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Identifying Low-risk Beta-Lactam allergy Patients in a UK Tertiary Centre

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Identifying Low-risk Beta-Lactam allergy Patients in a UK Tertiary Centre

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Conflict of Interest

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- 37 • **Background:** There are marked geographical as well as temporal differences
38 in patient sensitization profiles to beta-lactams (BL).
- 39 • **Objective:** To determine the utility of skin test reagents and identify a cohort
40 of patients where skin testing can be safely omitted in a cohort of patients
41 referred to a UK tertiary referral centre.
- 42 • **Methods:** A retrospective study of the clinical characteristics of 1092 patients
43 referred for BL allergy testing was analysed using multivariate regression
44 analysis. The effectiveness of skin test reagents was also evaluated.
- 45 • **Results:** Multivariate logistic regression identified that a history of
46 anaphylaxis (OR 10.98, $p=0.001$) and the patients recall of the index drug
47 (apart from Ampicillin and Meropenem, OR 3.51–12.43, $p<0.05$) were
48 independent predictors of type I BL allergic status and a time of <1 year
49 elapsed since index reaction significantly increasing the odds of a patient with
50 a history of anaphylaxis, having a type I BL allergy (OR 38.66, $p=0.003$). An
51 absence of anaphylactic severity, unknown name of the index drug and a
52 reaction occurring > 1 year prior to testing, has a NPV of 98.4%, which was
53 similar to the NPV of skin testing of 98.9% for type I BL allergy. The NPV of
54 skin testing with benzylpenicillin + amoxicillin $\pm$ index BL was similar with
55 (98.9%) or without (98.1%) the use of PPL and MD for type I BL allergy.
- 56 • **Conclusion:** We identified a “low risk” cohort of patients where the history is
57 of similar reliability to skin testing in predicting non-allergic status for BL
58 allergy.

59

Highlights box**1. What is already known about this topic?**

The vast majority of patients labelled as beta-lactam allergic can in fact tolerate these drugs. It is standard practice to skin test with penicillin allergic determinants prior to drug provocation challenge.

2. What does this article add to our knowledge?

History of anaphylaxis, known index drug and <1 year duration are associated with immediate beta-lactam hypersensitivity. In “low risk” patients history has a similar negative predictive value to skin testing.

3. How does this study impact current management guidelines?

Skin testing with benzylpenicillin + amoxicillin $\pm$ index beta-lactam prior to challenge may be sufficient in some populations. A suitably trained allergist may consider omission of skin testing in “low risk” patients following appropriate risk assessment.

Keywords

allergy, beta-lactam, challenge, hypersensitivity, intradermal test, penicillin, provocation, skin prick test

Abbreviations

95% CI	95% Confidence Interval
AC	Amoxicillin-clavulanate
BL	Beta-lactam
BP	Benzylpenicillin
DPT	Drug provocation test
IDT	Intradermal test
NHS	National Health Service
NPV	Negative Predictive Value
MD	Minor determinant, Sodium Benzylpenilloate
PPL	Penzylpenicillinpolylysine
PT	Piperacillin-tazobactam
SPT	Skin prick test

95 Introduction

96 The beta-lactam (BL) class of antibiotics are the most widely used class of antibiotics
97 and most frequently reported drug allergy. Approximately 10% of all patients report a
98 history of penicillin “allergy”, but up to 90% of these patients are not genuinely
99 allergic¹. This is likely due to a combination of probable initial misdiagnosis as well
100 as the waning of sensitivity over time². For example, it is well known that accurate
101 diagnosis of drug allergy vs. viral induced exanthems is notoriously difficult.
102 However, there are no known clinical predictors of genuine BL allergies and all
103 suspected cases must be verified with appropriate allergy testing. The limitations in
104 capacity and costs (as well as availability of allergists) remain a significant barrier to
105 more comprehensive BL allergy testing^{3,4}. Therefore, the availability of better clinical
106 predictors and streamlining of diagnostic tests would be of immense benefit.

107 A thorough investigation of suspected hypersensitivity includes history taking, skin
108 tests (skin prick (SPT) and intradermal (IDT) tests), and drug provocation tests (DPT)
109^{5,6}. DPT remains the “gold standard”, but application of these tests are often limited.
110 Skin tests thus remain the mainstay of investigation, essentially performed to quantify
111 the risk of an IgE-mediated reaction to DPT.

