

Retrospective case series analysis of penicillin allergy testing in a UK specialist regional allergy clinic

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ABSTRACT

Introduction Penicillin allergy is the most common drug allergy. Skin testing for the major (PPL) and minor determinants (MDMs) of penicillin offers increased sensitivity and specificity over *in vitro* testing alone.

Following a worldwide absence of reagents, a new kit was licensed in the UK in 2008 (Diater, Spain) and this report evaluates its use in a UK specialist allergy clinic.

Methods Prospective data on 50 consecutive patients tested with the new reagents were collected. The departmental protocol is adapted from the 2003 EAACI position paper.

Results 14% (7/50) and 12% (6/50) of patients were diagnosed with immediate and non-immediate reactions respectively. The negative predictive value of the PPL and MDM reagents at the neat concentration for an immediate reaction was 93% (true negatives 37, false negatives 3). Two patients experienced systemic reactions to DPT in the absence of demonstrable specific IgE. None of the patients were diagnosed using skin prick testing alone or at lower concentrations of IDT. Five patients were diagnosed at the IDT stage and two at the DPT stage in the absence of demonstrable specific IgE. Six patients were diagnosed with non-immediate reactions, two on IDT alone and four following IDT and DPT.

Conclusion The new PPL and MDM determinants offer enhanced sensitivity when evaluating β -lactam hypersensitivity; however, there are limitations to the current testing regimens. The UK would benefit from local guidelines, which incorporate the new reagents and acknowledge the high amoxicillin prescription rate and the relatively lower specialist-to-patient ratio in this country.

INTRODUCTION

Hypersensitivity reactions to β -lactam antibiotics are classified as immediate (type-1) or non-immediate. Immediate reactions usually occur within an hour of exposure to the drug, are immunoglobulin E (IgE) mediated and present with a range of symptoms from urticaria, angioedema, bronchospasm and rarely near fatal/fatal anaphylaxis. Non-immediate reactions are less well understood but usually occur later, are less likely to culminate in anaphylaxis and are considered to be T cell mediated particularly when there is a latent period of 48–72 h following exposure to the drug.¹

Diagnosis of an immediate hypersensitivity reaction is based on a supportive history and the demonstration of either specific IgE *in vitro* and/or eliciting a positive skin test or drug provocation *in vivo*. Conjugation of the β -lactam to carrier

molecules, *in vivo*, induces the antigenic determinants benzylpenicilloyl poly-L-lysine (PPL) and other minor determinant mixtures (MDMs). Sensitisation to side chain structures as seen in amoxicillin and cephalosporin allergy is also well recognised. Self-reporting of β -lactam allergy is high; however, only 10–20% of such individuals have demonstrable type-1 hypersensitivity.^{2–3} Given the widespread incorrect labelling of β -lactam allergy and the potentially life-threatening consequences of incorrect diagnosis, understanding the usefulness and the limitations of the tests employed in the diagnosis of penicillin allergy is essential.

Skin testing with the penicillin determinants is reported to be more sensitive than using whole (native) drugs and is the recommended practice in Europe.⁴ However, in 2004, Allergopharma and Hollister-Stier ceased the production of PPL and MDM resulting in a worldwide dearth of reagents. Recently PPL and MDM have been manufactured by a different company (Diater, Spain), exhibiting good concordance with the previous reagent.^{5–6} It has been acknowledged in the European Academy of Allergy and Clinical Immunology (EAACI) position paper (2003) that there are different patterns of sensitisation depending on prescribing practice.⁴ It follows that the sensitivity and specificity of a test is altered depending of the frequency of sensitisation, highlighting the need for local knowledge.

This is the first report analysing the routine use of the newly available skin test reagent kit (Diater, Spain) in the diagnosis of β -lactam allergy in a UK specialist allergy clinic. Our case series aims to analyse the usefulness and limitations of the test and highlights the important resource implications involved in applying the EAACI protocol within the UK NHS allergy service framework.

