

Varying penicillin allergy testing practices in the United States: A time for consensus

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Clinical Implications

- Based on the survey results of American Academy of Allergy, Asthma & Immunology practitioners, there is significant variability in penicillin and β -lactam allergy testing and reporting of results that could have an impact on effectiveness. This suggests the need for standardization of β -lactam allergy practice parameters.

TO THE EDITOR:

Penicillin and β -lactam allergies are the most common drug-related allergies in the United States, with 8% of the population reporting penicillin allergy and 1% reporting cephalosporin allergy.¹ More than 95% of the patients who report a penicillin allergy have negative results on properly performed skin tests using current commercially available reagents and pass a confirmatory oral amoxicillin challenge, if the skin test result is negative. An unverified penicillin allergy has been associated with increased hospitalizations, antibiotic-resistant infections, and increased health care costs.^{1,2} This has triggered a public health initiative to decrease the use of broad-spectrum, nonpenicillin class antibiotics by widely using penicillin allergy testing.¹ Routine allergist evaluation of penicillin allergy and the training of allergy fellows have been hampered by previous lack of commercial availability of the major determinant penicilloyl polylysine (PPL) over the last decade. There is also an ongoing debate as to the current utility of various locally produced minor determinant mixtures (MDMs), which have never been commercially available in the United States.³ The most recent allergy practice parameter strongly recommends using PPL when testing for penicillin allergy, but leaves the use of MDMs, aminopenicillins, or penicillin G up to individual providers.⁴ There is no current official recommendation to oral challenge all individuals with negative skin test results, though this criterion standard test has been shown to be safe and effective in both the United States and abroad.^{5,6} The practice parameter also states that some patients may be eligible for penicillin graded challenge without skin testing on the basis of history, leaving even more room for variability in both method of testing and reagents used.⁴ The safe use of direct oral challenge to confirm penicillin tolerance after benign rashes has been reported by several groups.^{7,8} New data are also convincingly demonstrating the lack of clinically significant immunologic cross-reactivity between penicillins and cephalosporins, and even between cephalosporins that lack similar side chains.⁹ Although our understanding of penicillin allergy has significantly advanced, many new allergists in practice received minimal training regarding penicillin allergy testing during their fellowships, thus contributing to the low rate and variability in penicillin allergy testing by allergists in the

United States. At the same time there has been an increased interest in penicillin allergy testing, particularly in relation to driving antibiotic appropriateness, by infectious disease specialists, hospitalists, and pharmacists.

From the primary care provider (PCP) viewpoint, the convenience of using an alternative antibiotic often outweighs the desire to remove the β -lactam allergy label.² However, even among allergy specialists, in 1 study (Puchner and Zacharisen²), only 13% reported that they would perform penicillin skin testing and the majority surveyed would instead use an alternative antibiotic. This is in contrast to a study performed more than 20 years ago surveying American Academy of Allergy, Asthma & Immunology (AAAAI) members and fellowship program directors in which more than 85% of the respondents advocated penicillin skin testing.¹⁰ This survey showed PPL and penicillin G to be the most common reagents used, with 40% of the respondents using MDMs. Most respondents were using skin prick plus intradermal testing for penicillin allergy, and less than 1% were performing oral challenge alone.¹⁰

Given recent imperatives to improve antibiotic use and improve health care outcomes, we were interested in determining current β -lactam allergy testing and reporting practice as well as the perception of testing effectiveness among allergists practicing in different settings.

An e-mailed survey was distributed to the AAAAI membership between September 23, 2014, and October 7, 2014, with an overall response rate of 15% (652 of 4330 allergists) from across the United States. The impact of years in practice and type of practice was assessed using chi-square tests.

Most of the allergists (89%; 583 of 652) provide skin testing (either skin prick and/or intradermal testing). Approximately 6% of the allergists who responded to the survey do not offer evaluation for β -lactam allergy, and do not perform skin testing or oral challenge, with the most common reasons being lack of reagents, resources, and infrastructure. If anything, this survey may underestimate the number of providers not offering β -lactam testing, considering an inherent bias toward survey completion only by those providers who have an interest and do offer testing.

