Original Article

Comparing Direct Challenge to Penicillin Skin Testing for the Outpatient Evaluation of Penicillin Allergy: A Randomized Controlled Trial

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What is already known about this topic? The benefits of penicillin allergy delabeling are well established. Penicillin skin testing is a proven approach to penicillin allergy delabeling, but there is emerging data regarding direct challenges without prior skin testing in low-risk individuals.

What does this article add to our knowledge? This article is the first randomized controlled trial comparing penicillin skin testing to a 2-step direct challenge in penicillin-allergic patients with cutaneous-only symptoms.

How does this study impact current management guidelines? This study demonstrates the safety and utility of 2-step direct challenges in low-risk patients with a 30-minute monitoring period as compared with penicillin skin testing for delabeling of penicillin allergy in the outpatient setting.

BACKGROUND: Direct challenge (DC) may be a safe and effective alternative to penicillin skin testing (PST) in low-risk patients.

OBJECTIVE: To complete a prospective, randomized, controlled trial comparing PST followed by a challenge to amoxicillin versus a 2-step DC to amoxicillin without preceding skin testing in a predefined low-risk patient population.

METHODS: Penicillin allergy histories were reviewed in patients presenting to an outpatient allergy/immunology practice from April 2018 to August 2018. Patients 5 years or older with a cutaneous-only or unknown reaction (>1 year ago for those aged 5-17 years, >10 years ago for those 18 years or older) were randomized 1:1 to PST or 2-step DC. All children younger than 5 years underwent DC, and patients with extracutaneous reaction histories underwent PST. All groups were monitored 30 minutes after administration of amoxicillin.

RESULTS: Penicillin allergy was reported in 363 of 2465 (14.7%) patients, of which 185 consented to further evaluation. Thirteen patients younger than 5 years underwent DC; all were negative. Thirteen patients with angioedema and/or extracutaneous symptoms underwent PST; 2 of 13 patients had positive PST result. A total of 159 patients were randomized to DC (49.7%) or PST (50.3%). PST result was negative in 70 of 80 (87.5%) patients. All 70 patients had a negative amoxicillin challenge. DC was negative in 76 of 79 (96.2%) patients; positive DC reactions were minor. Average time for patients undergoing PST was 72.7 ± 5.3 minutes and for patients undergoing DC was 66.7 ± 4.8 minutes.

CONCLUSIONS: In low-risk patients, DC provided a safe and effective alternative to PST in delabeling penicillin allergy. Compared with PST, DC may also take less time, cost less money, and lead to fewer penicillin allergy evaluations with false-positive results. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;■:■-■)

Key words: *Penicillin allergy; Penicillin allergy screening algorithm; Penicillin skin testing; Stewardship; Drug allergy; De-labeling; Direct challenge*

INTRODUCTION

The penicillin allergy label carries significant ramifications for individual patients and health care systems. Despite the established harms of the penicillin allergy label, approximately 10% of the US population carries this label.[1,2] Reported penicillin allergy has been associated with increased adverse effects from second-line antibiotics, risk of resistant organisms, such as methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, and *Clostridium difficile*, increased length and cost of

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Conflicts of Interest: S. S. Mustafa is on the speakers bureau for Genentech, Regeneron, Astra Zeneca, Teva, and CSL Behring and has received research funding from CSL Behring, Regeneron, and Shire (now Takeda). K. Conn has no relevant conflicts of interest. A. Ramsey is on the speakers bureau for Sanofi/Regeneron and has received research funding from CSL Behring, Regeneron, and Shire (now Takeda).

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Abbreviations used
DC- Direct challenge
PST- Penicillin skin testing

hospital stay, and decreased cure rates.[3-7] Given these risks, the American Academy of Allergy, Asthma, and Immunology,[8] the Infectious Disease Society of America,[9] and the Centers for Disease Control and Prevention[10] have all advocated for penicillin allergy delabeling. More than 90% of patients are not truly allergic to penicillin after evaluation, with these negative evaluations leading to significant individual and public health benefits.[1,2,8-10]

There are many studies from various health care settings supporting the use of penicillin skin testing (PST) for penicillin allergy delabeling, and PST has been the standard approach to evaluate a penicillin allergy history suggestive of an IgE-mediated reaction or to rule out an immediate reaction in patients with unclear histories.[11-17] More recently, there is emerging data on the utility of direct challenges (DCs) without preceding PST to evaluate penicillin allergy in low-risk patient populations.[18-22] Incorporation of DC into penicillin allergy evaluations has many potential benefits, including the ability to increase the capacity to delabel penicillin allergy across the health care continuum, because the availability of PST can be a limiting factor for penicillin allergy delabeling.[3] However, there is neither consensus regarding characteristics comprising a low-risk population nor agreement surrounding the approach to DC.[23]

We sought to further elucidate the appropriate history for and approach to a DC by conducting a prospective, randomized, controlled trial comparing PST followed by a challenge to amoxicillin versus a 2-step DC to amoxicillin without preceding skin testing in a predefined low-risk patient population.

