Original Article

Improving the Effectiveness of Penicillin Allergy De-labeling

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What is already known about this topic? Most penicillin allergy-labeled patients can be de-labeled with skin testing and oral challenge, which is safe and efficacious.

What does the article add to our knowledge? The changing nature of beta-lactam allergy requires re-evaluation of agents routinely used in skin testing, and consideration of alternative strategies for low-risk patients.

How does this study impact current management guidelines? Risk stratification should be used to determine appropriate testing strategies. Improved communication to the patients and primary health care team can increase compliance with clinic recommendations.

BACKGROUND: Approximately 10-20% of hospitalized patients are labeled as penicillin allergic, and this is associated with significant health and economic costs.
OBJECTIVES: We looked at the effectiveness of penicillin allergy de-labeling in clinical practice with the aim of deriving risk stratification models to guide testing strategies.
METHODS: Consecutive patients aged 15 years or more, referred to a Western Australian public hospital drug allergy service between 2008 and 2013 for beta-lactam allergy, were included. Follow-up surveys were conducted. Results of skin prick testing and intradermal testing (SPT/IDT) and oral challenge (OC), and follow-up of post testing antibiotic usage were the main outcomes.
RESULTS: SPT/IDT was performed in 401 consecutive patients with immediate (IMM) (≤1 hour) (n = 151) and nonimmediate (NIM) (>1 hour) (n = 250) reactions. Of 341 patients, 42 (12.3%) were SPT/IDT+ to ≥1 penicillin reagents, including 35/114 (30.4%) in the IMM group and 7/227 (3.1%) in the NIM group ($P < .0001$). Of 355 SPT/IDT patients, 3 (0.8%), all in the IMM group, had nonserious positive OC reactions to single dose penicillin VK (SPT/IDT negative predictive value [NPV] 99.2%). Selective or unrestricted beta-lactam was recommended in almost 90% overall, including 238/250 (95.2%) in the NIM group and 126/151 (83.4%) in the IMM group ($P = .0001$). Of 182 patients, 137 (75.3%) were following the allergy label modifications (ALM) at the time of follow-up.
CONCLUSIONS: Penicillin SPT/IDT/OC safely de-labels penicillin-allergic patients and identifies selective beta-lactam allergies; however, incomplete adherence to ALM recommendations impairs effectiveness. Infrequent SPT/IDT+ and absent OC reactions in patients with NIM reactions suggest OC alone to be a safe and cost-effective de-labeling strategy that could improve the coverage of penicillin allergy de-labeling in lower risk populations. © 2015 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2015;3:365-74)

Key words: *Penicillin; Allergy; Skin testing; De-labeling; Oral challenge; Stewardship*

Approximately 10-20% of all patients in clinical practice are labeled as penicillin allergic.[1-4] Most do not have either true or persistent allergies, with >90% able to tolerate penicillin after thorough assessment.[1,3] Unnecessary avoidance of penicillin increases health care costs, due to the use of more expensive and/or less effective alternative antibiotics, and contributes to the development of antibiotic resistance.[5,6] Penicillin de-labeling strategies are an increasingly recognized as a valuable component of antibiotic stewardship programs.[7] Assessment of penicillin allergy in clinical practice varies widely with regard to the testing reagents used, whether skin testing is followed by oral challenge (OC), how the information from testing is

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Abbreviations used
ADRs- Adverse drug reactions
ALM- Allergy label modifications
BP- Benzylpenicillin
Ig- Immunoglobulin
IMM- Immediate
MDM- Minor determinants mixture
PCP- primary care provider
penicillin VK- Penicillin V potassium
PPL- penicilloyl poly-L-lysine

disseminated to the patient and their health care providers, and in the measures of effectiveness of how testing results are used in clinical practice.

Penicillin skin prick testing and intradermal skin testing (SPT/IDT) and OC are safe and efficacious methods for assessing a penicillin allergy label in large studies.[2,8-10] The major determinant of penicillin (penicilloyl poly-L-lysine, PPL) was historically the most relevant, and positive in 70-90% of patients with an immediate allergy history.[8,11] Use of the minor antigenic determinants of penicillin (minor determinants mixture, MDM) was also considered to be important as some studies suggested that 10-20% of patients with penicillin allergy were PPL SPT/IDT− but positive to MDM.[11]

However, recent studies show that the sensitivity of penicillin SPT/IDT using PPL/MDM is lower than that previously reported.[2,12] The epidemiology of penicillin allergy has changed with declining rates of SPT/IDT+ to benzylpenicillin (BP) and MDM/PPL since the 1990s.[13] It is likely that the decreasing use of parenteral penicillins, and increased utilization of semisynthetic penicillins such as aminopenicillins and cephalosporins in community practice have contributed to this trend, leading to an increase in patients with selective and presumably side-chain-specific allergic reactions.[11,14] A high proportion of patients will have histories of reactions to aminopenicillins, many of whom will have SPT/IDT selectively positive to aminopenicillins such as amoxicillin due to side-chain reactions, which suggests that their inclusion in the panel of reagents for penicillin skin testing is useful.[11,12,15] There are no large studies that provide good evidence regarding the sensitivity and specificity of cephalosporin skin testing, and its utility compared with penicillin skin testing is less clear. However, it is still recommended that cephalosporins be included in the panel of skin test reagents if clinically indicated.[11] Cephalosporin skin testing is likely to have some utility when used in combination with OC, by assisting with characterization of selective cephalosporin allergy compared with broad cephalosporin or beta-lactam allergy. OC is important to increase the sensitivity of penicillin testing and increase the negative predictive value (NPV) to 100% as false-negative skin tests can occur.[16] Single dose OC is most important for ruling out immediate or IgE-mediated reactions, and OC over multiple doses and days may be required to rule out the propensity to a delayed or T-cell-mediated reaction.