METHODS

This was a retrospective study (September 2008–October 2010) of the first 50 adult patients evaluated for β -lactam allergy using the Diater skin test reagents. The cohort includes consecutive patients investigated in a specialist regional allergy clinic according to a protocol based on the EAACI position paper.⁴ Data collection from case notes included patient demographics, culprit (index) drug, serum-specific IgE (SSIgE), skin prick test (SPT), intra-dermal test (IDT) and drug provocative test (DPT) results. The presenting histories were graded using the 'Mueller classification' system. In short, allergic reactions are grouped from grade I to IV according to severity: grade I—urticaria,

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pruritus, malaise; grade II—angioedema, chest tightness, nausea, vomiting, abdominal pain, dizziness; grade III—dyspnoea, wheeze, stridor, dysphagia, hoarseness; grade IV—hypotension, collapse, loss of consciousness, incontinence, cyanosis.⁷

SSiGE was determined in vitro using the Immuncap reagents (Phadia): penicilloyl G (benzylpenicilloyl), penicilloyl V (phenoxymethyl penicilloyl) and amoxicilloyl.

SPT was performed with the undiluted PPL (0.04 mg/ml) and MDM reagents (0.5 mg/ml of sodium benzylpenicillin disodium benzylpenicilloate and benzylpenicilloic acid mixture). Parenteral amoxicillin (25 mg/ml) was used for SPT and IDT at the published non-irritant concentration.⁵ Parenteral flucloxacillin (25 mg/ml) and benzylpenicillin (6 mg/ml) were included depending on the 'index' reaction. IDT for PPL was performed at 1:10 and an undiluted concentration and for MDM at 1:100, 1:10 and an undiluted concentration as per the manufacturer's instructions. A weal response of ≥ 3 mm, in comparison with negative control, was considered as a positive SPT after 15 min. For IDT, an increase in weal diameter of ≥ 3 mm was considered positive at 20 min, or maximal weal size if large at an earlier time point. In selected patients with indeterminate history and/or where there was a suspicion of a previous non-immediate reaction, skin test sites were inspected at 48–72 h for delayed hypersensitivity and patients were advised to obtain a digital image with a reference tape measure if changes occurred earlier.

DPT was performed according to departmental protocol. In brief, DPT was considered in patients where specific IgE could not be demonstrated and when a β -lactam would improve treatment options for the patient. After obtaining informed consent and documenting baseline observations, a graded DPT was performed. The local DPT protocol starts with a lip rub. If this is negative, 15 min later, a 5 mg dose of drug (amoxicillin, flucloxacillin and penicillin V) is given. At half-hourly intervals, further doses of 25, 75, 150 and 250 mg are given with a cumulative dose of 505 mg. Patients were monitored closely for symptoms and signs of allergic reactions and vital parameters including heart rate, blood pressure and peak expiratory flow rates were checked prior to each step. The patients were asked to remain in the department for 1 h following the last dose. An accelerated protocol was employed if the history was considered 'low risk' (table 1).

The risk of IgE-mediated reaction was determined using a set of points from the clinical history (table 2). This was validated for our clinic by asking an independent specialist to review the clinical notes of all patients and based on the criteria assess patients as being at 'high risk' or 'low risk'. When compared with the final outcome, this exercise showed these criteria to have a 100% negative predictive value and a 50% positive predictive value in determining IgE-mediated reactions.

Table 1 Accelerated protocol for β -lactam skin testing* and DPT

Step	Drug	Time	Total time
SPT*	PPL and MDM, neat	15 min	15 min
IDT	Amoxicillin $\pm$ culprit β -lactam (25 mg/ml)	60	1 h 15 min
	1. 1 PPL (1:10), MDM (1: 100 MDM)		
	2. PPL (neat), MDM (1:10)		
DPT	3. Neat MDM, amoxicillin $\pm$ culprit β -lactam (25 mg/ml)	2 h	3 h 15 min
	Amoxicillin 5 mg, 25 mg and 250 mg		

The three-step protocol is accelerated in comparison with the five-step DPT stated in the Methods section.

*Each IDT is performed in separate steps in the manufacturer's protocol, rather than in the three steps performed in this accelerated protocol.

DPT, drug provocation test; IDT, Intra-dermal test; MDM, minor determinant mixture; PPL, penicilloyl poly-L-lysine; SPT, skin prick test.