METHODS

The study was conducted at the Rochester Regional Health outpatient allergy practice in Rochester, NY, from April 2018 through August 2018 and was approved by the institutional review board. There are 4 full-time and 2 part-time allergists in the practice who see patients in 3 separate office locations. Two of the 6 physicians participated in this study. We conducted a prospective, randomized, outpatient trial comparing penicillin skin test followed by an oral amoxicillin challenge versus a 2-step DC to amoxicillin without a preceding penicillin skin test. Inclusion criteria included a history of documented penicillin allergy in the electronic medical record. Patients younger than 5 years and patients with a history including extracutaneous symptoms underwent evaluation, but were not part of the randomized study cohort. To be eligible for the randomized study cohort, patients needed to be aged 5 to 17 years with a history of cutaneous-only reaction to penicillin more than 1 year ago, or aged 18 years and older with a history of cutaneous-only reaction more than 10 years ago. Exclusion criteria included pregnancy, as well as symptoms suggestive of a severe cutaneous non—IgE-mediated adverse drug reaction (fever, blistering, involvement of mucus membranes) or a serum sickness-like reaction.

A detailed penicillin allergy history was obtained on all patients presenting to the practice, regardless of chief complaint. Patients with an appropriate history underwent informed consent. A drug allergy history screening algorithm was created to risk stratify patients for avoidance of beta lactams, penicillin skin testing, or 2-step DC (Figure 1, *A* and *B*). Any patient with a history suggestive of severe, cutaneous, non—IgE-mediated adverse drug reaction to penicillin or a serum sickness-like reaction was told to continue avoidance of penicillin. All individuals with a high-risk history of IgE-mediated penicillin allergy (anaphylaxis, angioedema, respiratory symptoms, hemodynamic changes) underwent PST followed by an oral amoxicillin challenge. All children younger than 5 years with a history of cutaneous-only reaction underwent DC to amoxicillin. Individuals aged 5 to 18 years with a history of cutaneous-only reaction more than 1 year ago were randomized 1:1 to PST followed by an oral amoxicillin challenge or a 2-step DC to amoxicillin (Figure 1, *A*). Similarly, adults older than 18 years with a history of cutaneous-only reaction more than 10 years ago were also randomized 1:1 to PST followed by an oral amoxicillin challenge or a 2-step DC to amoxicillin (Figure 1, *B*). Patients with a family history of penicillin allergy but no personal history of clinical reaction to penicillin or with a history suggestive of drug intolerance were delabeled for their reported penicillin allergy without any testing.

Patients who underwent DC received 1/10 of the target dose of amoxicillin, were monitored for 30 minutes, then received a full dose of amoxicillin, and were monitored for an additional 30 minutes. Children undergoing DC received amoxicillin 20 and 200 mg or 40 and 400 mg depending on age, weight, and provider preference, whereas adults received amoxicillin 40 and 400 mg. PST was administered on the volar forearm using the Quintip testing device (Hollister-Stier, Spokane, Washington) with benzylpenicilloyl polylysine (Pre-Pen, ALK, Round Rock, Texas) as the major determinant, penicillin G 10,000 U/mL as the minor determinant, histamine 6 mg/mL as the positive control, and sodium chloride 0.9% as the negative control.[24] Negative skin prick testing was followed by intradermal testing administered on the upper arm with the same materials except a histamine concentration of 0.02 mg/mL. The major and minor determinants were performed in duplicate. Patients were observed for 15 minutes after both the skin prick test and the intradermal test. Skin test results were measured in millimeters. A positive test result for each step was defined as a wheal diameter (that was) at least 3 mm more than that of the saline control in the presence of a histamine control ($\geq$3 mm of induration). The following data were collected for each patient: demographic data (age, race, sex), penicillin allergy history, penicillin allergy algorithm data, presenting chief complaint, and time to complete the penicillin allergy evaluation. Skin testing results and the outcomes of the DC were also collected. For patients not undergoing penicillin allergy evaluation, the reason for the evaluation not being completed was recorded. Finally, cost was calculated per the Revenue Integrity fee schedule, which is the Rochester Regional Health fee schedule of usual and customary prices billed for the specific type of testing.

Statistical analysis

For the statistical analysis, we used descriptive analysis for patient characteristics, the penicillin allergy history, and the reasons patients did not undergo penicillin allergy evaluation. Fisher exact test as well as *t* test and Mann-Whitney *U* test (as appropriate) were used to compare reaction rates and time between the randomized DC and PST groups. All analysis were conducted using SPSS V24 (IBM Corporation, Armonk, NY) and Microsoft Excel software (Microsoft Corporation, Redmond, Wash).

