uneventful administration of penicillin. On average, PDs were more concerned about resensitization than were members of the AAAI group. Although 80% of PDs would repeat ST before future penicillin courses if anaphylaxis were the previous reaction history, this number was slightly lower (67%) among AAAI respondents. As the severity of the past reaction decreased, so did the percentage of respondents who believed repeated ST to be important. For a patient previously allergic (but not having anaphylaxis) to penicillin who underwent ST 6 weeks after an uneventful penicillin course and continued to have negative ST results, the percentages of those performing further ST declined between 13% and 17%.

DISCUSSION

Suspected β -lactam allergy is a common complaint evaluated by practicing allergists. Reactions to β -lactams are the most commonly reported cause of anaphylaxis.² This survey demonstrates, however, that as with so many problems in medicine, many strategies are used to diagnose and manage β -lactam allergy.

The choice of antigens for penicillin ST has been thoroughly discussed in the literature.^{1, 3-6} The majority of respondents in this survey reported use of fresh penicillin G and benzylpenicilloyl-polylysine (Pre-Pen) reagents with an epicutaneous technique, followed by intradermal testing if the prick test result is negative. Many allergists expressed frustration at the lack of commercially prepared MDMs, which are known to increase anaphylaxis predictability compared with Pre-Pen and fresh penicillin G alone.¹ Some respondents even reported refusing to perform ST until MDMs become commercially available. Despite this nonavailability, more than 40% of allergists reported either making their own

MDM or obtaining MDM from nearby academic centers.

Only 3% of respondents mentioned using specific penicillin derivatives for ST; however, this report may not mirror the true frequency of their use. The small percentage reported may instead reflect the wording of this question. A respondent had to take the time to write the specific penicillin derivative in the "other—specify" space, something a busy clinician may not always take the time to do.

Who undergoes ST depends on the history. Few respondents would perform ST for a family history of penicillin allergy alone. On the other hand, few are willing to risk not performing ST when a patient remembers few details about a reaction in the distant past. Urticarial reactions were nearly always considered grounds for ST, whereas a history of anaphylaxis would move slightly fewer allergists to perform ST. Some expressed concern about ST reinduction of anaphylaxis; some said that ST was superfluous with a good anaphylaxis history. Although maculopapular rashes are thought not to be IgE mediated,⁶ many allergists still perform ST, perhaps not trusting the patient's ability to describe adequately the nature of the rash. An urticarial component could be missed in a retrospective description.

After negative ST results are obtained, respondents differed over how long a wait is permissible before beginning PCN penicillin therapy. Concerns about resensitization from environmental penicillin products or from the minute amounts of penicillin G introduced during the ST has caused some researchers to recommend waiting no longer than 72 hours.⁵ Despite these printed recommendations, many respondents in both groups were willing to wait longer. The fact that 34% of AAAI respondents and 21% of PDs suggest no time limits implies that many believe the actual risk of environmental resensitization to be small. A definitive study answering this issue should be performed.

Cross-reactivity between penicillins and cephalosporins was another area of variation among respondents. As has been suggested in the literature,⁶ later generation cephalosporins and monobactam antibiotics are more readily used by allergists in the patient allergic to penicillin. The incidence of first-generation cephalosporin cross-reactivity is estimated to range from 5.4% to 16.5%.⁵ Many respondents, however, perceived the incidence among patients with self-reported penicillin allergies to be lower.

It is interesting that 8% of respondents were unsure about the use of monobactams in patients allergic to penicillin. This uncertainty is possibly a consequence of reports involving monobactam hypersensitivity reactions occurring in patients with cystic fibrosis who were allergic to penicillin.⁷ In this study, 19 patients with cystic fibrosis who had well-documented allergic reactions to β -lactam drugs underwent ST with the monobactam aztreonam. One of these 19 patients had a positive ST result despite never having received the drug before. The other 18 patients with negative ST results received aztreonam without allergic reaction. Two of those 18 patients, however, later had systemic allergic reactions when exposed to aztreonam a second time. Despite this report, most patients can be safely given monobactams even when positive results of penicillin ST are documented.⁸

The use of cephalosporins as ST antigens has not been standardized.⁵ Despite this, more than 40% of respondents use cephalosporins in various concentrations when evaluating a possible cephalosporin reaction or when a cephalosporin is to be used in a patient allergic to penicillin. The cephalosporin concentrations that respondents used for ST were diverse. The majority seemed to use parenteral drug concentrations around 1 to 3 mg/ml for prick tests and a 1000-fold dilution of this for intradermal injection. Others, however, wrote in concentrations that were sometimes 1000 to 10,000 times more dilute, whereas some went to the other extreme and reported pricking through a "puddle test" with full-strength oral suspensions. We are aware of nothing in the literature that supports full-strength "puddle tests," and believe this may be too strong for accurate reaction interpretation. Work done by Brandt et al.⁹ at Southwestern supports the 1 to 3 mg/ml concentration for parenteral cephalosporins. These investigators found this dose generally nonirritating in both patient and control populations.

Finally, from the results of our survey, whether ST is repeated in the future after uneventful completion of a course of penicillin is an area of disagreement. The literature suggests a more than 15% resensitization rate for ST (3/17 adult hospitalized patients) after parenteral treatment with penicillin.¹⁰ A certain percentage of these patients would presumably react clinically on future penicillin administration. Fewer than half of the respondents, however, recommended repeated ST for most reaction histories. Only a previous his-

tory of anaphylaxis caused more than half of respondents (67%) to recommend ST again. These percentages dropped even further if repeated ST 6 weeks after the first uneventful course of penicillin yielded negative results. We could find no literature to firmly support or refute this practice. Of note is the more conservative approach the PDs again take with an issue compared with the AAAI group. On average, 10% to 20% more of the PDs would repeat ST before future courses of penicillin than would the AAAI group. A more conservative approach is probably wise when teaching fellows in training, whose firsthand personal experience is less. Graduating fellows can earn their "wisdom" and gray hairs as they liberalize their approach to some of these issues later in their careers.

In summary, it is apparent that the evaluation of suspected β -lactam drug allergy has no uniformly practiced protocol in this country. Although guidelines for many of the issues surveyed with this questionnaire now exist in the available literature, these guidelines are not universally understood, followed, or even accepted. The vast majority of respondents seem to be practicing within reasonable parameters and in agreement with PDs of active allergy-immunology training programs. A few, however, have approaches to this common clinical problem that have little objective, studied support. Perhaps the working committees on drug allergy for the AAAI and the American College of Allergy and Immunology could propose practice guidelines for this important area of clinical allergy practice. These guidelines could be periodically updated as further information based on scientific study becomes available. Certainly such guidance would not fall on deaf ears.

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