The effect of penicillin IDT/SPT/OC on future antibiotic use has not been extensively studied. Rates of adverse drug reactions (ADRs) to beta-lactams after negative penicillin skin testing have been found to be very low in a multiyear follow-up, and no higher than those to non-beta-lactams.[17] Studies have also suggested the potential for improved antibiotic utilization in patients with negative penicillin skin test results.[18,19] Conversely, penicillin avoidance has been reported in a pediatric cohort despite negative skin testing and OC, with parental fear being the major reason.[20] Avoidance of penicillin after negative SPT/IDT has also been identified in adults, although these patients had not undergone OC.[21]

This study assessed the safety and efficacy of penicillin testing strategies in a contemporary population of penicillin allergy-labeled patients to derive a model of risk stratification to rationalize future testing strategies. The effectiveness of testing strategies was measured by determining adherence to the allergy label modification (ALM) made after testing, and whether future antibiotic prescribing and use were influenced by the ALM recommendations.

METHODS

Study population

The Institutional Review Boards at the hospitals involved approved the penicillin skin testing protocols and the use of the Diater reagents. The review of outcomes and safety of testing was a quality assurance project required as part of the approval of the testing protocols. A total of 405 consecutive patients aged 15 years or more were included. The patients were referred to 1 of 2 drug allergy clinics associated with tertiary care public hospitals in Perth, Western Australia, with a history of an allergic reaction to penicillin or other beta-lactam antibiotics and had subsequently undergone SPT/IDT/OC between June 2008 and June 2013. Information regarding the implicated antibiotic, the timing and nature of reaction, comorbidities, and comedication was collected before SPT/IDT/OC, and hospital and/or laboratory records were later reviewed to verify the results of SPT/IDT/OC and serum-specific IgE testing to penicilloyl V and G, amoxicilloyl, ampicilloyl, and cefaclor. The reaction history was classified as immediate (likely IgE mediated, $\leq$1 hour), accelerated (possibly IgE mediated, $\leq$72 hours), delayed (non-IgE mediated, any reaction >72 hours), or other. Patients with a history suggestive of a delayed reaction with severe cutaneous, mucosal, systemic, or organ involvement were not included.

Clinical testing protocol

A standard testing protocol was performed for each patient (Figure 1) with Diater-DAP PPL (benzylpenicilloyl poly-L-lysine; 0.04 mg/mL) and MDM (sodium benzylpenicillin, benzylpenicilloic acid, sodium benzylpenicilloate; 1.5 mg/mL), BP (SPT 10,000 U/mL; IDT 1000 U/mL and 10,000 U/mL in parallel), amoxicillin (20 mg/mL), cefazolin (1 mg/mL), and ceftriaxone (1 mg/mL). Additional SPT/IDT with other penicillins, cephalosporins, or carbapenems was performed if clinically indicated. Therapeutic standard parenteral drug preparations were used for skin testing, using published nonirritating concentrations.[22] Testing was not performed using oral drug preparations (eg, cephalexin), as there are no standardized guidelines. Positive skin tests required wheal 3 mm more than control wheal and flare $\geq$5 mm more than control flare, read after 15 minutes. Some patients were tested for serum-specific IgE antibodies before skin testing at the discretion of the clinician. Penicillin VK OC (250 mg single dose, followed by 2 hours of observation) was performed in patients who were SPT/IDT− or who had selectively positive amoxicillin, ceftriaxone, or cefazolin SPT/IDT. OC to specific beta-lactam antibiotics at a later stage was performed as clinically indicated. Cephalexin OC was performed in patients who were SPT/IDT+ to penicillin determinants or amoxicillin, or had penicillin VK OC+, to exclude broad beta-lactam allergy.