112 Traditionally, most authorities advocate skin testing with the “penicillin allergenic
113 determinants” (benzylpenicillinpolylysine (PPL) and minor determinant (MD, Sodium
114 Benzylpenilloate)), benzylpenicillin (BP), amoxicillin and, if available, the
115 index/suspected culprit BL to maximize sensitivity^{1,5,6}. However, the requirement of
116 these reagents has been debated. Some authorities have upheld the importance of
117 including both PPL and MD, while others have advocated using only PPL and BP for
118 skin tests, followed by an amoxicillin challenge^{1,5-10}. There are marked geographical
119 and temporal differences, with data suggesting fewer patients monosensitized to PPL
120 in Europe, and reports of declining positive skin tests in chronological American
121 studies^{8,11,12}. These differences may result from varying prescribing practices (for
122 example, due to differences in microbial resistance patterns or differences in
123 prescribing semi-synthetic penicillins), selection bias in testing amongst clinicians,
124 and alterations to patient sensitization profiles. Therefore, the optimal choice of skin
125 testing reagents likely remains both region- and time-specific.

126 Very few studies have examined the clinical characteristics or predictors of BL
127 allergy. Associations with gender, atopy, age and racial differences were reported,
128 but studies have mostly been based on patients with self-reported histories rather
129 than confirmed genuine allergies¹³⁻¹⁶. Furthermore studies that investigated the use
130 of predictive models to diagnose both BL allergy and drug allergy have been shown
131 to underperform compared to conventional allergy evaluation^{17,18}.

Updated and region-specific epidemiological studies of BL allergy are therefore urgently needed to optimize modern allergy testing. In this retrospective study, we evaluated the clinical characteristics and predictors of proven BL allergy, as well as the utility of skin test reagents in a large cohort of patients referred to a UK tertiary referral centre.

Methods

Data Collection

Medical records of all patients who were referred for and underwent BL allergy testing at Guy's and St Thomas' (GSTT) National Health Service (NHS) Foundation Trust, United Kingdom, between July 2010 to December 2016 were reviewed. Our centre receives referrals from all healthcare professionals in the eastern and southern counties of England. All referrals were reviewed unselectively and likely represent the population of suspected BL allergic patients referred to everyday-practicing local allergists during the study period. All patients attending clinic for suspected BL allergies were offered skin testing. Clinical data extracted included: age; gender; ethnicity; index drug (i.e. the suspected BL implicated in the index reaction); symptoms of index reaction; duration between testing and index reaction; SPT, IDT (immediate and delayed); and outcomes of DPT. Patients were diagnosed with BL allergy if they had a congruent history together with positive SPT, IDT or DPT. All patients underwent SPT/IDT prior to DPT. Only immediate (type I) and delayed (type IV) hypersensitivities were recorded. Type I hypersensitivity was defined as an immediate IgE mediated reaction, manifesting as urticaria, angioedema, cardiorespiratory compromise suggestive of anaphylaxis which occurs within an hour of BL administration ⁶. Type IV hypersensitivity was defined as a delayed T cell mediated reaction manifesting as maculopapular exanthema and fixed drug eruptions ¹⁹. Patients who had severe cutaneous adverse reactions (i.e. Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, acute generalised exanthematous pustulosis) as well as patients with suspected type II and type III reactions were not included in this study.

This study was conducted as part of an approved audit within the department. The data were collected in a database that was then reviewed and checked for inconsistencies by two independent investigators. Any discrepancies were then discussed between the two independent investigators and unresolved discrepancies referred to the senior investigator for a final decision.

168

169 Beta-lactam skin testing (SPT/IDT)

170 All patients underwent skin testing, and SPT was performed prior to IDT. All patients
171 had skin testing performed with PPL (benzylpenicillinpolylysine 0.04mg/ml, Diater
172 Laboratorios, Madrid, Spain), MD (sodium benzylpenilloate 0.5mg/ml, Diater
173 Laboratorios), BP (6mg/ml, Genus Pharmaceuticals, Huddersfield, United Kingdom),
174 and amoxicillin (25mg/ml, Ibigen Srl, Aprilia, Italy). Histamine 1.0% with Phenol 0.5%
175 (Allergy Therapeutics, Worthing, United Kingdom) was used as positive control and
176 Phenol 0.5% (Allergy Therapeutics) was used as negative control.

177 If clinically indicated or if it was the index BL, selected patients would also undergo
178 SPT/IDT with amoxicillin-clavulanate (AC, 25mg amoxicillin and 5mg clavulanic
179 acid/ml, Sandoz, Holzkirchen, Germany), flucloxacillin (SPT: 50mg/ml, IDT: 5mg/ml;
180 Wockhardt UK Ltd, Wrexham, United Kingdom), piperacillin-tazobactam (PT, 200mg
181 piperacillin and 25mg tazobactam/ml, 20mg piperacillin and 2.5mg tazobactam/ml;
182 Wockhardt UK Ltd), cephalosporins (depending on index reaction, 2mg/ml) and
183 meropenem (SPT 50mg/ml, IDT 5.0mg/ml; AstraZeneca UK Ltd, Luton, United
184 Kingdom).