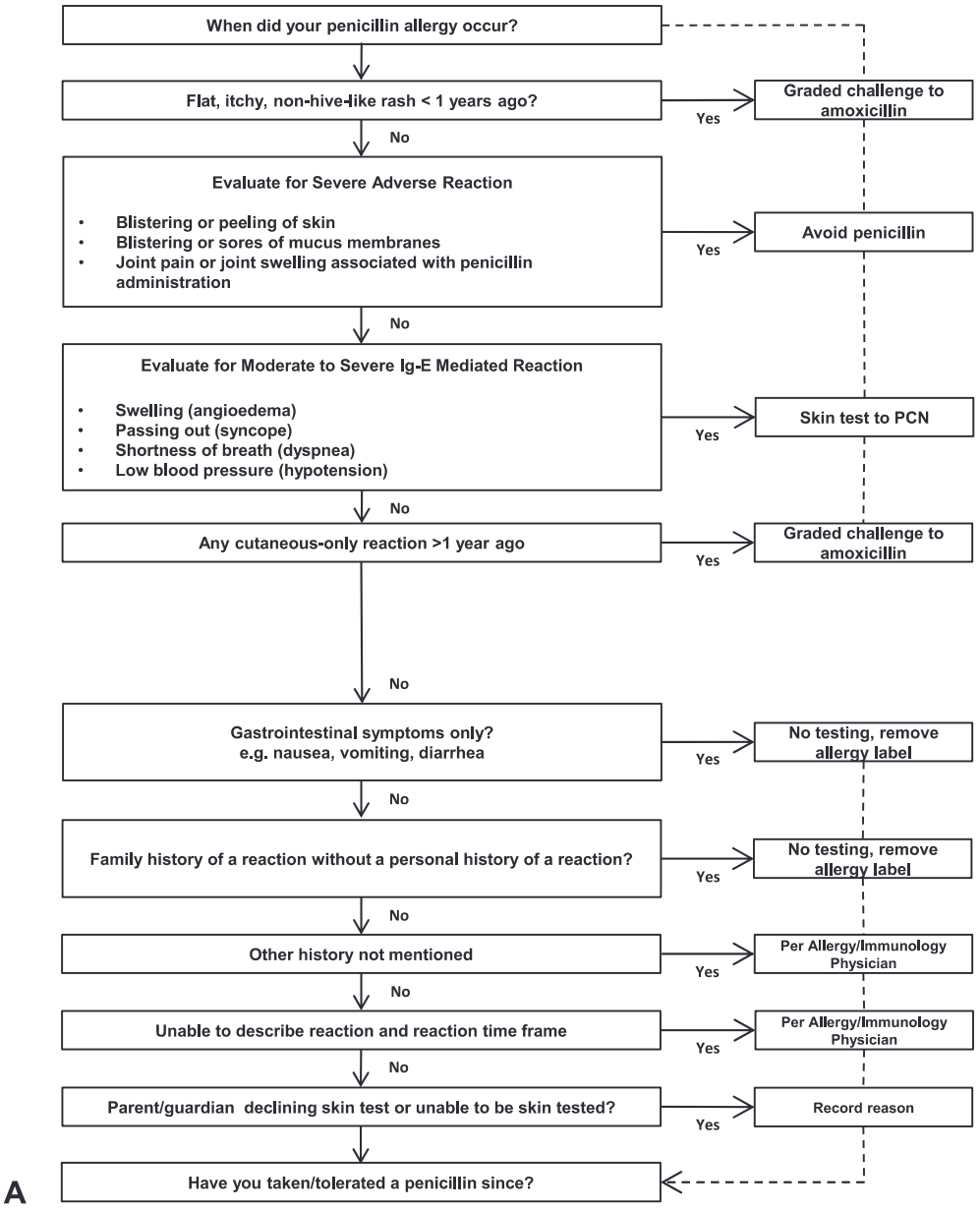

FIGURE 1. Risk stratification algorithms. **A,** Penicillin allergy history algorithm: younger than 5 years, population not randomized. **B,** Penicillin allergy history algorithm: 5 years and older, randomized population. *GC,* Graded challenge; *PCN,* penicillin.

RESULTS

From April 2018 through August 2018, of 2465 patients, 363 (14.7%) reported a penicillin allergy (Table I). Of these 363 patients, 207 (57%) presented new patient evaluations, whereas 156 (43%) were follow-up visits. One hundred seventeen (32.2%) subjects were male, and 246 (67.8%) subjects were female. The average age was 35.3 ± 25.3 years, with a range of 1 to 90 years. The most common presenting chief complaints was evaluation of penicillin or drug allergy, for 82 of 363 (22.6%) patients. Other common presenting complaints were as follows: 80 of 363 (20.0%) chronic rhinitis/sinusitis, 70 of 363 (19.3%) asthma, 43 of 363 (11.8%) food allergy, 31 of 363 (8.5%) urticaria, and 57 of 363 (15.7%) other chief complaints. Historical reactions to penicillin are shown in Figure 2, *A*. Of the 363 patients, 280 (77.1%) reported cutaneous-only manifestations. Of these 280 patients, 171 (61.1%) reported a rash, while 109 (38.9%) patients reported urticaria. Other manifestations of historical penicillin allergy included angioedema, pruritus, dyspnea, and anaphylaxis, or a combination of symptoms. Eight (2.2%) patients reported a history suggestive of non–IgE-mediated mechanism, and 20 (5.5%) patients did not recall their clinical history. Most reported clinical reactions to penicillin occurred more than 10 years ago (52.6%) (Figure 2, *B*). Fifty-eight (16.0%) reactions occurred between 5 and 9 years ago, 63 of 363 (17.4%) occurred 1 to 4 years ago, and 23 of 363 (6.3%) occurred within 1 year. Twenty-eight (7.7%) patients could not recall when their reported penicillin reaction occurred.