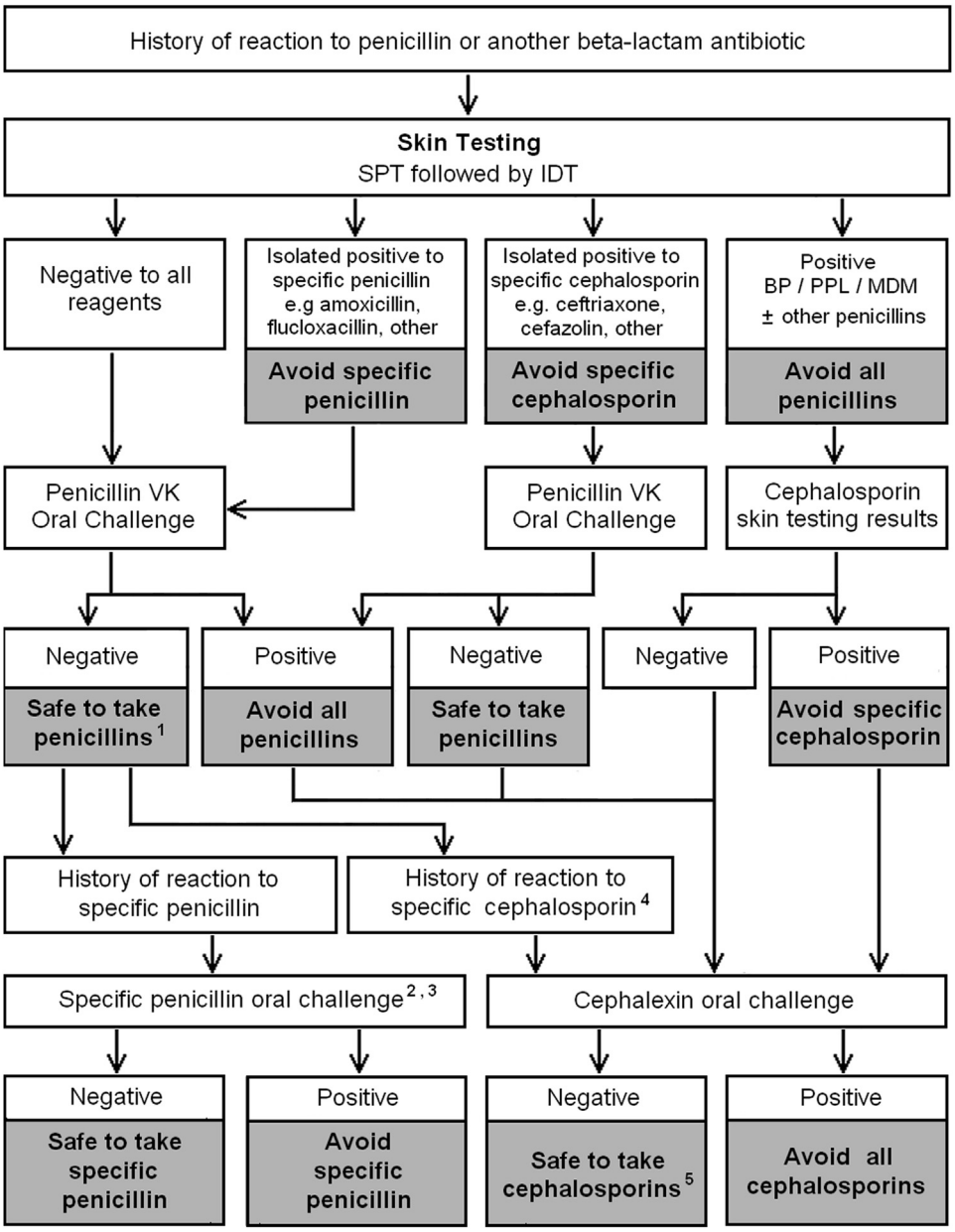

FIGURE 1. Clinical testing protocol. Testing procedures that were applied to 405 consecutive patients referred for assessment of penicillin allergy. 1—Excluding skin test positive specific penicillins; 2—Unless skin testing is positive to that specific penicillin; 3—If oral challenge to specific penicillin cannot be performed (eg, parenteral-only product), then it should be avoided, even if the skin test is negative; 4—Whenever possible, skin testing to the specific cephalosporin should be performed; 5—Excluding skin test positive cephalosporins (and those with shared side chains); specific cephalosporin responsible for reaction until oral challenge has been performed, even if the skin test is negative. *SPT*, skin prick testing; histamine 1 mg/mL, normal saline, BP 10,000 U/mL, Diater PPL, Diater MDM, amoxicillin 20 mg/mL. *IDT*, intradermal testing; normal saline, BP 1000 U/mL, BP 10,000 U/mL, Diater PPL, Diater MDM, amoxicillin 20 mg/mL, cefazolin 1 mg/mL, ceftriaxone 1 mg/mL. *BP*, benzylpenicillin; *MDM*, minor determinants mixture; *PPL*, penicilloyl poly-L-lysine.

Patient follow-up

Patients were contacted to establish their understanding of their allergic status and their antibiotic exposure after either positive or negative SPT/IDT/OC. The interview questioned the nature and type of antibiotic use since testing and ADR occurrence (see Table S1 in this article's Online Repository at www.jaci-inpractice.org for questions and accepted responses). Patients who had not used antibiotics during the follow-up period, or who had avoided beta-lactams for which they had been allergy de-labeled, were asked if they were intentionally avoiding antibiotics and the rationale for this. If any patient had taken multiple medications or there was confusion regarding penicillin use since SPT/IDT/OC, his or her GP was contacted for clarification.

In an effort to improve adherence to recommendations (unrestricted beta-lactam use, avoidance of all penicillins and/or cephalosporins, or avoidance of specific beta-lactam(s) only), the format

and distribution of testing results and recommendations were modified from July 2011 onward. Changes included a summary table within the clinic discharge letter that contained details of each drug investigated and clearly worded recommendations to the patient and his or her primary care provider (PCP) regarding which antibiotics could be tolerated and which should be avoided based on testing results. Immediate counseling and recommendations were given to the patient at the time of his or her appointment, and written documentation of the results of testing and the associated recommendations were received by the patient and his or her most responsible health care provider(s) either at the appointment or within 1 week of his or her appointment. Two groups of patients were interviewed at different time points, with Group 1 patients undergoing testing in the clinic between June 2008 and May 2011 and Group 2 patients between June 2012 and June 2013.

RESULTS

Demographics

The mean age of the patients in the study was 47.4 years (range 15−85 years). There were 272 (67.1%) female patients.

Nature of penicillin allergy

Patients with multiple reactions (either to the same or different beta-lactams) were classified as immediate (IMM) if any of their reactions met that classification (≤1 hour from dosing). Otherwise classification was based on the most recent reaction. Of 401 patients, 151 (37.7%) were classified as IMM, with the remainder in the nonimmediate (NIM) group. Penicillin (n = 181), amoxicillin (n = 94), amoxicillin-clavulanate (n = 49), and cephalexin (n = 56) were the most commonly implicated antibiotics with 60 (15%) patients reporting previous reactions to ≥2 different beta-lactam antibiotics. A total of 341 (85%) patients had a history of a reaction to a penicillin, with 49 (14.4%) having a reaction to a cephalosporin as well. There were 60 (15%) patients with a history of a reaction to a nonpenicillin only, with 59 to a cephalosporin only and 1 to ertapenem.

Skin testing was performed within 6 months of reaction in 108/401 (26.9%) patients, 6 to 12 months in 52/401 (13%), 1 to 5 years in 54/401 (13.5%), 5 to 10 years in 24/401 (6%), and after more than 10 years in 163/401 (40.6%). For those with multiple reactions, the date of the most recent reaction was used for classification.