Of the 518 respondents who completed the survey, the most common reagents used in skin testing were Pre-Pen (commercially available major determinant), penicillin G, and MDMs. Penicillin G was reported as being used more frequently (75.2%; 412 of 548) than MDMs (38.3%; 210 of 548). Those practices that test to MDMs were more likely to be academic practices (44% academic vs 36% other; $P = .09$). More than 80% of all practitioners routinely offer oral challenge after negative skin test results. In particular, those providers who have been in practice for less than 10 years are more likely to perform oral challenge (93% vs 85%; $P = .01$). Pre-Pen was reported overall as the most prevalent skin test positive agent (66% of the responses); however, 15% of the providers who tested for ampicillin reported it as the most prevalent positive agent. This could indicate a changing pattern of allergy in our population.

We assessed the quality and consistency of advice given to patients regarding future β -lactam antibiotic use after negative test results (Table 1). Providers who offer both skin testing and

TABLE I. Recommendations to patients after negative test results

Recommendation	Oral challenge offered after skin test	No oral challenge offered
Recommendation if negative		
"I do not offer a recommendation; I only offer a skin test (and oral challenge) report and I leave it up to the patient and PCP to determine what recommendations they follow."	15 (3.3)	3 (4.9)
"Tell them it is safe to take ALL penicillins and cephalosporins."	163 (35.7)	13 (21.3)
"Tell them it is safe to take only penicillins or cephalosporins with negative skin testing."	40 (8.8)	20 (32.8)
"Tell them it is safe to take only the β -lactams to which they passed an oral challenge."	120 (26.3)	4 (6.6)
"Tell them it is safe to take penicillins or cephalosporins if the benefit outweighs the risk."	74 (16.2)	18 (29.5)
Other	45 (9.8)	5 (8.2)

Values are n (%).

TABLE II. Feedback from PCPs after testing

Feedback from PCP	With oral challenge	No oral challenge
No response	4 (0.9)	
No, I do not offer specific recommendations. I offer only test results and I do not receive feedback about future β -lactam antibiotic use.	7 (1.5)	0 (0)
No, I receive no feedback and I'm not sure if my recommendations are followed.	317 (69.4)	38 (62.3)
Yes, I receive feedback that despite negative testing the penicillin allergy label tends to remain with the patients and they continue to avoid penicillins and/or other β -lactams.	8 (1.8)	3 (4.9)
Yes, other providers let me know that my recommendations are followed and whether patients tolerate penicillins or β -lactams in the future.	108 (23.6)	18 (29.5)
Other	13 (2.8)	2 (3.3)

Values are n (%).

oral challenge were most likely to advise patients that it was safe to take all penicillins and cephalosporins (35.7%) or that it was safe to take only those medications to which they had passed an oral challenge (26.3%). Those not offering both skin testing and oral challenge were most likely to advise patients that they should take only those penicillins or cephalosporins to which they had negative skin test results (32.8%) or to advise that it is safe to take penicillins or cephalosporins only if the benefit outweighs the risk (29.5%). More than 60% of the providers who perform testing never receive feedback from the PCP about whether their recommendations are followed and β -lactams are prescribed (Table II), but more than 60% of the providers believe that patients are confident with their testing and would be willing to take a course of β -lactam antibiotics (Table III).

TABLE III. Feedback from patients after testing

Patient feedback	With oral challenge offered	No oral challenge offered
No response	2 (0.4)	
I am unaware of how the patients perceive and act on results from penicillin skin testing and/or oral challenge.	38 (8.3)	3 (4.9)
No, I never or seldom hear from the patients as to whether or not they receive or are willing to receive penicillin or other β -lactam antibiotics.	66 (14.4)	11 (18.0)
Yes, my patients are confident with testing results and they are willing to take penicillins or other β -lactam antibiotics after negative skin test and/or oral challenge results.	334 (73.1)	41 (67.2)
Yes, the patients tell me that they are still unwilling to take a penicillin or β -lactam antibiotic.	7 (1.5)	3 (4.9)
Other	10 (2.2)	3 (4.9)

Values are n (%).

