Brief report

The role of major and minor determinants in penicillin allergy testing: Time to revisit an old friend?

Syed B. Ali, MBBS, FRACP,[a] Thanh-Thao Adriana Le, MBBS, FRACP,[a] Aida Ahmadie, BNurs,[a] Chino Yuson, MBBS, FRACP,[a] Frank Kette, MBBS, FRACP,[a] Pravin Hissaria, MD, FRACP, FRCPA,[a,b] and William B. Smith, MBBS, FRACP, FRCPA, PhD[a] *Adelaide, Australia*

Background: Skin testing is an important step in evaluation of penicillin allergic reactions. It includes testing to the following: amoxicillin, benzyl penicillin, and products generated *in vivo* after penicillin administration, the major determinant hapten penicilloyl-polylysine (PPL) and the minor determinant mixture (MDM). Although PPL and MDM are available as a commercial kit, their supply and cost remain problematic.
Objective: We aimed to evaluate the performance and utility of PPL and MDM in penicillin allergy testing.
Methods: A retrospective audit over a 5-year period was undertaken for those with penicillin testing in a tertiary immunology unit.
Results: In all, 214 patients were identified. Of those patients, 151 (70.6%) were female and the average age was 58 years. Unspecified penicillin was the most common index drug (n = 127 [59.3%]), followed by amoxicillin (n =3 [24.8%]) and amoxicillin-clavulanic acid (n = 21 [9.7%]). The result of skin testing was positive in 23 patients (10.7%); skin prick testing was positive in 10 patients (4.7%), and intradermal testing (IDT) was positive in 13 patients (6.1%), the majority of whom had identified amoxicillin or amoxicillin-clavulanic acid as the index drug (n = 22 [95.7%]). The result of testing to PPL and/or MDM was positive with IDT only (n=5 [23.8%]). PPL and MDM positivity coexisted with a positive reaction to amoxicillin IDT in 2 patients, 1 of whom passed an amoxicillin challenge. Additionally, 2 positive tests to PPL were present with a negative result for MDM; of these 2 positive results, 1 was positive to amoxicillin IDT. In only 1 case were the results of testing for MDM and PPL both positive, with negative results to all native β-lactams tested; the patient tolerated an amoxicillin challenge. Overall, the negative predictive value for both skin prick testing and IDT was 89.5%.
Conclusion: Benzyl penicillin and amoxicillin alone may be sufficient for *in vivo* testing in suspected individuals with penicillin allergy. (J Allergy Clin Immunol Global 2023;2:100132.)

Key words: *Penicillin skin testing, penicillin, drug allergy, allergic reaction*

INTRODUCTION

Self-reported penicillin allergy label is common, with a prevalence of 9.3% in adults.[1] The majority of these individuals do not have penicillin allergy and can be safely delabeled.[2] A penicillin label has important implications, such as increased risk of microbial resistance and longer hospital stay, which contribute a high financial burden on the health care system.[3-5]

Testing for penicillin allergy can involve a blood test for penicillin-specific IgE, skin testing, and challenge. Skin testing is indicated in those with a history consistent with type I or IgE-mediated hypersensitivity.[6-8] This involves skin prick and intradermal injection of diluted amoxicillin and benzylpenicillin, and when available, products generated *in vivo* after penicillin administration, such as the putative major determinant hapten penicilloyl-polylysine (PPL) and the minor determinant mixture (MDM), the inclusion of which is thought to increase the sensitivity of the test.[9]

PPL and MDM are available as a commercial kit; however, the supply is subject to interruption, and the product is expensive. In our experience, interruption of the supply between 2004 and 2006 did not alter the outcomes of penicillin allergy testing, as was also found by others.[10] The clinical utility of PPL and MDM in conjunction with amoxicillin and benzylpenicillin is further questionable given the increase in aminopenicillin prescriptions and proportion of aminopenicillin-specific allergy cases.[11] The use of these products not only carries a significant financial cost but also adds time to the test. There has been an ongoing debate on the utility of these kits, and as yet, there is no clear consensus.[12-14] Therefore, the aim of this retrospective audit was to evaluate the performance and utility of PPL and MDM in penicillin allergy testing.