Skin testing

A total of 405 patients underwent penicillin SPT/IDT in the study period. In 4 patients, skin tests were not interpretable, either due to a positive response to the saline negative control (n = 3) or to an inadequate histamine response (n = 1), and these patients were not included in further analysis (Table I). In patients with a history of a reaction to penicillins, there were 42 (12.3%) positive skin tests to ≥1 reagents and 299 (87.7%) negative skin tests. A total of 29 patients were SPT/IDT+ to ≥1 penicillin determinants (BP, PPL, MDM), with 18 SPT/IDT+ to either BP or PPL/MDM but not both. There were no patients who were SPT/IDT+ to MDM alone or both MDM and PPL in the absence of BP, and only 1 patient was positive to PPL alone. A further 15 patients reacted only to a specific beta-lactam but not BP/PPL/MDM, which suggested a selective side-chain reaction (Table I). This included 14/15 to amoxicillin, all of which had a history of a reaction to only amoxicillin or amoxicillin-clavulanate.

Only 1 patient, who was amoxicillin IDT+, had a mild systemic reaction (generalized pruritus) to skin testing. Another 4 patients had delayed positive responses, all occurring 4-24 hours after testing at the amoxicillin IDT site. All 4 patients had tolerated primary penicillin VK OC before the development of the delayed reaction.

A much higher proportion of SPT/IDT+ occurred in the group tested ≤6 months since their reaction compared with those tested >6 months (27/73 [37.0%] vs 15/268 [5.6%], $P < .0001$). The IMM group also had a significantly higher proportion of positive skin tests than the NIM group (35/112 [31.3%] vs 7/229 [3.1%], $P < .0001$). Patients skin tested ≤6 months since their reaction and also in the IMM group had the highest proportion of positive skin results compared with other patients (Figure 2). There were no differences in the proportion of positive skin tests based on age or gender.

In patients with histories of a reaction only to nonpenicillins, there were 51 (85%) negative skin tests and 9 (15%) positive skin tests to ≥1 reagents (Table I). This included 2/9 (22.2%) with penicillin determinants and specific beta-lactams, and 7/9 (77.8%) to specific beta-lactams only. No patients had positive skin tests to penicillin determinants only. There were no delayed positive responses. Likely because of the smaller numbers in this group, there were no statistically significant differences in time since testing or reaction type between SPT/IDT positive and negative groups, although there was a trend towards higher proportions of patients tested ≤6 months since reaction and those having had IMM reactions in the SPT/IDT positive group (Figure 2).

Oral challenge

Penicillin VK OC was undertaken in 355 patients with negative skin testing to penicillin determinants, with only 3 OC+ all of whom had histories of IMM reactions (NPV 99.2%). There was a higher proportion of OC+ with amoxicillin (4/64, 6.25%) and cephalexin (13/91, 14.3%). OC to amoxicillin-clavulanate (n = 4) and flucloxacillin (semisynthetic antistaphylococcal penicillin used in Australia) (n = 11) were also undertaken if indicated, which were all negative (Table II). All OC reactions occurred within 45 minutes of the challenge, and all were mild cutaneous or subjective reactions.

Selective reactivity

A significant proportion of SPT/IDT+ patients had selective reactivity to individual beta-lactams (23/42, 54.8%), most commonly to amoxicillin (14/23, 60.8%). Of these 23 patients, 20 (87%) had completed their planned follow-up OC. Also, 21/23 (91.3%) patients underwent penicillin VK challenge, which all tolerated, and 16/23 (69.6%) tolerated another beta-lactam on subsequent OC.

There were 143 patients with a history of a reaction to amoxicillin or amoxicillin-clavulanate, with 58/143 (40.6%) in the IMM group. Of the 143 patients, 33 (23.1%) were SPT/IDT+ to ≥1 reagents, with 28/33 (84.8%) having amoxicillin SPT/IDT+. Of the 28 patients with amoxicillin SPT/IDT+, 14 (50%) were selectively positive, with BP/PPL/MDM SPT/IDT−. All 14 patients tolerated penicillin VK OC.

A history of a reaction to a cephalosporin was recorded for 108/401 (26.9%) patients, with 49/108 (45.4%) also having a history of a reaction to a penicillin. This included 61 (56.5%) from the IMM group. Cefazolin or ceftriaxone IDT+ occurred

TABLE I. Skin testing results

Skin test result	Total Number	Reaction history		IMM vs NIM, *P*-value
		IMM	NIM	
All patients, No. (%)	401 (100)	151 (37.7)	250 (62.3)	
Patients with reaction to a penicillin, No. (%)	341 (85.0)	114 (75.5)	227 (90.8)	
Positive, No. (%)	42 (12.3)	35 (30.4)	7 (3.1)	<.0001
Penicillin determinants* only, No. (%)	4 (9.5)	3 (8.6)	1 (14.3)	.53
BP only, No.	2	2	0	
PPL only, No.	1	1	0	
MDM only, No.	0	0	0	
BP and PPL, No.	0	0	0	
BP and MDM, No.	1	0	1	
Penicillin determinants* and individual beta-lactam(s)†, No. (%)	23 (54.8)	17 (47.2)	6 (85.7)	.11
Individual beta-lactam only, No. (%)‡	15 (35.7)	15 (42.9)	0 (0.0)	.04
Amoxicillin, No.	14	14	0	
Cefazolin, No.	1	1	0	
Piperacillin, No.	1	1	0	
Negative, No. (%)	299 (87.7)	80 (69.6)	219 (96.9)	<.0001
Delayed positive intradermal test, No. (%)	4 (1.2)	0 (0.0)	4 (1.8)	.30
Amoxicillin, No.	4	0	4	
Patients with reaction to a nonpenicillin beta-lactam only, No. (%)	60 (15.0)	39 (25.8)	21 (8.4)	
Positive, No. (%)	9 (15.0)	8 (20.5)	1 (4.8)	.14
Penicillin determinants* only, No. (%)	0 (0.0)	0 (0.0)	0 (0.0)	
Penicillin determinants* and individual beta-lactam(s)†, No. (%)	2 (22.2)	2 (25.0)	0 (0.0)	.33
Individual beta-lactam only, No. (%)‡	7 (77.8)	6 (75.0)	1 (100)	1.00
Amoxicillin, No.	2	2	0	
Cefazolin, No.	5	4	1	
Cefuroxime, No.	1	1	0	
Negative, No. (%)	51 (85.0)	31 (79.5)	20 (95.2)	.15
Delayed positive intradermal test, No. (%)	0 (0.0)	0 (0.0)	0 (0.0)	