Table 2 Criteria for determining the risk of immunoglobulin E-mediated reaction

High risk*	Suggestive history of IgE-mediated reaction: (a) Pruritic urticarial rash (b) Angioedema (c) Bronchospasm (d) Anaphylaxis (e) Haemodynamic instability (f) Symptoms within 2 h
Low risk	Suggestive of non-IgE-mediated reaction: (a) Symptoms at >2 h (b) Maculopapular or other non-urticarial rash (c) 'Unclear' or 'non-specific' symptoms (d) History 'indeterminate' and nothing to suggest a 'serious' episode (e) Childhood history with no details (f) Other (allergy/immunology) diagnosis likely

*Patients with significant co-morbid conditions (moderate/severe asthma and other significant cardiopulmonary disorders) were managed as 'high risk'.

RESULTS

Fifty patients underwent evaluation with the Diater skin test reagents. The male to female ratio was 17:33 and average age was 44.0 ± 14.9 years (mean $\pm$ SEM). Seven patients (14%) were diagnosed with immediate β -lactam sensitivity and six (12%) with non-immediate reactions. The presenting histories varied in severity from an indeterminate history (16 (32%)) to grade I (17 (34%)), grade II (6 (12%)), grade III (6 (12%)) and grade IV (5 (10%)) hypersensitivity reaction as per the Mueller classification (data summarised in table 3).⁷

Serum-specific IgE

Case 41 (see table 3) demonstrated SSiGE to penicillin V. This test was inadvertently requested as the index reaction to ciprofloxacin. Skin testing for the standard β -lactam panel as described above was negative and the patient tolerated an amoxicillin challenge, so the SSiGE was considered false positive. Case 23 had SSiGE to amoxicillin but tolerated penicillin V DPT and was diagnosed as having side chain sensitivity.

Skin prick test

None of the patients in our cohort showed a positive response to PPL or MDM in the SPT. Case 10 had a positive skin prick to amoxicillin and subsequently a positive IDT to MDM at the undiluted concentration and was not challenged.

Intra-dermal test

Five patients had a diagnosis of immediate β -lactam sensitivity based on positive IDT results. Case 21 was positive to PPL and cases 10, 12 and 30 to MDM. Case 23 was diagnosed with a side chain allergy following positive IDT to amoxicillin and successful DPT to penicillin V. Positive IDTs were seen only at the undiluted concentrations of PPL and MDM.

Drug provocation test

Two patients had a positive reaction to amoxicillin DPT with a 25 mg dose, despite negative skin testing and SSiGE. Case 24 experienced anaphylaxis with erythema, cardiovascular instability and wheeze, and case 27 developed generalised erythema.

Non-immediate reactions

Non-immediate reactions were diagnosed in six patients. Four patients (cases 22, 35, 36 and 37) had evidence of erythema and induration at the skin test sites that commenced between 8 and 24 h after skin testing. Cases 22 and 37