Patients who underwent penicillin allergy testing at the Royal Adelaide Hospital immunology department between January 2015 and December 2019 were included. Demographic data,

From [a]the Department of Clinical Immunology and Allergy, Royal Adelaide Hospital, and [b]the Department of Immunopathology, SA Pathology, Adelaide.
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Corresponding author: William B. Smith, MBBS, FRACP, FRCPA, PhD, Department of Clinical Immunology and Allergy, Royal Adelaide Hospital, 1 Port Road, Adelaide, Australia. E-mail: William.smith@sa.gov.au.

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Abbreviations used
IDT: Intradermal testing
MDM: Minor determinant mixture
PPL: Penicilloyl-polylysine
SPT: Skin prick testing

information regarding Brown grading of anaphylaxis,[15] specific penicillin-based antibiotic, and time since reaction were collected. Brown grading of anaphylaxis was defined as follows: mild (grade 1, with skin and subcutaneous tissues only), moderate (grade 2, with features suggesting respiratory, cardiovascular, or gastrointestinal involvement), and severe (grade 3 with hypoxia, hypotension, or neurologic compromise).[15]

Skin prick testing (SPT) (concentration 1:1) and intradermal testing (IDT) (volume 0.02 mL; concentrations of 1:100, 1:10, and 1:1) to amoxicillin (20 mg/mL), benzyl penicillin (5 mg/mL), and cefazolin (3 mg/mL), as well as to PPL and MDM (Diater DAP, Spain), were performed according to the manufacturer's instructions. Individuals with a positive SPT or IDT result had testing continued for an alternate penicillin. Cephalexin (3 mg/mL) SPT and IDT was performed only in those with a history of prior reaction. A positive SPT result was defined as a wheal measuring at least 3 mm after 15 minutes, and a positive IDT result was defined as an increase in wheal size by at least 2 mm at 20 minutes. If the results of SPT and IDT were negative, patients underwent graded oral amoxicillin challenge, and for those with a history of delayed reactions, a prolonged course was provided for 5 days. Patients received graded oral penicillin V challenge if the result of *in vivo* amoxicillin testing was positive, and in some instances. oral cephalexin at the discretion of the treating immunologist.

TABLE I. Patient demographics and baseline data

Indicator	Value
Patients (no.)	214
Average age (y), no. (range)	57.9 (20-94)
Sex (no.)	
Female	151
Male	63
Index penicillin (no.)	
Unspecified penicillin	127
Amoxicillin	53
Amoxicillin + clavulanate	21
Flucloxacillin	7
Piperacillin + tazobactam	5
Phenoxymethylpenicillin	1
Patients with other listed medication allergies (no.)	
All	105
1	54
2	20
≥3	31
Patients with cephalosporin allergy (no.)	44
Cephalexin	28
Trimethoprim + sulfamethoxazole	18
Opioids	11
Others	114
Brown grade anaphylaxis (no.)	
NA	22
Grade 1	118
Grade 2	38
Grade 3	38
Time to testing (no.)	
<6 mo	14
6-12 mo	28
13 mo-5 y	32
6-10 y	19
11-19 y	21
>20 y	88
Not specified	12

NA, Not available.

RESULTS AND DISCUSSION

A total of 214 patients were identified; their average age was 57.9 years (range 20-94 years). There was a female predominance (n = 151 [70.6%]). Unspecified penicillin was the most common index drug (n = 127 [59.3%]), followed by amoxicillin (n = 53 [24.8%]) and amoxicillin-clavulanic acid (n = 21 [9.7%]) (Table I). Medication allergy in addition to penicillin was common and present in 105 patients (49.0%); the medications involved included cephalosporins (n = 44), with cephalexin (n = 28) and trimethoprim-sulfamethoxazole (n=18) accounting for around half of the cases (Table I).