BP, benzylpenicillin; *IMM*, immediate; *MDM*, minor determinants mixture; *NIM*, nonimmediate; *PPL*, penicilloyl poly-L-lysine.
*BP ± PPL ± MDM.
†One or more of amoxicillin, cefazolin, ceftriaxone ± other.
‡One patient positive to both amoxicillin and cefazolin.

in 8/108 (7.4%). Cephalexin OC was undertaken in 58/108 (53.7%), with 9/58 (15.5%) OC+ in total. Included in the 58 patients challenged with cephalexin were 4 patients with a history of a reaction to cefazolin who had cefazolin IDT+ but ceftriaxone IDT−. Cephalexin OC was positive in only 1 (25%) of these 4 patients.

In vitro testing

There were 120 patients who had specific IgE to penicilloyl V and penicilloyl G measured, with 5/120 (4.2%) positive results. For these patients, SPT/IDT was negative in 2 cases, positive in 2 cases, and indeterminate for 1 patient. Neither of the 2 patients with positive specific IgE but SPT/IDT− had positive penicillin VK OC.

Allergy label modification

The ALM recommendation was given to each patient and his or her referring doctor after testing. De-labeling that resulted in a recommendation for either selective or unrestricted beta-lactam use occurred in 89.9% patients overall, which included 238/250 (95.2%) in the NIM group and 126/151 (83.4%) in the IMM group ($P = .0001$).

Follow-up survey

Follow-up surveys were conducted with patients who had completed all testing to determine details and tolerance of antibiotic use. A total of 182 patients were interviewed after their ALM recommendation was made (median 15 months). Group 1 (n = 125) included patients tested before the communication changes and Group 2 (n = 57) included those tested after the changes (Table III).

In a model that adjusted for time between ALM and interview, adherence to ALM recommendations was positively associated with having an SPT/IDT+ result ($P = .04$). If the groups were considered separately, within Group 1, 15/16 (94%) SPT/IDT+ patients were following ALM compared with 74/109 (68%) SPT/IDT− patients ($P = .04$). In Group 2, there was no difference between SPT/IDT+ and SPT/IDT− patients in the adherence to ALM recommendations. Also, the percentage of SPT/IDT− patients following ALM was higher in Group 2, 46/54 (85%), compared with 74/109 (68%) in Group 1 ($P = .02$). There was no significant association between ALM adherence and the type of reaction history, or the time between reaction and testing. In patients not adherent to the ALM recommendation, the most common reason cited was reservation by the patient and/or their PCP.