185 Both SPT and IDT were read at 15 minutes as an immediate reading. A positive SPT
186 for type I hypersensitivity was defined as a wheal ≥ 3 mm diameter on immediate
187 reading. A positive IDT for type I hypersensitivity was defined as a wheal expansion
188 of ≥ 3 mm from the original bleb on immediate reading ⁶. Delayed IDT results were
189 read at 48 to 72 hours after skin testing. Patients were asked to send photos of the
190 skin-testing site to our secure departmental email address. The clinician who
191 performed the IDT reviewed the photos and, if appropriate, a diagnoses of a type IV
192 hypersensitivity was made if the pictures showed erythema, induration, infiltration,
193 papules and vesicles at the site of skin testing ¹⁹. If there were any doubts in the
194 diagnosis of a type IV hypersensitivity from the photos, the patient would proceed to
195 undergo a DPT to confirm or refute the equivocal positive delayed skin test result.
196 Patients with positive skin tests were deemed likely genuinely allergic (therefore
197 recommended to avoid BL) and did not proceed with subsequent DPT. An exception
198 was if there was incongruence between skin test results and clinical history, where
199 very cautious DPT may be offered even in positive skin test results, at the discretion
200 of the combined decision between the Allergist and individual patient.

201

202 Beta-lactam DPT

Patients with negative skin tests were invited for DPT with the same BL as per their index reaction (and if the index BL was unknown, DPT was performed with the BL most clinically relevant for the patient). All patients underwent an immediate DPT, and if negative, a delayed DPT. DPT protocols were according to GSTT trust protocols and further individualized according to each patient. For example, in patients with a history of a likely reaction to BL, DPT may be performed with sequential of doses 10%, 30% and 60% of the therapeutic dose; whereas those with an history of an unlikely reaction to a BL, DPT may be performed with a single 100% therapeutic dose. Patients who had a negative immediate reaction on immediate DPT proceeded to a delayed DPT, which was usually 50% of the daily therapeutic dose over a period of 3 days for patients with histories of an unlikely reaction, again individualized and according to GSTT trust protocols. Any immediate and delayed reactions were assessed by the patients' respective clinicians and diagnosed accordingly. A patient who developed symptoms of urticaria, angioedema, or cardiorespiratory compromise suggestive of a severe anaphylaxis within an hour after the last dose of BL was diagnosed to have a type I BL allergy⁶. A patient who developed symptoms of a maculopapular exanthema or a fixed drug eruption occurring more than an hour after DPT was diagnosed to have a type IV BL allergy¹⁹. Patients who declined or defaulted DPT were not included in subsequent analysis.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics v24 (International Business Machines Corp., Armonk, NY, United States of America). Multivariate binary logistic regression analysis was performed. The results were used to identify characteristics of the patient history that are highly associated with BL allergy. From this we characterised a "low risk" cohort which had all of the following features: "no history of anaphylaxis to BL", "a reaction to a BL more than 1 year prior to referral" and "patients who could not recall what the index drug was" (For further details see supplementary methods).

Results

Between July 2010 to December 2016, 1096 patients were referred for and underwent BL allergy testing, 4 patients were excluded at this stage of the analysis as these patients had an incongruence between their history of presentation and skin test results and subsequently had a negative DPT. In the remaining 1092 patients the male:female ratio was 1:3.1 (32%:68%) and the median age was 48 (range: 15-95) years. Sixty-six percent of patients tested were of white ethnicity; while the remaining patients tested were of Black, Middle Asian, East Asian, or mixed ethnicity. The index drug was unknown in over half of patients (i.e most patients just reported a suspected allergy to “an unknown penicillin” or BL class of antibiotic). Amoxicillin (13.8%) and AC (13.4%) were the most commonly specifically implicated penicillin-based/BL antibiotics (Table 1).

Thirty-three percent of patients presented with a history of non-specific rash, while over 25% of patients presented with urticaria and/or angioedema. Only 5% of our cohort presented following anaphylaxis (defined as 2 or more organ systems involved²⁰). The vast majority of patients (97.8%) were referred more than a year following the index reaction, while a minority were referred within a year of the index reaction (1.3%).

Please refer to Figure 1 for a summary of our patient diagnostic pathway and outcomes. Only 122 (11.2%) patients referred for allergy testing were finally diagnosed with highly-suspected/confirmed BL allergy – patients with positive skin test results did not undergo subsequent DPT due to high risk. Eighty-three (7.6%) patients had an immediate-type (type I) hypersensitivity and 39 (3.6%) had delayed-type (type IV) hypersensitivities. Three additional patients were diagnosed with a delayed hypersensitivity to clavulanic acid. These 3 patients had positive delayed IDT to AC but negative to amoxicillin; and all 3 had a subsequent negative DPT with amoxicillin.