Of those patients with documented severity, more than half had mild reactions with cutaneous signs only (Brown grade 1) whereas 40% had a history of systemic reactions (grades 2 and 3) (Table I). The proportion of patients who had had a reaction more than 20 years before testing was higher than the proportion with a reaction less than 12 months before testing (Table I).

The result of *in vivo* testing was positive in 23 patients (10.7%), including 10 patients (4.7%) with a positive SPT result and 13 patients (6.1%) with a positive IDT result. Brown grade anaphylaxis score was higher (grade 2) in patients with a positive SPT and/or IDT result than in patients with a negative (grade 1) result ($P < .0001$). In those with positive *in vivo* test results, the median time to testing was shorter (6-12 months) than in those with a negative result (10-20 years). Even though unspecified penicillin was the most common index drug, positive *in vitro* test results were predominantly found in patients who specified amoxicillin or amoxicillin-clavulanic acid as the culprit index drug (n = 22 of 23 patients).

Of the positive SPT results, 6 were to amoxicillin, 1 was to amoxicillin-clavulanic acid, and 2 were to clavulanate; there were no positive SPT results to PPL or MDM (Table II). Two of the patients with SPT positive to amoxicillin and benzylpenicillin also had positive reactions on subsequent IDT (Table II). Two patients with who tested positive for a reaction to clavulanate (with amoxicillin and all other IDT results negative) had a positive amoxicillin challenge result.

More than half of the positive IDT results were to amoxicillin (n = 7 [53.8%]), with 2 of them also positive to benzylpenicillin (Table II). One IDT result was positive to amoxicillin-clavulanic acid; in this patient, amoxicillin was tolerated, thereby confirming clavulanate as the culprit. Overall negative predictive value for both SPT and IDT was 89.5%.

The results of PPL and/or MDM IDT were positive in 5 patients (23.8%). MDM and PPL positivity coexisted with a positive amoxicillin IDT result in 2 patients, 1 of whom had a negative amoxicillin challenge (Table II). Additionally, 2 patients with positive PPL test had a negative MDM result; of these 2 patients,

TABLE II. Patients with a positive result of skin testing to penicillin-based antibiotic, MDM, and/or PPL

Positive results						
Penicillin or cephalosporin	MDM/ PPL	Index drug	Time since index	Brown grade anaphylaxis	Challenge	*In vitro* testing
SPT						
AMX	Negative	AMX	1 mo	3	Penicillin VK	Specific IgE negative
AMX	Negative	AMX	3 mo	2	NA	Specific IgE positive to amoxicilloyl
AMX	IDT + PPL	Amoxicillin-clavulanic acid	13 mo	3	NA	Specific IgE negative
AMX	Negative	AMX	19 mo	3	Cephalexin positive	Specific IgE negative
Clavulanate	Negative	Amoxicillin-clavulanic acid	4 mo	1	AMX positive	Specific IgE negative
AMX	Negative	AMX	1-5 y	3	Penicillin VK	Specific IgE negative
AMX, amoxicillin-clavulanic acid	Negative	Amoxicillin-clavulanic acid	<6 mo	2	Penicillin VK	Specific IgE negative
AMX	Negative	AMX	<6 mo	3	Penicillin VK	Specific IgE negative
AMX	Negative	AMX	19 mo	3	Cephalexin positive	Specific IgE negative
Clavulanate	Negative	Amoxicillin-clavulanic acid	4 mo	1	AMX positive	Specific IgE negative
IDT						
AMX 1:100 BP 1:10	Negative	AMX	3 mo	3	Cephalexin: negative	Specific IgE negative
AMX 1:100	Negative	AMX	28 mo	2	Penicillin VK: negative	BAT-positive to AMX, amoxicillin-clavulanic acid, cephalexin
FLU, TAZ, BP 1:1	Negative	NA	8 mo	2	No challenge undertaken	Specific IgE negative
BP, AMX, Cfz 1:1	MDM and PPL	AMX	>20 y	2	AMX: negative	Specific IgE negative
AMX 1:1	MDM and PPL	Amoxicillin-clavulanic acid	Unknown	2	Cephalexin: negative	Specific IgE negative
Cfz 1:1	PPL	Amoxicillin-clavulanic acid	>20 y	1	Cephalexin: positive (mouth ulcers)	Specific IgE negative
SPT AMX BP 1:10	Negative	AMX	19 mo	3	Cephalexin: positive	Specific IgE negative
SPT AMX IDT BP: 1:1	PPL	Amoxicillin-clavulanic acid	13 mo	3	NA	Specific IgE negative
AMX, Cax 1:1	Negative	AMX	7 mo	1	Penicillin VK: negative	Specific IgE negative
AMX 1:10	Negative	AMX	9 mo	2	Penicillin VK: positive (angioedema)	Specific IgE equivocal to amoxicilloyl
AMX, Cfz 1:1	Negative	AMX	1 mo	2	Penicillin VK: negative	Specific IgE positive to amoxicilloyl
Negative	MDM and PPL	Unspecified penicillin	>20 y	1	AMX: negative	Specific IgE negative
Amoxicillin-clavulanic acid	Negative	Amoxicillin-clavulanic acid	6 mo-1 y	2	Amoxicillin	Specific IgE equivocal to penicilloyl V and penicilloyl G