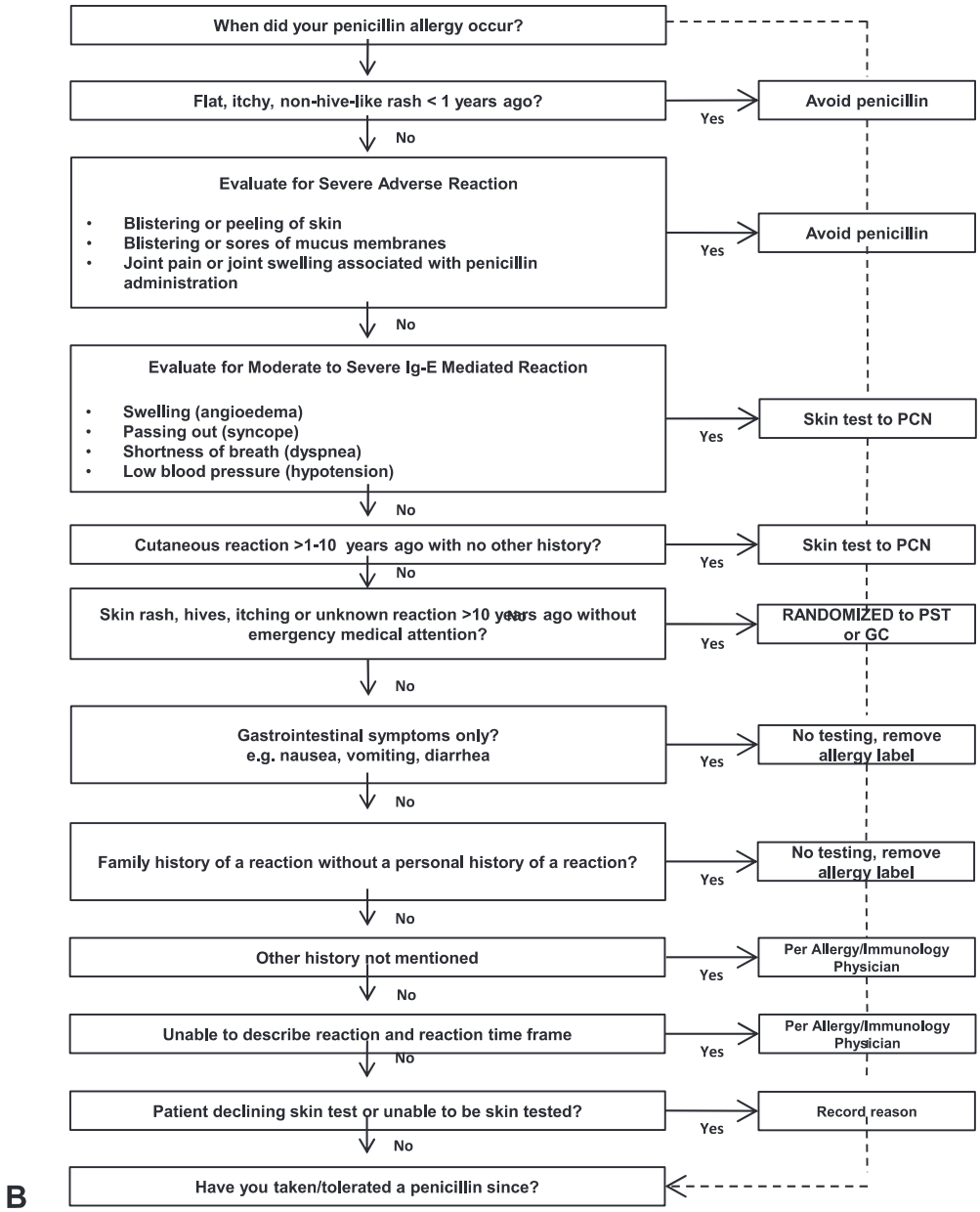

FIGURE 1. (*CONTINUED*).

Of the 363 patients who presented with a reported history of penicillin allergy, 185 (51%) completed an evaluation. Reasons for not completing a penicillin allergy evaluation are shown in Figure 3. The most common reason to defer an evaluation was patient time constraint, cited by 39 of 178 (22%) patients. Of the 178 patients not completing an evaluation, 23 (13%) declined for a host of reasons, including fear of needles. Twenty-one of 178 (12%) patients were delabeled on history alone, and an additional 4 patients (2%) were delabeled on the basis of a reported penicillin allergy due to positive family history alone. Provider time constraint resulted in 12 of 178 (7%) patients not being evaluated, and 16 of 178 (9%) were not evaluated because they were on medications with antihistaminic properties. Of the 185 patients who underwent penicillin allergy evaluation (Figure 3), 13 were younger than 5 years and reported cutaneous symptoms only, and underwent DC to amoxicillin. All 13 (100%) passed the DC and were delabeled for penicillin allergy. Thirteen patients 5 years and older reported extracutaneous reactions, and subsequently underwent PST. Two of 13 (15.4%) had a positive PST result, whereas 11 of 13 (84.6%) had a negative evaluation. Of the remaining 159 patients, 80 were randomized to the PST group and 79 were randomized to the DC group (Table II). There were no significant differences in demographic characteristics and reported penicillin allergy history between the randomized groups.