Of the 122 suspected/confirmed BL allergies, 96 (78.6%) were diagnosed by skin testing (74 [60.7%] immediate, 22 [18.0%] delayed), while 26 (21.3%) were confirmed by DPT (9 [7.4%] immediate, 17 [13.9%] delayed). Of note, none of the positive DPT suffered anaphylaxis and none required treatment with adrenaline (Table 2). All patients who had a negative skin test were invited for DPT, 797 patients attended for challenges while 199 patients did not undergo DPT.

The initial multivariate logistic regression (Table 3, Model 1) identified that the variables, history of reaction ($p < 0.001$), time of reaction ($p = 0.004$) and index drug ($p = 0.001$) were independently and significantly associated with type I BL allergy. While patients with a history of anaphylaxis (OR 38.67, 95% CI 13.26 – 112.89, $p <$

0.001) were 39 times more likely to have a type I BL allergy compared to those with other symptoms, those with cutaneous symptoms only were not (OR 1.26, 95% CI 0.57 – 2.80, $p = 0.564$). Furthermore if a patient could recall what their index BL was (apart from Meropenem) they were 4 to 15 times more likely to have a type I BL allergy compared to those who could not recall their index BL (OR 3.97 – 14.78, $p < 0.05$). Patients with <1 year elapsed since index reaction were 2.5 times more likely to have a type I BL allergy compared to those with >1 year elapsed since index reaction (OR 2.69, 95% CI 1.38 – 5.23, $p = 0.004$).

An improved multivariate logistic regression model was constructed with the inclusion of the variable history of reaction less than 1 year ago (Table 3, Model 2). In the final model history of reaction ($p = 0.004$), index drug ($p = 0.001$) and history of reaction less than 1 year ago ($p = 0.001$) were independently and significantly associated with type I BL allergy. Patients with a history of anaphylaxis (OR 10.98, 95% CI 2.58 – 46.76, $p = 0.001$), those who could recall what their index BL was (apart from Ampicillin and Meropenem, OR 3.51 – 12.43, $p < 0.05$), and a reaction <1 year ago, particularly in patients with a history of anaphylaxis (OR 38.66, 95% CI 3.46 – 432.13, $p = 0.003$) was associated with increased odds of type I BL allergy.

We characterised a “low risk” cohort which had all of the following features in the patient history: “no history of anaphylaxis to BL”, “a reaction to a BL more than 1 year prior to referral” and “patients who could not recall what the index drug was”. The NPV of the history at presentation for a type I hypersensitivity reaction with the 3 characteristic traits of the “low risk” cohort was 98.4% ($n = 493$, 95% CI 97.2% – 99.4%) which is similar to the NPV of skin testing for a type I hypersensitivity reaction in the whole cohort of 98.9% (95% CI 98.1 – 99.5%). Of note the NPV of the history for BL allergy in the cohort of patients classified as not “low risk” (i.e. the entire cohort excluding the “low risk” cohort) was 80.6% (95% CI 76.9 – 84.6%). For the low risk cohort, 1% (95% CI 0.2% – 1.9%) of patients had a positive immediate skin test reading, 1.6% (95% CI 0.6% – 2.8%) of patients had a positive delayed skin test reading, 0.6% (95% CI 0.0% – 1.4%) of patients had a positive immediate DPT, while 1.8% (95% CI 0.8% – 3.2%) of patients had a positive delayed DPT.

The index drug was unknown in the majority of referrals (56.8%) as neither the patient nor the referring clinician was able to provide the name of the drug involved in the index reaction. For the remaining patients, amoxicillin or AC were the most frequently suspected culprit with a frequency of approximately 4 times more than BP (the second most frequent) and 7 times more than flucloxacillin (the third most frequent) (Table 1).

Of 74 patients who had an immediate reaction on skin testing, 80% of patients tested positive to amoxicillin. Almost half (48%) of patients were monosensitized to amoxicillin while 70% of patients had a negative skin test to both PPL and MD. The diagnosis of immediate hypersensitivity by skin testing could be made in 92% of patients with the utilization of only BP + amoxicillin $\pm$ index BL (i.e. without the need for PPL and MD). The utilization of only BP + amoxicillin $\pm$ index BL for skin testing is estimated to have a NPV for a type I hypersensitivity reaction of 98.1% (95% CI 97.1% – 99.0%), a reduction of approximately 1% when compared to the NPV for skin testing with PPL + MD + BP + amoxicillin $\pm$ index BL which is 98.9% (95% CI 98.1 – 99.5%).