Specific IgE: penicilloyl V, penicilloyl G, and amoxicilloyl were tested.
AMX, Amoxicillin; *BAT*, basophil activation test; *BP*, benzyl penicillin; *Cax*, cephalexin; *Cfz*, cefazolin; *VK*, V potassium.

1 had a positive IDT to amoxicillin (Table II). One of these patients had a history of Brown grade 3 anaphylaxis and no challenge was undertaken. In only 1 case was the IDT for PPL and MDM positive with all other skin testing results being negative; this patient had a negative amoxicillin challenge result (Table II).

In all, 15 patients (7.0%) had a positive challenge result. Of these 15 patients, 3 required treatment: 2 of these patients received H1 antihistamines for immediate urticaria; the third, who developed delayed urticaria, was also managed with H1 antihistamines (Table III).

The cost of PPL and MDM kits for these patient tests was $124,120, not including nursing time for testing or duration of hospital admission (Table IV).

There remains a strong role for penicillin skin testing in those with a recent history of moderate-to-severe anaphylaxis (ie, a Brown grade anaphylaxis score of 2 or 3). The longest interval to a clinically meaningful positive skin test result was 28 months. There were 3 patients with positive IDT results in whom reactions had occurred more than 20 years earlier, but these patients had negative challenge results (or in 1 case, a reaction not consistent with IgE-mediated allergy). Several other studies have indicated that skin testing is less likely to show positive results with the passage of time[16,17] and false-positive test results can occur when there is a low pretest probability.[18]

Voelker et al, in a large series of patients undergoing penicillin skin testing,[11] identified a significant subset of patients with sole

TABLE III. Challenge outcomes for both groups, including single-day and prolonged drug challenge

Challenge outcomes	Single day	Prolonged drug challenge
Objective positive (n = 15)	1/10th dose: urticaria T10 and T45 (n = 2) Neat: urticaria T30 (n = 1), erythema and pruritis T95 (n = 1), angioedema T60 (n = 1), cough and dyspnoea T30 (n = 1) Neat dose: Urticaria T360 (n = 1)	Urticaria (n = 5) Asthma exacerbation (n = 1) MPE (n = 2)
Subjective positive/intolerance (n = 9)		

MPE, Maculopapular exanthem.