The outcomes of the randomized evaluations are presented in Table III. Of the 80 patients randomized to undergo PST, 10 of 80 (12.5%) had a positive skin test result and 70 of 80 (87.5%)

TABLE I. Patient characteristics

Characteristic	n (%)
Patients screened, n	2465
Patients with reported penicillin allergy	363 (14.7)
Patients completing penicillin evaluation	185 (51.0)
Males	117 (32.2)
Females	246 (67.8)
Age (y), mean ± SD	35.3 ± 25.3
New patient evaluation	207 (57)
Chief complaint	
Penicillin/drug allergy	82 (22.6)
Chronic rhinitis/sinusitis	80 (20.0)
Asthma	70 (19.3)
Food allergy	43 (11.8)
Urticaria	31 (8.5)
Other	57 (15.7)

had a negative skin test result. For the 79 patients who were randomized to undergo a DC, 3 of 79 (3.8%) had a positive DC and 76 of 79 (96.2%) had a negative DC. DC resulted in 8.7% fewer positive evaluations as compared with PST (superiority; $P = .079$). For PST, the mean time to complete the evaluation (including a 30-minute observation period) was 72.7 ± 5.3 minutes, as compared with 66.7 ± 4.8 minutes needed to complete a DC ($P < .001$). Per the Revenue Integrity fee schedule, each PST cost $393.66, for a total of $29,092.80 for the 80 patients. Each DC cost $53.66, for a total of $4239.14 for the 79 patients. On an individual basis, DC cost $340.00 less to complete as compared with PST. Of note, none of the 80 patients who underwent PST experienced a systemic reaction. Of the 3 failed DCs, each resulted in cutaneous-only manifestations and all were successfully treated with oral antihistamines. There were no reactions that required administration of epinephrine.

DISCUSSION

To our knowledge, this is the first randomized controlled trial comparing PST followed by an amoxicillin challenge versus a direct amoxicillin challenge without preceding PST. Although PST remains the test of choice to evaluate patients with a high-risk penicillin allergy history, our work adds to the emerging data demonstrating the safety of DC in select low-risk patients.[18-22] A cohort study in children by Mill et al[18] demonstrated the safety of DCs in children with cutaneous-only reactions in which 94% of 818 children tolerated a DC to amoxicillin. Although the number of children in our study was much lower, our results are similar regarding the safety of these challenges. Our results are also in line with the initial retrospective data in adults. A study of Marine recruits suggested DCs to be safe, with only 5 of 328 recruits (1.5%) reacting to a DC.[19] Another study of 2-step or multistep challenges for adverse reactions to any drug class had a subset of patients who underwent challenge to a beta-lactam drug. Most of these patients underwent skin testing (221 patients), but 36 did not.[25]

Prospective studies examining DCs have also recently been published. Confino-Cohen et al[20] performed DC on 617 patients with a history of a nonimmediate reaction to penicillin-based antibiotics regardless of skin test result, and only 9 patients (1.5%) experienced an immediate reaction, all of which were mild.[20] In contrast, our aim was to evaluate for immediate reactions in a low-risk group defined as cutaneous-only reactions, including the historical reaction of hives, an IgE-mediated reaction characteristic. Our study also could have potentially captured delayed reactions as well. A more recent study looked at DCs preceded by a placebo step in 155 patients older than 7 years with low-risk reaction histories.[21] Only 4 of 155 (2.6%) had a positive challenge. Unlike our study, this study was not randomized, and used historical controls. However, like our study, this study included patients with a history of urticaria.[21] Our data are also similar to those in a study by Trubiano et al,[22] including hematology/oncology patients in which 46 patients with a low-risk reaction underwent single-dose challenge and all challenges were tolerated. However, this study excluded patients reporting a history of hives.[22]

Our study raises the important question as to whether PST "overcalls" penicillin allergy and thus keeps low-risk patients labeled where a DC would serve to delabel them. We demonstrated that a greater number of patients undergoing PST had a positive evaluation as compared with DC, with this result just missing statistical significance. This increased number of positive PST results as compared with DC was also observed in the study by Iammatteo et al[21] discussed above. We suspect that our results reflect the lower specificity of PST as compared with DC. PST has an excellent negative predictive value, but a less precise positive predictive value. Our study also supports the safety of DC in our defined low-risk group, because only 3 patients developed immediate reactions, and all were treated with an antihistamine. No patients required epinephrine.

We believe our data may be generalized to other outpatient allergy/immunology practices, which could help to increase penicillin allergy delabeling. Obviating the need for PST potentially makes penicillin allergy evaluations more accessible, less cumbersome, and more efficient for the practicing allergist. Our results support allergists performing DC in patients whom they would previously have offered skin testing on the basis of usual practice. Furthermore, it is conceivable that with appropriate training, DCs could be performed by other appropriately educated health care providers in hopes of expanding antibiotic stewardship. Given that there are 25 million to 30 million patients labeled as penicillin-allergic in the United States, and less than 0.1% undergo PST,[3] increasing access to include other specialties, including pharmacists, would help with penicillin allergy delabeling. There is already literature supporting other specialties, such as infectious disease specialists and pharmacists, performing PST.[15,26,27]

The 30-minute observation period in our study is unique and has previously been reported by us with PST followed by amoxicillin challenge.[28] Previous studies have used waiting periods of 1 to 2 hours.[21,22] We did not have any patients experience a reaction outside of 30 minutes in our cohort of 185 patients undergoing either PST or DC. Our study speaks to the safety of a shorter waiting period, and this shorter waiting period is beneficial for both patient convenience and office flow. We hypothesize that adopting a 30-minute wait period as standard of practice would help facilitate more penicillin allergy evaluations.