Table 3 Details of β -lactam testing in patients diagnosed with allergy

Case	Index case		SSiGE			SPT			IDT			DPT		Outcome
	Drug	Severity	Ax	Pen V	Pen G	Ax	PPL	MDM	Ax	PPL	MDM	Drug	Result	
1	β -lactam	1	—	—	—	—	—	—	—	—	—	Ax	—	0
2	Ax	2	—	—	—	—	—	—	—	—	—	Ax	—	0
3	β -lactam	1	—	—	—	—	—	—	—	—	—	Ax	—	0
4	Flu	2	—	—	—	—	—	—	—	—	—	Flu	—	0
5	β -lactam	3	—	—	—	—	—	—	—	—	—	Ax	—	0
6	β -lactam	0	—	—	—	—	—	—	—	—	—	Ax	—	0
7	β -lactam	4	—	—	—	—	—	—	—	—	—	Ax	—	0
8	Ax	1	—	—	—	—	—	—	—	—	—	Ax	—	0
9	Ax	0	—	—	—	—	—	—	—	—	—	Ax	—	0
10	Ax	4	—	—	—	+	—	—	ND	—	+	ND	ND	1
11	β -lactam	1	—	—	—	—	—	—	—	—	—	Ax	—	0
12	β -lactam	0	—	—	—	—	—	—	—	—	+	ND	ND	1
13	β -lactam	0	—	—	—	—	—	—	—	—	—	Ax	—	0
14	Flu	0	—	—	—	—	—	—	—	—	—	Ax	—	0
15	β -lactam	1	—	—	—	—	—	—	—	—	—	Ax	—	0
16	β -lactam	0	—	—	—	—	—	—	—	—	—	Ax	—	0
17	β -lactam	0	—	—	—	—	—	—	—	—	—	Ax	—	0
18	β -lactam	2	—	—	—	—	—	—	—	—	—	Ax	—	0
19	β -lactam	0	—	—	—	—	—	—	—	—	—	Ax	—	0
20	Augmentin	4	—	—	—	—	—	—	—	—	—	Ax	—	0
21	Ax	3	—	—	—	—	—	—	—	+	—	ND	ND	1
22	β -lactam	2	—	—	—	—	—	—	D	D	D	Ax	D	2
23	Augmentin	3	+	—	—	—	—	—	+	—	—	Pen v	—	1
24	Augmentin	4	—	—	—	—	—	—	—	—	—	Ax	+	1
25	Ax	0	—	—	—	—	—	—	—	—	—	Ax	—	0
26	β -lactam	0	—	—	—	—	—	—	—	—	—	Ax	—	0
27	Ax	3	—	—	—	—	—	—	—	—	—	Ax	+	1
28	β -lactam	1	—	—	—	—	—	—	—	—	—	Ax	—	0
29	Augmentin	1	—	—	—	—	—	—	—	—	—	Ax	—	0
30	Ax	3	—	—	—	—	—	—	—	—	+	ND	ND	1
31	β -lactam	1	—	—	—	—	—	—	—	—	—	Ax	—	0
32	β -lactam	1	—	—	—	—	—	—	—	—	—	Ax	—	0
33	Augmentin	4	—	—	—	—	—	—	—	—	—	Ax	—	0
34	Ax	1	—	—	—	—	—	—	—	—	—	Ax	D	2
35	Ax	1	—	—	—	—	—	—	D	D	D	ND	ND	2
36	β -lactam	2	—	—	—	—	—	—	D	D	D	ND	ND	2
37	β -lactam	1	—	—	—	—	—	—	—	—	—	Ax	D	2
38	β -lactam	1	—	—	—	—	—	—	—	—	—	Ax	—	0
39	Augmentin	1	—	—	—	—	—	—	—	—	—	Ax	—	0
40	Pen V	0	—	—	—	—	—	—	—	—	—	Ax	—	0
41	Ciprofloxacin	1	—	+	—	—	—	—	—	—	—	Ax	—	0
42	β -lactam	1	—	—	—	—	—	—	—	—	—	Ax	—	0
43	Cefalexin	0	—	—	—	—	—	—	—	—	—	Ax	—	0
44	Flu	1	—	—	—	—	—	—	—	—	—	Flu	D	2
45	Cefuroxime	3	—	—	—	—	—	—	—	—	—	Ax	—	0
46	Pen V	1	—	—	—	—	—	—	—	—	—	Ax	—	0
47	Pen V	1	—	—	—	—	—	—	—	—	—	Ax	—	0
48	Pen V	0	—	—	—	—	—	—	—	—	—	Ax	—	0
49	Augmentin	2	—	—	—	—	—	—	—	—	—	Augmentin	—	0
50	Flucloxacillin	1	—	—	—	—	—	—	—	—	—	Flu	—	0

The index case is described with the culprit drug (if known or β -lactam if unknown) and severity of initial reaction.

A zero grade denotes an indeterminate history and grades 1–4 are based on the Mueller grading system.⁷ —, negative test; +, positive immediate sensitivity (SPT weal >3 mm at 15 min, IDT weal 3 mm $>$ baseline, DPT immediate sensitivity reaction within 1 h), ND, not done; D, delayed reaction (IDT induration of injection site at >12 h, DPT reaction at >12 h).

Outcome: 0, no β -lactam sensitivity; 1, immediate sensitivity to β -lactam; 2, non-immediate sensitivity to β -lactam.

DPT, drug provocation test; IDT, intra-dermal test; MDM, minor determinant mixture; PPL, penicilloyl poly-L-lysine; SSiGE, serum-specific immunoglobulin E; SPT, skin prick test; Ax, amoxicillin; Flu, flucloxacillin; pen V, penicillin V; augmentin, co-amoxiclav.

had successfully undergone a DPT, that is, no immediate hypersensitivity response, but cases 35 and 36 had strong histories for non-immediate reactions and were diagnosed based on their IDT result without undergoing DPT. Case 22 had a widespread rash and skin induration at the IDT site at 12 h after DPT and IDT testing. Cases 34, 37 and 44 had no

delayed reactions at the IDT sites but had systemic symptoms between 8 and 24 h after DPT, which corresponded with their index reaction.