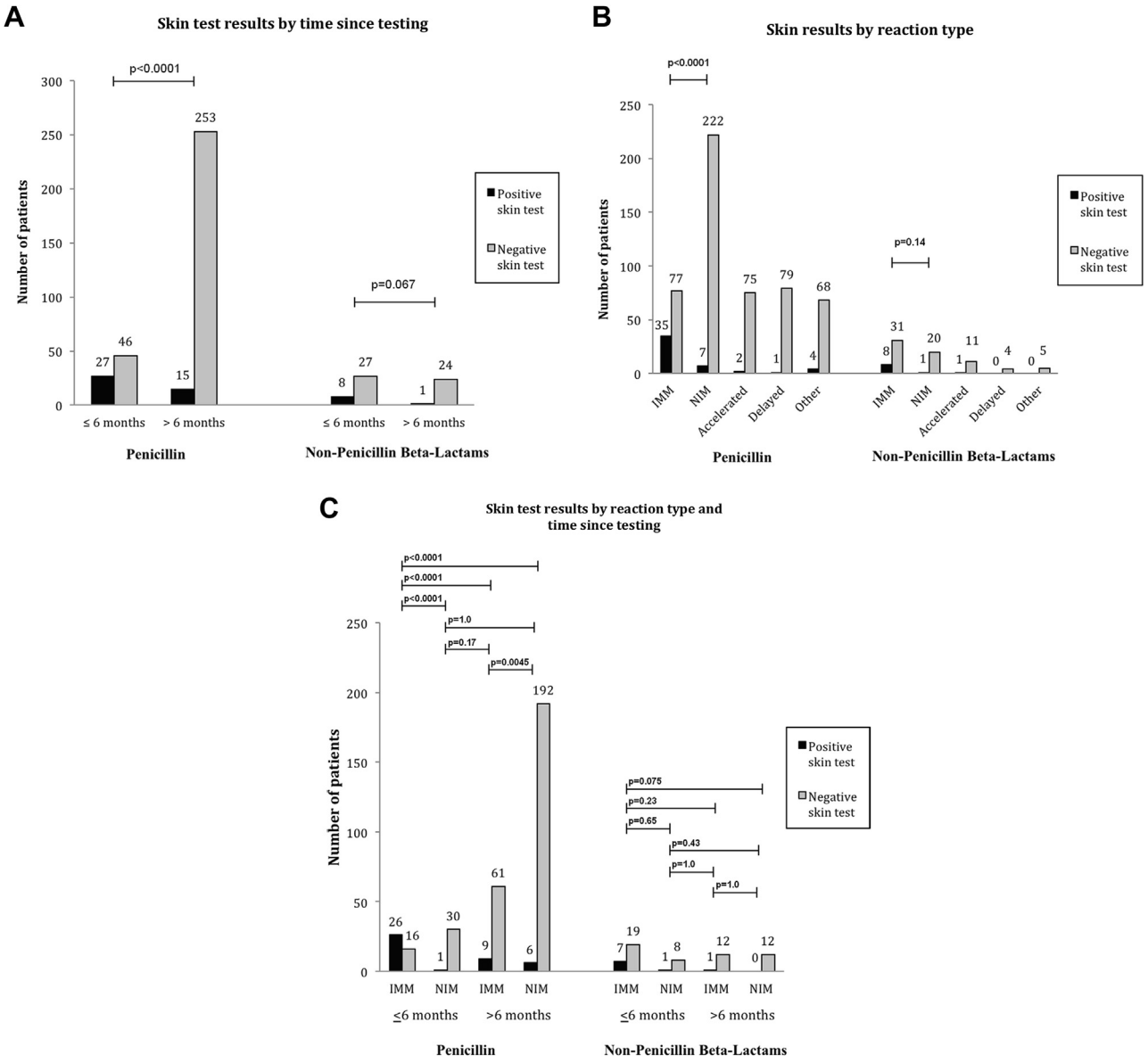

FIGURE 2. Skin test results, reaction time and time since testing. (**A**) Skin test results by time since testing. (**B**) Skin test results by reaction type. (**C**) Skin test results by reaction type and time since testing. Risk for positive skin prick testing and intradermal testing (SPT/IDT) occurs mainly in patients with immediate reactions occurring <6 months before SPT/IDT. Lowest risk patients have nonimmediate reaction histories that occur >6 months from testing. *IMM*, immediate reaction history; *NIM*, nonimmediate reaction history. Patients grouped based on implicated antibiotic into penicillin (n = 341) or nonpenicillin beta-lactams (n = 60, with 59/60 to a cephalosporin, 1/60 to ertapenem).

Of the 101 patients who had subsequently received antibiotics, 17 (16.8%) self-reported an ADR. There were no cases of IMM reactions in patients who had been de-labeled of their beta-lactam allergy. This information was self-reported, and it was not always possible to confirm the antibiotics responsible for the reactions.

DISCUSSION

Penicillin SPT/IDT/OC de-labels most patients with a label of penicillin allergy in contemporary clinical practice,[2] and safety has been demonstrated in studies with a very large number of patients.[8,9] In our study, the NPV of skin testing alone is >99%, and 100% when combined with OC. It is well recognized that even after negative penicillin skin testing, there will be a predictable rate of new adverse drug reactions with subsequent antibiotic use, including those with non-beta-lactam antibiotics. In a large cohort study, this rate was found to be 2.9% per treatment course for penicillins and 2.7% for sulfonamide antibiotics, which was not significantly different.[23,24] Currently, almost 90% of our patients have a recommendation that they can tolerate ≥1 beta-lactam antibiotics. This high NPV is predicated on the use of multiple SPT/IDT reagents, and our results indicate that some patients would be missed if a combination of both penicillin determinants and individual beta-lactam antibiotics

TABLE II. Results of oral challenges

	Oral challenge drug				
Oral challenge result	**Penicillin VK**	**Amoxicillin**	**Amoxicillin-clavulanate**	**Cephalexin**	**Flucloxacillin**
All patients					
Total, No.	355	64	4	91	11
Positive, No. (%)	3 (0.8)	4 (6.3)	0 (0.0)	13 (14.3)	0 (0.0)
Negative, No. (%)	345 (97.2)	60 (93.8)	4 (100)	73 (80.2)	11 (100)
Indeterminate, No. (%)	7 (2.0)	0 (0.0)	0 (0.0)	5 (5.5)	0 (0.0)
Penicillin history					
Total, No.	301	60	4	58	10
Positive, No. (%)	3 (1.0)	4 (6.7)	0 (0.0)	9 (15.5)	0 (0.0)
Negative, No. (%)	292 (97.0)	56 (93.3)	4 (100)	47 (81.0)	10 (100)
Indeterminate, No. (%)	6 (2.0)	0 (0.0)	0 (0.0)	2 (3.4)	0 (0.0)
Nonpenicillin history					
Total, No.	54	4	0	33	1
Positive, No. (%)	0 (0.0)	0 (0.0)	0	4 (12.1)	0 (0.0)
Negative, No. (%)	53 (98.1)	4 (100)	0	26 (78.8)	1 (100)
Indeterminate, No. (%)	1 (1.9)	0 (0.0)	0	3 (9.1)	0 (0.0)

TABLE III. Results of the follow-up survey

		Group 1	Group 2	
Period of testing	**Total**	**June 2008 to May 2011**	**June 2012 to June 2013**	**Group 1 vs Group 2 *P*-value**
Total patients, No. (%)	182 (100)	125 (68.7)	57 (31.3)	
Positive skin test, No. (%)	19 (10.4)	16 (12.8)	3 (5.3)	.19
Negative skin test, No. (%)	163 (89.6)	109 (87.2)	54 (94.7)	.19
IMM history, No. (%)	58 (31.9)	45 (36)	13 (22.8)	.09
NIM history, No. (%)	124 (68.1)	80 (64)	44 (78.9)	.09
Following ALM recommendations, No. (%)	137 (75.3)	89 (71.2)	48 (84.2)	.07
Positive skin test, No. (%)	17 (89.5)	15 (93.8)	2 (66.7)	.30
Negative skin test, No. (%)	120 (73.6)	74 (67.9)	46 (85.2)	.02
Positive vs Negative, *P*-value	.17	.04	.41	
IMM history, No. (%)	41 (70.7)	29 (64.4)	12 (92.3)	.08
NIM history, No. (%)	95 (76.6)	60 (75.0)	35 (79.5)	.66
IMM vs NIM, *P*-value	.46	.22	.43	
Subsequent antibiotic use, No. (%)	101 (53.4)	75 (60.0)	26 (43.3)	.08
Beta-lactam, No. (%)	64 (63.4)	43 (57.3)	21 (80.8)	.04
Non-beta-lactam, No. (%)	37 (36.6)	32 (42.7)	5 (19.2)	.04
Adverse reaction, No. (%)	17 (16.8)	15 (20.0)	2 (7.7)	.23