Discussion

In our cohort we identified that a historical reaction of anaphylaxis, knowing the index drug and a reaction <1 year ago, particularly in patients with a history of anaphylaxis, were associated with a type I beta-lactam hypersensitivity. Furthermore, in patients who have no history of anaphylaxis, and a reaction of > 1 year from presentation, who are unable to recall the index drug, the NPV of the history is similar to that of skin testing, with 1% of these patients having a positive immediate skin tests and 0.6% having a positive immediate DPT in this “low risk” cohort. We also found in our cohort that including the penicillin allergenic determinants (PPL and MD) for skin testing, in comparison to the use of BP + amoxicillin ± index BL did not significantly affect the NPV of skin testing for our cohort.

A historical reaction of anaphylaxis was significantly more common in patients with immediate-type hypersensitivity. This resonates with our clinical observation that the patients presenting with anaphylaxis following BL administration are more likely to have a positive DPT and/or positive SPT/IDT. This may reflect the objectivity and higher specificity of anaphylactic reactions for true IgE-mediated responses in comparison to other manifestations. Patients with positive skin testing or DPT were more likely to be aware of the index BL and presented for investigation within a year since their reaction. This is supported by previous reports of BL sensitivity waning over time ². While these associations may be due to referral bias or underlying correlations with reaction severity (attending clinicians and patient may refer earlier and be more aware of the index BL); nonetheless, ascertaining these parameters during history taking will aid the allergist in pre-test evaluation and clinical decision making. Our data provides further evidence that history with predictive models is unable to completely replace conventional allergy testing for BL allergy ^{17, 18}. Our NPV of the history for BL allergy in the rest of the cohort of patients (i.e. the entire cohort excluding the “low risk” cohort) was 80.6% which is comparable to the models used by Chiriac et al.¹⁸ whose models had NPVs between 81 to 83% and that of Hierro Santurino et al¹⁷ whose model had a NPV of 84%. For our “low risk” cohort however the NPV of the history at presentation for a type I hypersensitivity reaction was 98.4% which is similar to that of skin testing in our cohort of 98.9%. Our results imply that skin testing in our “low risk” cohort does not significantly alter the risk benefit ratio of DPT above that of history. However in view of the low prevalence of severe anaphylaxis in our cohort, we are unable to ascertain from our data whether patients in the “low risk” cohort are at lower or higher risk of developing severe anaphylaxis during DPT. A suitably trained allergist could therefore consider with due caution the omission of skin testing from this “low risk” cohort of patients prior to DPT.

We found that only 4%, 1% and 3% of our BL allergic patients were solely sensitized to PPL, MD and PPL+MD, respectively. Almost half (48%) of patients with positive skin tests were monosensitized to amoxicillin (Figure 2). This low level of sensitization to PPL and MD is similar to previous reports from smaller European cohorts^{12, 21, 22}. These findings likely reflect the specific prescribing practices in the UK, with amoxicillin and AC being the most commonly prescribed BL in England between 2006 to 2016, with around 13-17 million prescriptions per year (approximately 6 times that for BP and 4 times that for flucloxacillin)²³. Our results are comparable to previous studies showing a very high positive aminopenicillin allergy testing rate in Europe, where amoxicillin use is higher,^{2, 24, 25} suggesting regional/geographic differences in pattern of sensitivity to the major and minor determinants compared to the United States of America. This regional variability in response rates to penicillins other than the minor and major determinants has also be highlighted in studies in Kuwait and Canada²⁶⁻²⁸. We postulate that most of our BL allergic patients were sensitized to amoxicillin, rather than natural penicillins, leading to a lower rate of sensitization to PPL and MD. However, as amoxicillin skin test/DPT positive patients did not undergo DPT with other BL, the role of side chain sensitization remains to be further investigated.

The availability of penicillin allergenic determinants are still major restrictions to BL allergy testing. In our cohort, the omission of PPL and MD from the standard SPT and IDT reduced the NPV by approximately 1 percentage point to an NPV of 98.1%. The omission of PPL and MD in our cohort of patients would results in 6 out of 1092 patients (1 in 182 patients) testing negative on skin test who would otherwise test positive with the utilisation of PPL and MD. Evidence from a large review paper from the United States of America suggests that using the minor and major determinants in detecting penicillin allergy has a NPV of 97%²⁹. This reflects the geographical variability and therefore in areas of low prevalence of BP usage and allergy (i.e. the United Kingdom/Europe), the use of determinants could be considered less beneficial and the practicing allergist could potentially omit them. However, in cases of anaphylaxis or higher BP allergy prevalence (i.e the United States of America) then omitting would be less desirable. Overall however, we strongly recommend that any decision to omit the major and minor determinants should only be made by a suitably qualified allergist who understands cohort prevalence data, geographical variability and awareness of risk stratification for penicillin allergy testing.