Our approach of DC in individuals with a low-risk history of penicillin allergy also offers benefits to the patient. Time constraint was the leading cause of declining a penicillin allergy evaluation in this study and in our previous study.[28] Our analysis showed a significantly shorter time period with DC compared

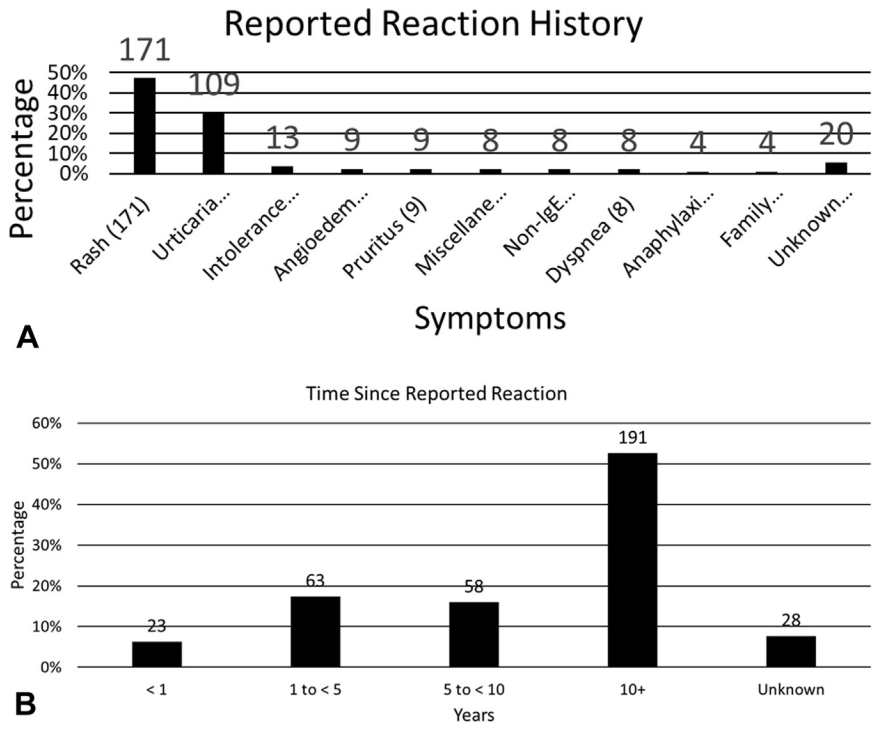

FIGURE 2. **A,** Reaction history. **B,** Time since reaction.

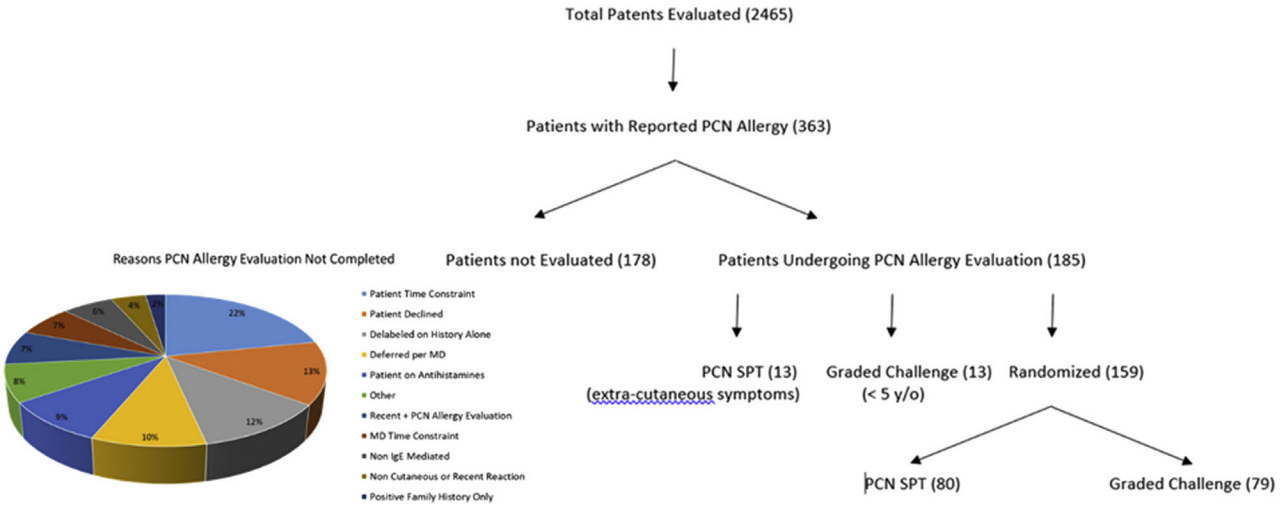

FIGURE 3. Study flowsheet and reasons penicillin evaluation not completed. *PCN,* Penicillin; *SPT,* skin prick test.

with PST. Although the time saved was modest, the decreased time used for DC could lead to improved office flow, particularly in offices completing multiple penicillin evaluations in a day. Saving 5 minutes per patient translates to over an hour in a day with 12 patients. Furthermore, we have previously demonstrated that fear of needles is a barrier for some patients to undergo PST.[28] Proceeding to a DC would facilitate an evaluation in this subset of concerned patients. Finally, our simple cost analysis also demonstrated that DC in low-risk patients is less expensive than PST, which may also be helpful to patients who are responsible for a higher percentage of their health care costs.