Safety

There were no systemic reactions to skin testing.

In summary

In the cohort, 14% (7/50) and 12% (6/50) of patients were diagnosed with immediate and non-immediate reactions, respectively, to β -lactams. In our clinic, the negative predictive value of the PPL and MDM reagents (Diater) at the undiluted concentration for an immediate reaction was 93.5% (true negatives 43, false negatives 3, including the side chain reactor) and the sensitivity was 57.1% (true positives 4 and false negatives 3). None of the patients was diagnosed using SPT alone or at lower concentrations of IDT. Five patients were diagnosed at the IDT stage and two at the DPT stage in the absence of demonstrable specific IgE. Six patients were diagnosed with non-immediate reactions. Two were diagnosed on IDT alone and of the four who underwent IDT and DPT, one experienced skin induration and systemic symptoms and the remaining three experienced only systemic symptoms.

CASES

Four of the cases are summarised in further detail to highlight some of the difficulties associated with β -lactam testing.

Case history 24

A woman in her 30s attended the allergy clinic following a well-documented perioperative anaphylaxis during general anaesthesia. The patient had negative investigations to latex, muscle relaxants, propofol, fentanyl, local anaesthetics and dexamethasone. There was a discrepancy in SSiGE testing at the time of reaction, 5 years prior to β -lactam testing, with negative and weak positive results reported to penicillin V and amoxicillin from two different laboratories. When repeated again at our centre at the time of β -lactam testing, SSiGE was not detectable to penicilloyl G, penicilloyl V and amoxicilloyl. The results were confirmed from a different laboratory. She had tolerated penicillin as a child.

SPT and IDT were negative and SSiGE was not demonstrable to the standard panel as stated above. Within 5 min of administering an oral amoxicillin dose (25 mg), the patient became drowsy, disorientated and short of breath. She vomited, developed a wheeze, widespread urticarial rash, tachycardia (pulse 124 bpm) and low blood pressure (BP 85/60 mm Hg). She was resuscitated successfully.

Case history 27

A man in his 60s had a history of widespread, pruritic macular rash, hypotension and shortness of breath 35 min after the first dose of a second course of amoxicillin, having tolerated this drug 4 weeks prior to the episode. No specific IgE could be demonstrated in vitro or in vivo to the standard panel as stated above and he underwent a DPT with amoxicillin. Thirty minutes after a cumulative 25 mg dose of amoxicillin, he developed a diffuse erythematous rash over his torso. He recovered following oral antihistamine administration.

Case history 35

A pregnant woman was diagnosed with syphilis. She was given amoxicillin but after two doses (approximately 10 h after the initial dose), she developed a generalised urticarial rash and was referred for investigation. There was no evidence of in vitro or in vivo specific IgE; however, she developed induration and erythema at the site of the MDM and amoxicillin intra-dermal injections at 10 h post-procedure (which corresponded to the temporal association given in the clinical history) and remained visible at 48 h.

Case history 37

An HIV-positive man required penicillin for the treatment of neurosyphilis. Twenty years ago he had developed a self-limiting, non-pruritic generalised, haemorrhagic rash on day 3 of a course of penicillin. There was no evidence of specific IgE in serum and on skin testing to the standard panel as stated above and he tolerated a cumulative dose of 250 mg of oral amoxicillin. His observations remained stable throughout the DPT but he developed a widespread haemorrhagic maculopapular rash 6 h later. There was no evidence of a delayed reaction at the skin testing sites.

DISCUSSION

This report reviews the usefulness of the new allergy skin testing kit in the diagnosis of β -lactam allergy in a UK regional specialist allergy clinic. Our experience also highlights some of the practical difficulties and limitations when assessing a patient for β -lactam allergy.

The Diater reagents have been available in the UK since 2008 and provide the opportunity to test the skin with penicillin determinants. In our hands, the kit had a negative predictive value of 93.5%, which improved to 95.6% when amoxicillin testing was included. Amoxicillin is more commonly prescribed than penicillin and this is likely to affect the sensitivity and specificity of PPL and MDM skin testing.⁸

SSiGE tests have a sensitivity of 10–50% depending on the population tested although the true sensitivity and specificity are difficult to evaluate due to ethical considerations.⁹ The discrepancy in SSiGE, in case history 24, raises issues surrounding lack of quality assurance schemes for SSiGE for drugs in the UK. It should be noted that both laboratories used the same Pharmacia CAP system and are Clinical Pathology Accreditation approved.