were not used. In the United States and many other countries, MDM is not commercially available and approved by regulatory agencies that prompt many groups not to use MDM in penicillin skin testing but to use BP and a major determinant product (Pre-pen, PPL) with or without other reagents. In our study, only 1 patient out of a total of 51 SPT/IDT+ who had an isolated IDT+ to PPL was picked up by use of the Diater DAP-kit (PPL/MDM). There were no patients who were only SPT/IDT+ to MDM; however, 2 patients both with histories of IMM reactions were SPT/IDT+ to BP in the absence of SPT/IDT+ to either PPL or MDM (Table I), which highlighted the utility of BP in routine penicillin SPT/IDT. In addition, our study highlights the potential declining importance of PPL and, in particular, MDM to identify penicillin allergy in contemporary practice where use of oral aminopenicillins and cephalosporins now dominates with decreasing use of ambulatory intramuscular forms of penicillins. In our population, the use of PPL and MDM did not significantly contribute to the NPV of skin testing; however, further studies in other populations are needed before a broad testing recommendation can be made. A high proportion of SPT/IDT+ patients reacted only to a specific antibiotic and not PPL/MDM/BP consistent with other recently published cohorts, supporting the use of individual beta-lactams to increase the sensitivity and NPV of SPT/IDT.[11]

The use of OC to multiple drugs can also assist in defining specific beta-lactam allergies, especially as side-chain reactions have become more prevalent. Most reactions to cephalosporins are directed at side-chain structures rather than the shared beta-lactam or cephalosporin rings. Cephalexin OC following SPT/IDT+ to penicillin determinants or amoxicillin is useful to rule out broad cross-reactivity with cephalosporins, or cross-reactivity to a shared side-chain structure with amoxicillin. As the rate of

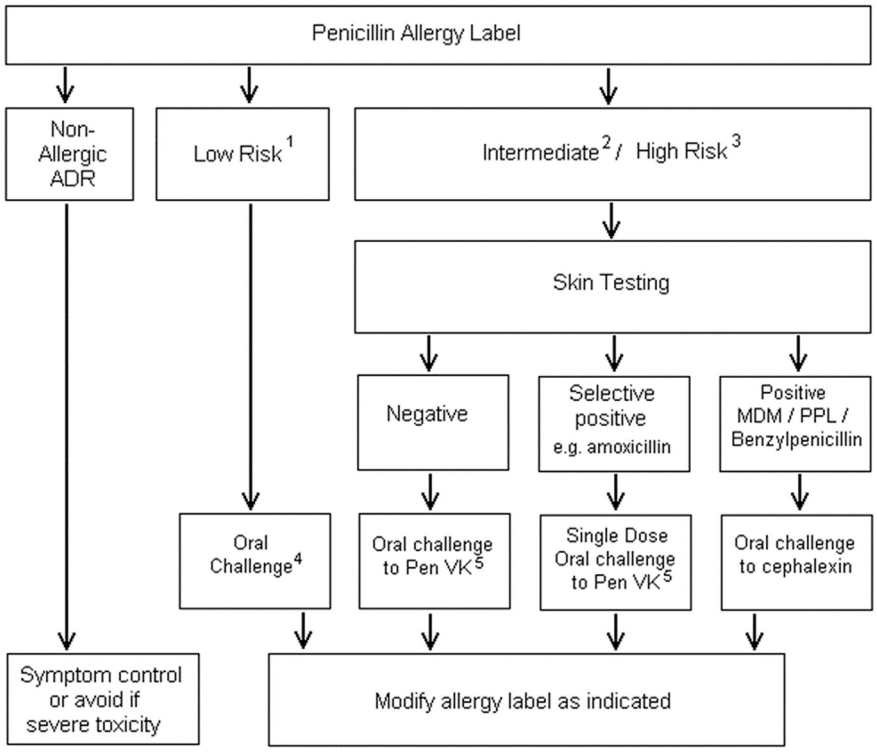

FIGURE 3. Proposed modified testing protocol. If applied to our cohort, 252 (62.2%) of patients would have proceeded to oral challenge (OC) without skin prick testing and intradermal testing (SPT/IDT) with up to 8 additional positive OC. 1—Nonimmediate history (onset >1 hour after dosing, reaction localized to skin), 2—Immediate history, reaction >6 months before testing, 3—Immediate history, reaction <6 months before testing, 4—Initially to penicillin VK, followed by other beta-lactams if indicated. Single vs multiple dose depending on history, 5—Plus further beta-lactam challenges as indicated. *ADR*, adverse drug reaction; *MDM*, minor determinants mixture; *PPL*, penicilloyl poly-L-lysine.

cross-reactivity with penicillin is higher for first generation cephalosporins than for second or third generations, a negative cephalexin challenge rules out cross-reactivity based on the shared cephalosporin dihydrothiazine ring. For patients with a history of a reaction to a specific cephalosporin, such as cefazolin, a negative cephalexin OC supports that there is no cross-reactivity to the shared cephalosporin ring and that in the absence of shared side-chain structures avoidance of that specific cephalosporin only is warranted.