We note several limitations to our study. Our sample size is relatively small given the overall low incidence of anaphylaxis to penicillin.[29] We also recognize that our algorithm may be too conservative in that patients with a cutaneous-only reaction within the past year were told to continue avoiding penicillin and that we likely could have recommended a DC in these patients. We also could potentially have decreased our time since reaction to 5 years instead of 10 for the randomized population. We acknowledge our cost analysis is basic compared with more detailed accounts in the literature,[30] and is also specific to our region. Furthermore, some allergy/immunology providers may

TABLE II. Characteristics of randomized patients*

Characteristic	Penicillin SPT	DC
Patients	80	79
Age (y), mean ± SD	39.6 ± 24.8	36.8 ± 25.2
Sex: female, n (%)	57 (71.3)	54 (68.4)
Time since reaction (y), mean ± SD	25.8 ± 19.7	24.1 ± 18.2
Rash, n (%)	45 (56.3)	49 (62.0)
Urticaria, n (%)	35 (43.7)	30 (38.0)

SPT, Skin prick test.
*There were no significant differences between groups.

TABLE III. Outcomes of randomized penicillin allergy evaluations

Outcome	Penicillin SPT	DC	Difference
Patients	80	79	
PST Positive/DC fail, n (%)	10 (12.5)	3 (3.8)	8.7% ($P = .079$)
PST Negative/DC pass	70 (87.5)	76 (96.2)	
Time (min)			
Mean ± SD	72.7 ± 5.3	66.7 ± 4.8	6.0 ($P < .001$)
Median (IQR)	73.5 (68.8-75.3)	66.0 (62-70)	7.5 ($P < .001$)
Cost			
Each	$393.66	$53.66	$340.00
Total	$29,092.80	$4,239.14	$24,853.66

IQR, Interquartile range.

not be financially incentivized to offer DC as compared with PST. Our approach may also not be applicable to all outpatient allergy/immunology offices, because our office performs a high volume of penicillin evaluations and has highly trained and efficient staff. Our population may also not be representative of other allergy/immunology practices. We also did not challenge patients with positive PST results in the randomized cohort to prove our suspicion that PST may lead to an overdiagnosis of penicillin allergy, but this practice has been discouraged.[31] We did not formally follow up patients who underwent penicillin allergy evaluations, but patients were instructed to call with concerns. In addition, it is possible that patients delabeled on the basis of history alone followed by DC only, in the absence of a "formal skin test," may harbor some fear that they may still be allergic to penicillin and may continue to avoid its future use. Finally, we did not track the impact of our evaluation on the use of penicillin-based antibiotics going forward in this cohort of patients to see whether the anticipated benefit of delabeling has been realized.

In summary, we have demonstrated the equivalent safety profile of PST and DC in a predefined low-risk group of cutaneous-only reactions, including urticaria. DC has the potential to decrease the number of false-positive evaluations as compared with PST. Furthermore, its characteristics may be more attractive to both patients and allergy/immunology practices because it took a shorter amount of time and was less costly than PST. PST continues to have a role in the evaluation of higher risk patients, but DCs are a safe and effective alternative for delabeling low-risk patients with a cutaneous-only reaction to penicillin.