The 8% of patients detected by major and minor determinant testing in our cohort translates to a low frequency of patients who have a positive DPT despite a negative skin test in view of the low prevalence of BP clinical allergy and general usage in the United Kingdom and Europe. Geographical variability therefore has a significant

impact on penicillin allergy prevalence data and thus would impact skin testing methodology, practice and sensitization pattern²⁹. Therefore the omission of major and minor determinants from standard testing is based on a population's low prevalence of BP usage and allergy and conversely higher prevalence rates of amoxicillin usage and allergy. The major and minor determinants are being replaced with BP, amoxicillin and the index drug. It is important to note that there is published data indicating that more severe BL allergies are due to the minor determinants²⁹ and that amoxicillin allergy is less likely to cause a severe allergic reaction^{30, 31}. Therefore in cases where prevalence of BP allergy is higher or there is a strong history of anaphylaxis, the use of major and minor determinants would be recommended. The allergist may consider skin testing with BP, amoxicillin and index agents only, in situations where there is a lack of availability of the major and minor determinants. The consideration of the geographical variability of penicillin allergy and sensitization patterns, as well as the ability to consistently mix the reagents (which are pharmaceutical grade licensed medications) is important to be weighed in this decision. A suitability-qualified allergist must interpret this with awareness of the prevalence data of BL allergy to have appropriate risk stratification.

Our data also indicates that in "low risk" patients skin testing may be omitted prior to DPT, which is the gold standard for establishing a diagnosis of tolerance to penicillins. Especially in populations where skin testing capacity is limited, this may translate to a greater number patient that can be evaluated without compromising diagnostic accuracy (as all patients will undergo DPT). Prospective studies are therefore required to confirm our findings that may be beneficial to patient care.

The main limitations of this retrospective study stem from the limitation of medical records review. Certain variables such as demographics, duration since reaction and index reactions were not available for every patient. Following a negative skin test, 199 declined DPT despite invitation and therefore allergy could not confidently excluded. Retrospective data collection also includes potential referral or selection bias; for example, referring clinicians may tend to refer patients with more severe reactions or not refer patients with clear-cut histories of genuine BL allergies. Furthermore, patients who defaulted their clinic appointments or declined skin testing were not included. The variable "time of reaction" could only be categorized into <1 year or ≥1 year due to limitations of medical records. This highlights the necessity of future prospective studies. Furthermore, patients with skin tests showing monosensitization to amoxicillin did not undergo DPT and we could not ascertain if they were genuine selective responders to amoxicillin (rather than false negative results with other reagents). We are planning future studies into this selective cohort of patients. More importantly, results from our cohort are region-specific and likely

pertain to local prescribing practices and sensitization profiles. Therefore, in populations with high prevalence of BL allergy, skin testing should always be performed prior to DPT irrespective of the history. Of note in patients with 'low risk' features the risk of anaphylaxis during DPT is not completely absent. Thus, omission of skin testing prior to DPT in patients with 'low risk' features should be only performed in a specialist centre with staff trained to recognize and treat allergic reactions, as well as weigh the risk benefit ratio of the omission of skin testing. We encourage further studies to corroborate the external validity of our findings. Lastly, all allergological investigations were performed by trained allergy nurses or specialists only and our results may not be directly translatable to non-allergists performing the same investigations.

In conclusion, we identified that an historical reaction of anaphylaxis, knowing the index drug, and a history of anaphylaxis or cutaneous symptoms less than 1 year ago were independently associated with beta-lactam hypersensitivity. We have identified a cohort of patients who are "low risk" whose NPV of history is similar to that of skin testing, and in these patients the omission of skin testing prior to DPT may not significantly change the risk benefit ratio of DPT. Furthermore in populations with a low background prevalence of PPL and MD sensitization, the use of BP + amoxicillin $\pm$ index BL for skin testing, prior to DPT, maybe adequate to risk stratify DPT. Nevertheless, when the prevalence of BL allergy in a region is high, a detailed history followed by skin testing and DPT, if appropriate, should be always performed.

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Contributor Statement

Dr Leonard Siew and Dr Philip Li had obtained the data, performed data analysis and prepared the manuscript. Dr Prathap Pillai had aided in data collection and the review and editing of the manuscript. Dr Kok Loong Ue, Dr Iason Thomas, Dr Timothy Watts, Professor Stephen J. Till, Dr M. Rosario Caballero and Dr Krzysztof Rutkowski were involved in the review and editing of the manuscript. Dr Rubaiyat Haque was involved in the planning of the study as well as the review and editing of the manuscript.

Conflict of Interest

The authors wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. Professor Stephen J. Till has received grants from ASIT Biotech to conduct unrelated research work.