Our survey highlights the inconsistencies and hurdles in allergy practice that likely have a negative impact on the effectiveness of the β -lactam allergy evaluation. Reagents are perceived to be excessively costly and/or difficult to obtain, and even with the criterion standard of skin testing with validated reagents and oral challenge, there is still variability among providers regarding what advice should be given to patients after negative test results. Lack of engagement and feedback from the PCP may be an additional hurdle that has a negative impact on the effectiveness of β -lactam allergy delabeling.

A survey to evaluate β -lactam allergy testing practice administered to AAAAI members more than 20 years ago highlighted the marked inconsistency of practice and the need to introduce standard guidelines.¹⁰ Our survey of β -lactam allergy assessment in contemporary practice suggests the need to reevaluate and standardize not only the current testing practices but also the means by which these tests are reported and the quality of the information that is disseminated to the patients, their medical record, and their health care team.¹¹ Revised guidelines should aim to both critically address these challenges in real clinical practice and try evidence-based approaches of β -lactam testing strategies and reporting.

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Conflicts of interest: E. Phillips has received honoraria paid to her institution from Merck and ViiV; receives royalties from UpToDate; and has a patent for HLA-B*57:01 testing for abacavir HSR. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication February 9, 2015; revised March 10, 2015; accepted for publication March 18, 2015.

Available online April 25, 2015.

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2213-2198

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<http://dx.doi.org/10.1016/j.jaip.2015.03.010>

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Correction

With regard to the article in the July/August 2015 issue of JACI: In Practice entitled “Markers of Differential Response to Inhaled Corticosteroid Treatment Among Children with Mild Persistent Asthma” (*J Allergy Clin Immunol Pract* 2015;3:540-546), Table III was discovered to be incorrectly formatted (p 545). The corrected table is shown here. The journal regrets this error.

TABLE III. Summary of reported characteristics that may modify the response to daily treatment with an inhaled corticosteroid: TREXA, PEAK, CLIC, and PACT trials

	TREXA	PEAK	CLIC	PACT
Population	6-18 y	2-3 y	6-17 y	6-14 y
Sample size	288	285	126	191
Severity	Mild	Positive API	Mild-to-moderate	Mild-to-moderate
Duration	1 y	2 y	16 wk	1 y
ICS	Beclomethasone (40 µg bid)	Fluticasone (88 µg bid)	Fluticasone (100 µg bid)	Fluticasone (100 µg bid)
Comparison	Placebo	Placebo	Montelukast (5-10 mg qd)	Montelukast (5 mg qd)
Risk dimension	Time to first exacerbation	Oral corticosteroid use	% ΔFEV₁	Time to first exacerbation
	Ethnicity*	Gender	Age	Parental asthma history
	IgE level*	Prior health care use	Asthma control days	PC ₂₀ < 2 mg/mL prior ICS use
	Prior OCS use*	Race	Body mass index	
	Skin test†	Skin test	Eosinophil cationic protein	
			FEV ₁ /FVC	
		ED and urgent care visits		
		Prior health care use		
		Race		
		Skin test		
Control dimension	Asthma control days	Episode free days	Asthma control days	Asthma control days
	Gender‡	Gender	FENO	FENO > 25 ppb parental asthma history
	IgE level‡*	Prior health care use		
	Run-in control†,‡	Race		
	Skin test‡			

API, asthma predictive index; CLIC, Characterizing the Response to a Leukotriene Receptor Antagonist and an Inhaled Corticosteroid trial; ED, emergency department; FENO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroid; IgE, immunoglobulin E; PACT, Pediatric Asthma Controller trial; PC₂₀, methacholine concentration associated with 20% decline in FEV₁; PEAK, Prevention of Early Asthma in Kids trial; TREXA, Treating Children to Prevent Exacerbations trial.

*Both symptom-driving and daily ICS treatment (combined).

‡Daily ICS treatment (daily).

‡Symptom-driven ICS treatment (rescue).

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