Original Article

Improving the Effectiveness of Penicillin Allergy De-labeling

Jack Bourke, MBBS[a,b], Rebecca Pavlos, PhD[c], Ian James, PhD[c], and Elizabeth Phillips, MD[a,b,c,d] *Perth, Western Australia; and Nashville, Tenn*

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. © 2014 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2014;■:■-■)

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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

[a]Department of Clinical Immunology, Sir Charles Gairdner Hospital, Perth, Western Australia, Australia
[b]Department of Clinical Immunology, Royal Perth Hospital, Perth, Western Australia, Australia
[c]Institute for Immunology & Infectious Diseases, Murdoch University, Perth, Western Australia, Australia
[d]Vanderbilt University School of Medicine, Nashville, Tenn

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Corresponding author: Elizabeth Phillips, MD, Vanderbilt University School of Medicine, Division of Infectious Diseases, 1161, 21st Avenue South, A-2200 Medical Center North, Nashville, TN 37232-2582. E-mail: elizabeth.j.phillips@vanderbilt.edu.

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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.