REFERENCES

1. Solensky R, Khan DA. Drug allergy: an updated practice parameter. Ann Allergy Asthma Immunol 2010;105:259-73.
2. Macy E. Penicillin allergy: optimizing diagnostic protocols, public health implications, and future research needs. Curr Opin Clin Allergy Immunol 2015;15:308-13.
3. Macy E, Contreras R. Health care use and serious infection prevalence associated with penicillin "allergy" in hospitalized patients: a cohort study. J Allergy Clin Immunol 2013;133:790-5.
4. Lee CE, Zembower TR, Fotis MA, Postelnick MJ, Greenberger PA, Peterson LR, et al. The incidence of antimicrobial allergies in hospitalized patients: implications regarding resistance patterns and emerging bacterial resistance. Arch Intern Med 2000;260:2819-22.
5. Martinez JA, Ruthazer R, Hansjosten K, Barefoot L, Snydman DR. Role of environmental contamination as a risk factor for acquisition of vancomycin resistant enterococci in patients treated in the medical intensive care unit. Ann Intern Med 2003;163:1905-12.
6. Fridkin SK, Edwards JR, Courval JM, Hill H, Tenover FC, Lawton R, et al. The effect of vancomycin and third generation cephalosporins on prevalence of vancomycin-resistant enterococci in 126 US adult intensive care units. Ann Intern Med 2001;135:175-83.
7. MacFadden DR, LaDelfa A, Leen J, Gold WL, Daneman N, Weber E. Impact of reported penicillin allergy on inpatient outcomes: a multicenter prospective cohort study. Clin Infect Dis 2016;63:904-10.
8. Penicillin Allergy in Antibiotic Resistance Workgroup. Penicillin allergy testing should be performed routinely in patients with self-reported penicillin allergy. J Allergy Clin Immunol Pract 2017;5:333-4.
9. Barlam T, Cosgrove S, Abbo L, MacDougall C, Schuetz A, Septimus E, et al. Implementing an antibiotic stewardship program: guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis 2016;62:e51-77.
10. Centers for Disease Control and Prevention. Is it really a penicillin allergy? Evaluation and diagnosis of penicillin allergy for healthcare professionals. Available from: https://www.cdc.gov/antibiotic-use/community/pdfs/penicillin-factsheet.pdf. Accessed October 2, 2017.
11. Arroglia ME, Wagner W, Bobek MB, Hoffman-Hogg L, Gordon SM, Arroglia AC. A pilot study of penicillin skin testing in patients with a history of penicillin allergy admitted to a medical ICU. Chest 2000;4:1106-8.
12. Arroglia ME, Radojicic C, Gordon SM, Popovich MJ, Bashour CA, Melton AL, et al. A prospective observational study of the effect of penicillin skin testing on antibiotic use in the intensive care unit. Infect Control Hosp Epidemiol 2003;5:347-50.
13. Wall GC, Peters L, Leaders CB, Wille JA. Pharmacist-managed service providing penicillin allergy skin testing. Am J Health Syst Pharm 2004;61:1271-5.
14. Chen JR, Tarver SA, Alvarez KS, Tran T, Khan DA. A proactive approach to penicillin allergy in hospitalized patients. J Allergy Clin Immunol Pract 2017;5:686-93.
15. Ramsey A, Staicu ML. Use of a penicillin allergy screening algorithm and penicillin skin testing for transitioning hospitalized patients to first-line antibiotic therapy. J Allergy Clin Immunol Pract 2018;6:1349-55.
16. Sacco KA, Bates A, Brigham TJ, Imam JS, Burton MC. Clinical outcomes following inpatient penicillin allergy testing: a systematic review and meta-analysis. Allergy 2017;72:1288-96.
17. Unger NR, Gauthier TP, Cheung LW. Penicillin skin testing: implications for antimicrobial stewardship. Pharmacotherapy 2013;33:856-67.
18. Mill C, Primeau MN, Medoff E, Lejtenyl C, O'Keefe A, Netchiporouk E, et al. Assessing the diagnostic properties of a graded oral provocation challenge for the diagnosis of immediate and non immediate reactions to amoxicillin in children. JAMA Pediatr 2016;170:1-8.
19. Tucker MH, Lomas CM, Ramchandar N, Waldram JD. Amoxicillin challenge without penicillin skin testing in evaluation of penicillin allergy in a cohort of Marine recruits. J Allergy Clin Immunol Pract 2017;5:813-5.
20. Confino-Cohen R, Rosman Y, Meir-Shafrir K, Stauber T, Lachover-Roth I, Herhsko A, et al. Oral challenge without skin testing safely excludes significant delayed onset penicillin hypersensitivity. J Allergy Clin Immunol Pract 2017;5:669-75.
21. Iammatteo M, Alvarez Arango S, Ferastraoaru D, Akbar N, Lee AY, Cohen HW, et al. Safety and outcomes of oral graded challenges to amoxicillin without prior skin testing. J Allergy Clin Immunol Pract 2019;7:236-43.
22. Trubiano JA, Smibert O, Douglas A, Devchand M, Lambros B, Holmes NE, et al. The safety and efficacy of an oral penicillin challenge program in cancer patients: a multicenter pilot study. Open Forum Infect Dis 2018;5:ofy306.

23. Torres MJ, Adkinson NF Jr, Caubet JC, Khan DA, Kidon MI, Mendelson L, et al. AAAAI/WAO 2018 Symposium Penicillin and Cephalosporin Allergy Testing Working Group. Controversies in drug allergy: beta-lactam hypersensitivity testing. J Allergy Clin Immunol Pract 2019;7:40-5.
24. Joint Task Force on Practice Parameters representing the American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. Drug allergy: an updated practice parameter. Ann Allergy Asthma Immunol 2010;10:259.
25. Iammatteo M, Blumenthal KG, Saff R, Long AA, Banerji A. Safety and outcomes of test doses for the evaluation of adverse drug reactions: a 5-year retrospective review. J Allergy Clin Immunol Pract 2014;2:768-74.
26. Rimawi RH, Cook PP, Gooch M, Kabchi B, Ashraf MS, Rimawi BH, et al. The impact of penicillin skin testing on clinical practice and antimicrobial stewardship. J Hosp Med 2013;8:341-5.
27. Devchand M, Kirkpatrick CMJ, Stevenson W, Garrett K, Perera D, Khumra S, et al. Evaluation of a pharmacist-led penicillin allergy de-labelling ward round: a novel antimicrobial stewardship intervention. J Antimicrob Chemother 2019;74:1725-30.
28. Ramsey A, Mustafa SS. A penicillin skin testing initiative in an outpatient allergy office. J Allergy Clin Immunol Pract 2018;6:1756-7.
29. Lee P, Shanson D. Results of a UK survey of anaphylaxis after oral amoxicillin. J Antimicrob Chemother 2007;60:1172-9.
30. Blumenthal KG, Li Y, Banerji A, Yun BJ, Long AA, Walensky RP. The cost of penicillin allergy evaluation. J Allergy Clin Immunol Pract 2018;6:1019-27.
31. Park MA, Solensky R, Khan DA, Castells MC, Macy EM, Lang DM. Patients with positive skin test results to penicillin should not undergo penicillin or amoxicillin challenge. J Allergy Clin Immunol 2015;135:816-7.