TABLE IV. Cost of commercial kits and in-house kits, with overall savings

Indicator	Value in Australian dollars
Cost outline per patient	
Commercial kit (Diater DAP penicillin)	$580
Benzyl penicillin (5 mg/mL)	$11.83
Amoxicillin (20 mg/mL)	$10.26
In-house solution total	$22.09
Possible cost saving for cohort (n = 214)	
Total cost of commercial kit Diater DAP penicillin and in-house solutions (benzyl penicillin and amoxicillin)	$128,847
Total cost of in-house solutions	$4,727
Savings	$124,120

positive reactions to penicillin polylysine and/or minor determinants. Unfortunately, this article did not include information to address the question of pretest probability or any data on challenge. Our series included only 1 patient with sole positivity to PPL and MDM. In this patient, low pretest probability indicated that this result might be a false-positive result, and indeed the patient tolerated amoxicillin challenge. We suggest that further studies consider challenge of patients with sole positivity to PPL and MDM unless pretest probability and level of clinical suspicion of penicillin anaphylaxis are high.

We have demonstrated that skin testing with PPL and/or MDM was positive in 23.8% of patients with a clinically compatible history. Of these 6 patients, 5 had concurrent positive skin testing to amoxicillin or benzylpenicillin. In the 1 patient with a negative IDT to amoxicillin and benzylpenicillin with positive MDM and PPL IDT the patient subsequently tolerated oral amoxicillin challenge.

Table II shows a patient who had an initial index reaction to amoxicillin-clavulanic acid (generalized urticaria and tongue angioedema) more than 20 years previously and then underwent amoxicillin challenge with negative results. However, on reexposure to amoxicillin a year later, she developed facial angioedema and erythema. Subsequent testing showed a positive IDT result to cefazolin and PPL. Because of a history of reaction with reexposure to amoxicillin, she was challenged to cephalexin, with no immediate reaction but a report of oral burning sensation on day 2 of the course and confirmation of mouth ulcers by her primary care physician. Because this is not indicative of an IgE-mediated mechanism, the IDT results were not deemed to be relevant. Further challenge was not undertaken.

There were 7 patients (3%) with a positive oral challenge result; the majority were mild cutaneous reactions. This rate is similar to those in other reports.[19]

It is striking that even though unspecified penicillin was the most reported index drug, 95.7% of the patients with a positive skin testing result (22 of 23) had specified a history of reaction to amoxicillin or amoxicillin-clavulanic acid. Accordingly, the SPT and IDT were positive to amoxicillin in a large proportion of our skin test positive patients (17 of 23 [73.9%]). These findings likely reflect the rise in amoxicillin and amoxicillin-clavulanic acid prescriptions. Selective sensitization to aminopenicillins has been reported in up to 50% of patients in other series.[20-24] A study from the United Kingdom reported testing of more than 1000 patients, in whom monosensitization with amoxicillin was demonstrated in 48%, with 70% of the patients having a negative result of testing to major and minor determinants.[25] Given the rise in amoxicillin allergy, our findings suggest that a panel comprising amoxicillin and benzyl penicillin may be sufficient in at least Australian and European populations, in which amoxicillin use is predominant.[26,27] In this context, those patients with penicillin allergy are unlikely to be missed, even if the result of amoxicillin testing is negative.

Our findings have a significant financial implication, as outlined in Table IV. At the current rate of testing, the cost reduction with omission of PPL and MDM testing for our service would be at least $124,120 in Australian dollars over a 5-year period, without demonstrable loss of diagnostic accuracy. The potential issues of MDM and/or PPL shortage or availability are a further important consideration.

Our study is limited by its retrospective nature and variability in the reagents selected for challenge; although amoxicillin is the default challenge drug in our unit when a skin testing result is negative, in the presence of a positive skin testing result, the choice of alternate drug challenge was at the discretion of the treating immunologist. In addition, there was a high proportion of patients with a remote or even unknown penicillin allergy history. However, although this contributed to the relatively low rate of skin test result positivity, this would not change the absolute numbers of positive results or our key findings comparing the performance of native penicillins with MDM and/or PPL reagents.

From a cost-effectiveness perspective, the data support the position that in populations in which amoxicillin allergy is predominant, benzyl penicillin and amoxicillin alone may be sufficient for *in vivo* testing in individuals with suspected penicillin allergy.

DISCLOSURE STATEMENT

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

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