In vitro testing for serum-specific IgE antibodies to the major determinants of beta-lactams is regarded as a specific, noninvasive test that may identify patients at high risk for reactions to skin testing or OC.[25-27] The commercial specific IgE antibody assay lacked both sensitivity and specificity and therefore appeared to have no such utility in our cohort, a finding that has also been reported elsewhere.[26]

Prospective studies confirm that skin test reactivity is lost over time in penicillin-allergic patients with only 30-50% of patients with initial SPT/IDT+ to penicillin determinants remaining positive after 5 years.[28,29] Resources did not allow repeat testing to be performed within the timelines of our study, but this would be a potential strategy to identify such patients and it seems reasonable to alert patients to the lack of permanency of penicillin allergy and tendency for loss of skin test and clinical reactivity over time. The rate of loss of selective amoxicillin skin reactivity is even greater, with one study finding that all patients became skin test negative after 5 years.[28] For cephalosporins, approximately two-thirds of patients become SPT/IDT− by 5 years.[30] In our study, SPT/IDT− was significantly associated with longer time between reaction and testing, and is consistent with loss of skin reactivity over time, which has also been reported in other studies.[13] The fact that SPT/IDT− was highly predictive of OC− suggested that loss of skin reactivity does indicate loss of IgE-mediated allergy in most patients.

A penicillin allergy label is associated with increased health care costs due to longer hospital admissions and risk of serious infections with multiresistant organisms such as vancomycin-resistant enterococci, methicillin-resistant *Staphylococcus aureus*, and *Clostridium difficile*.[31] Penicillin SPT/IDT/OC used by allergy clinics and antibiotic stewardship programs to de-label patients can reduce some of these costs; however, they can also be time intense and costly and involve the use of the PPL and MDM reagents the latter of which is not commercially available in North America.[18,32] The coverage of penicillin allergy de-labeling is currently limited by the resources and capacity of most health care systems that could not support large-scale SPT/IDT. Patients who attend allergy clinics for assessment of penicillin and other drug allergies often have lower risk histories such as accelerated, delayed, or remote reactions. Our study identified that the main risk factor for skin test positivity was a history of an IMM reaction. Testing being performed within 6 months of the reaction was another important predictor of skin test positivity. Patients at low risk of an

immediate allergy to penicillin could be identified that may be appropriate for OC without prior SPT/IDT. Indeed all 3 patients with positive OC to penicillin VK in our study had a history of an IMM reaction and only 8/252 (3.2%) patients with NIM reaction histories had ≥1 positive SPT/IDT. Use of graded challenge without prior skin testing has been proposed previously for patients with low-risk reactions, such as type IV nonpruritic, morbilliform eruptions.[33]

A modified testing protocol that involves direct OC of low-risk patients is proposed (Figure 3). Applied to our cohort, 252 (62.2%) patients would have proceeded to OC without SPT/IDT, with up to 8 additional nonsevere OC+ anticipated if all SPT/IDT+ patients reacted on OC. Intermediate and high-risk patients (n = 151) would be tested as per the existing protocol, with 3 penicillin VK OC+ as previously described.

Patient interviews after testing examined the effectiveness of the ALM after SPT/IDT/OC. Many patients continued to avoid some or all of the beta-lactams de-labeled, and reasons for this nonadherence to ALM recommendations included lack of trust in the testing, ongoing perceived intolerance of those antibiotics, and uncertainty on the part of the PCP. Following simplification and wider distribution of the clinic discharge letter, adherence to ALM improved in SPT/IDT− patients.

These findings support a role for clearer reporting and improved communication to the patients and their health care providers regarding the outcomes and implications of testing, and this includes the widespread distribution of testing reports and recommendations.

CONCLUSIONS

A label of penicillin allergy is common and strategies to de-label and manage penicillin allergy could be an integral component of antibiotic stewardship programs. Penicillin SPT/IDT/OC of patients with a reported history of allergy to beta-lactam antibiotics is a safe and efficacious means to modify the allergy label. However, the effectiveness of penicillin de-labeling approaches is limited by the perception and attitudes of patients and prescribing doctors towards testing and outcomes. Reliable communication of testing results and recommendations to the patient and the entire health care team, including pharmacists, need to be optimized such that these results can be appropriately acted on to achieve the full benefits of penicillin allergy de-labeling. Recent studies have highlighted the public health and cost imperatives to address the high population burden of penicillin allergy-labeled patients. Modified testing protocols (Figure 3) to restrict full SPT/IDT/OC to the highest risk patients with utilization of observed OC alone in lower risk populations represent potentially safe and cost-effective approaches that could facilitate both the feasibility and coverage of penicillin allergy de-labeling and improve therapeutic options and antibiotic utilization. These approaches warrant further study.

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TABLE S1. Patient questionnaire

	Question	Accepted response
1	Have you been hospitalized since penicillin allergy testing in (date)?	Yes >check medical records No
2	Have you taken a course of antibiotics since penicillin allergy testing in (date)?	Yes No Unsure > contact GP
	Yes for (2)	
2b	If yes for (2), how many courses?	Number X
2c	If yes for (2), did you follow recommendations from the allergy clinic?	Yes No Unsure > contact GP
2d	What medication did you take specifically?	Beta-lactam Cephalosporin Unsure > check with GP (details noted)
2e	If yes for (2), did you experience any adverse reaction?	Yes No
2f	Can you provide details of any adverse reaction?	Details noted individually
	No for (2)	
3	Did you require penicillins and choose an alternative medication?	Yes No
	Yes for (3)	
3b	If Yes for (3), what was the reason to avoid penicillins?	1 = fear, 2 = GP advice, 3 = adverse reactions, 4 = confusion with results and/or history, other = 5, selective allergy = 6 (other reasons noted individually)
	No for (3)	
4	If No for (3), will you continue to avoid penicillins?	Yes No Will take medical advice
4b	If Yes for (4), for what reason?	1 = fear, 2 = GP advice, 3 = adverse reactions, 4 = confusion with results and/or history, other = 5, selective allergy = 6 (other reasons noted individually)