There are a number of reasons why immediate-type reactions may occur in the absence of demonstrable specific IgE. First, the patient may not be sensitive to the determinants included within this kit. How β -lactams degrade in vivo is difficult to ascertain and the MDM combination does not include unstable determinants that may be antigenic.¹⁰ Second, the non-irritant concentrations used may be different in the British population and control data are not available. Skin testing has been reported to be less sensitive for amoxicillin than for PPL or MDM allergy and relatively higher concentrations of amoxicillin are required to provoke a positive skin test than PPL or MDM.¹¹ Concentration of the drug does appear to be important as none of the patients reacted to the lower concentrations of PPL or MDM in this series. Lastly, delay in testing may reduce the sensitivity of skin testing. One case series found that 40% of PPL- and MDM-sensitive patients and 100% of amoxicillin-sensitive patients were negative to skin testing at 5 years post-reaction.¹² This series supports DPT as the gold standard for diagnosing or excluding immediate β -lactam hypersensitivity.

The safety profile of the reagents was excellent in our cohort, which is in concordance with a recent Spanish study where no systemic reactions were experienced in a large cohort.⁶ Current EAACI β -lactam testing protocols require significant staffing and clinic space with an initial clinic appointment and potentially two further appointments for skin testing and then DPT. An accelerated skin test and DPT protocol (table 1) could be considered in clinically 'low risk' patients to help restrict investigations to a single visit. Further acceleration of the protocol may be considered, as there were no positive IDT tests at the lower concentrations, but this would need validation in a larger prospective study.

Take-home messages

- ▶ The negative predictive value of the Diater PPL and MDM reagents was 93% for the diagnosis of a type 1 hypersensitivity reaction to β -lactam in our clinic.
- ▶ Drug provocation testing remains the 'gold standard' in the diagnosis of type-1 hypersensitivity to β -lactam antibiotics.
- ▶ Anaphylactic reactions can occur during drug provocation testing despite the absence of detectable specific immunoglobulin E.
- ▶ Reliability of skin tests for 'non-immediate' reactions to β -lactam antibiotics is not satisfactory.

Diagnosis of non-immediate β -lactam reactions is challenging and time consuming, highlighting the need for more robust diagnostic methods. Only half of the patients diagnosed with non-immediate reactions had delayed skin changes demonstrating the limitations of delayed reading of IDT. The EAACI position paper recommends re-evaluating all IDT sites at 48 and 72 h for non-immediate reactions; however, our experience suggests that the additional resources required for such recall of all patients may not be justified. As a compromise, our clinic asks patients to contact the clinic with a photograph if there is a delayed reaction. EAACI also recommends performing DPT in patients with non-immediate reactions with increasing doses over 3 weeks, a policy that would have major resource implications for UK NHS specialist allergy services.

Our experience is based on a relatively small cohort and a selection bias cannot be excluded. The time from reaction to testing was not always known and this time lapse may have affected the sensitivity of the skin test reagents. However, this is an unselected cohort of patients, which is representative of how the test will be used in a clinic setting. The skin test panel used in this study did not include benzylpenicillin, which has recently been reported to enhance the combined sensitivity of skin testing by up to 2.5% and has been included in a 2009 EAACI update.¹ None of the patients were recalled to look for resensitisation, as recommended by the EAACI position paper, due to limited resources and limited evidence for this practice.¹³ Lastly, as with many drug testing studies, the false positive rate of tests was not analysed due to ethical considerations. Case 41

demonstrates the possibility of false positive SSiGE results and highlights the importance of careful test selection.

In summary, the new PPL and MDM reagent (Diater, Spain) determinants offer enhanced sensitivity when evaluating β -lactam hypersensitivity. However, there are limitations to the current testing regimens. The UK would benefit from local guidelines, which incorporate the new reagents and acknowledge the high amoxicillin prescription rate and the relatively lower specialist-to-patient ratio in this country. Guidelines on patient selection criteria for investigation and a testing protocol, that is, mindful of allergy resources but that does not compromise patient safety, would help strategic planning in the UK allergy clinics.

Competing interests None.

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