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- 569
570

571 **Tables**

	Whole cohort n (%)	Allergic Type I n (%)	Type IV n (%)	Not Allergic n (%)
Total patients	1092	83	39	767
Male	358 (32.8)	21 (25.3)	11 (28.2)	285 (37.2)
Age in years (median, range)	48 (15-95)	53 (17-94)	46 (18-92)	49 (15-95)
<u>Ethnicity</u>				
White	718 (65.8)	51 (61.4)	25 (64.1)	529 (69.0)
Black	69 (6.3)	4 (4.8)	4 (10.3)	44 (5.7)
Middle Asian	21 (1.9)	2 (2.4)	0 (0)	17 (2.2)
Mixed	18 (1.6)	0 (0)	0 (0)	6 (0.8)
East Asian	13 (1.2)	1 (1.2)	0 (0)	7 (0.9)
Unknown	253 (23.2)	25 (30.1)	10 (25.6)	164 (21.4)
<u>Index reaction</u>				
Anaphylaxis	54 (4.9)	37 (44.6)	0 (0)	12 (1.6)
Cutaneous symptoms only	654 (59.9)	36 (43.4)	28 (71.8)	461 (60.1)
Others / unknown	384 (35.2)	10 (12.0)	11 (28.2)	294 (38.3)
<u>Index beta-lactam</u>				
Penicillin V / G	80 (7.3)	4 (4.8)	2 (5.1)	56 (7.3)
Amoxicillin	151 (13.8)	22 (26.5)	6 (15.4)	88 (11.5)
Amoxicillin-clavulanate	146 (13.4)	36 (43.4)	9 (23.1)	70 (9.1)
Flucloxacillin	44 (4.0)	4 (4.8)	4 (10.3)	24 (3.1)
Cephalosporins	29 (2.7)	2 (2.4)	1 (2.6)	14 (1.8)
Piperacillin-tazobactam	13 (1.2)	3 (3.6)	0 (0)	8 (1.0)
Ampicillin	5 (0.5)	1 (1.2)	0 (0)	4 (0.5)
Meropenem	4 (0.4)	0 (0)	0 (0)	2 (0.3)
Unknown	620 (56.8)	11 (13.3)	17 (43.6)	501 (65.3)
<u>Duration since reaction</u>				
<1 year	14 (1.3)	53 (63.9)	7 (17.9)	106 (13.8)
≥ 1 year	1068 (97.8)	30 (36.1)	32 (82.1)	651 (84.9)
Unknown	10 (0.9)	0 (0)	0 (0)	10 (1.3)

572

573 Table 1: Demographics, clinical features and outcomes of 1092 patients referred for
574 penicillin allergy testing from July 2010 to December 2016.

	Age/Sex	Index Drug	Provocation Drug (Doses)	Reaction	Treatment
1	52/F	Amoxicillin	Amoxicillin 50mg, 150mg	Pruritis, Urticaria	Cetirizine Prednisolone
2	68/M	Unknown	Flucloxacillin 50mg, 150mg	Pruritis, Urticaria, Angioedema	Cetirizine Prednisolone
3	26/F	Penicillin V	Penicillin V 50mg, 150mg	Pruritis, Urticaria	Cetirizine Prednisolone
4	70/M	Unknown	Amoxicillin 50mg, 150mg	Pruritis, Angioedema	Cetirizine Prednisolone
5	65/F	Penicillin V	Penicillin V 50mg, 150mg	Pruritis, Urticaria	Cetirizine Prednisolone
6	43/F	Amoxicillin-clavulante	Amoxicillin-clavulante 50mg, 150mg, 300mg	Pruritis, Urticaria	Cetirizine Prednisolone
7	27/F	Unknown	Penicillin V 50mg, 150mg	Pruritis, Urticaria	Cetirizine Prednisolone
8	48/F	Unknown	Amoxicillin 50mg, 150mg	Pruritis, Angioedema	Cetirizine Prednisolone
9	18/F	Amoxicillin	Amoxicillin 50mg, 150mg, 300mg	Pruritis, Urticaria	Cetirizine Prednisolone
10	29/F	Amoxicillin	Amoxicillin 250mg TDS for 1 day	Maculopapular rash	Cetirizine Prednisolone
11	70/M	Penicillin V	Penicillin V 250mg QDS for 1 day	Maculopapular rash	Cetirizine Prednisolone
12	41/M	Amoxicillin-clavulante	Amoxicillin-clavulante 375mg TDS for 1 day	Maculopapular rash	Cetirizine Prednisolone
13	60/F	Unknown	Amoxicillin 250mg TDS for 3 days	Maculopapular rash	Cetirizine Prednisolone
14	37/F	Amoxicillin-clavulante	Amoxicillin-clavulante 375mg TDS for 3 days	Maculopapular rash	Cetirizine Prednisolone
15	33/F	Unknown	Penicillin V 250mg QDS for 2 day	Maculopapular rash	Cetirizine Prednisolone
16	31/F	Amoxicillin-clavulante	Amoxicillin-clavulante 375mg TDS for 1 day	Maculopapular rash	Cetirizine Prednisolone
17	39/F	Unknown	Amoxicillin 250mg TDS for 3 days	Maculopapular rash	Cetirizine Prednisolone
18	76/F	Unknown	Amoxicillin-clavulante 375mg TDS for 1 day	Maculopapular rash	Cetirizine Prednisolone
19	31/F	Amoxicillin	Amoxicillin 250mg TDS for 3 days	Maculopapular rash	Cetirizine Prednisolone
20	64/F	Unknown	Amoxicillin 250mg TDS for 2 days	Maculopapular rash	Cetirizine Prednisolone
21	77/F	Penicillin V	Penicillin V 250mg QDS for 1 day	Maculopapular rash	Cetirizine Prednisolone
22	46/F	Unknown	Flucloxacillin 250mg QDS for 3 days	Maculopapular rash	Cetirizine Prednisolone
23	46/F	Unknown	Amoxicillin 250mg TDS for 3 days	Maculopapular rash	Cetirizine Prednisolone
24	42/F	Amoxicillin-clavulante	Amoxicillin-clavulante 375mg TDS for 1 day	Maculopapular rash	Cetirizine Prednisolone
25	52/F	Unknown	Amoxicillin 250mg TDS for 3 days	Maculopapular rash	Cetirizine Prednisolone
26	51/M	Unknown	Amoxicillin 250mg TDS for 3 days	Maculopapular rash	Cetirizine Prednisolone

Table 2: Clinical features and outcomes of a patients who had a positive drug provocation test. (TDS = Three times a day, QDS = Four times a day)

Variable	Odds Ratio	95% Confidence Interval of Odds Ratio		p-value
		Lower	Upper	
Model 1^a				
Age	1.02	1.00	1.04	0.07
History of reaction				< 0.01
Cutaneous symptoms only	1.26	0.57	2.80	0.56
Anaphylaxis	38.67	13.26	112.89	< 0.01
<1 year since reaction	2.69	1.38	5.23	< 0.01
Index drug				< 0.01
Amoxicillin	7.40	3.23	16.97	< 0.01
Penicillin V/G	3.97	1.17	13.53	0.03
Flucloxacillin	4.59	1.14	18.42	0.03
Cephalosporin	8.21	1.15	58.88	0.04
Piperacillin-Tazobactam	14.78	2.66	81.96	< 0.01
Ampicillin	11.39	1.07	121.18	0.04
Meropenem	0.00	0.00		1.00
<i>Hosmer and Lemeshow 0.04</i>		<i>Nagelkerke R² 0.46</i>		
Model 2^b				
Age	1.02	1.00	1.04	0.86
History of reaction				< 0.01
Cutaneous symptoms only	1.16	0.50	2.71	0.73
Anaphylaxis	10.98	2.58	46.76	< 0.01
Index drug				< 0.01
Amoxicillin	6.37	2.82	14.39	< 0.01
Penicillin V/G	3.51	1.05	11.78	0.04
Flucloxacillin	4.23	1.05	17.03	0.04
Cephalosporin	9.36	1.53	57.29	0.02
Piperacillin-Tazobactam	12.43	2.21	69.96	< 0.01
Ampicillin	9.90	0.95	103.53	0.06
Meropenem	0.00	0.00		1.00
History less than 1 year ago				< 0.01
Cutaneous symptoms less than 1 year ago	2.60	1.23	5.48	0.01
Anaphylaxis less than 1 year ago	38.66	3.46	432.13	< 0.01
<i>Hosmer and Lemeshow 0.06</i>		<i>Nagelkerke R² 0.48</i>		

^a Variables entered on step 1 were age, gender, ethnicity, time of reaction (<1 year since reaction), history of reaction and index drug

^b Variables entered on step 1 were age, gender, ethnicity, time of reaction (<1 year since reaction), history of reaction, index drug, and history of reaction less than 1 year ago

580 Table 3: Multivariate logistic regression (backward stepwise) of predictors associated
581 with type I beta-lactam hypersensitivity.

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Figure Legends

Figure 1: Flow diagram of patient diagnostic pathway and outcomes (please refer to text for breakdown of skin and provocation test results).

Figure 2: Edward-Venn diagram showing distribution sensitization pattern in positive skin tests. Values represent percentages. PPL – benzylpenicillinpolylysine, MD - minor determinant (MD).

1 **Methods**

2

3 Statistical Analysis

4 A multivariate binary logistic regression analysis was performed on our cohort of
5 patients. 199 patients who had negative skin prick testing who defaulted challenge
6 (lost to follow-up or decline DPT after consent), 10 patients who had unknown
7 history, index drug and time of reaction and 4 patients who were challenged with a
8 cephalosporin were excluded from the regression analysis. Multivariate binary
9 logistic regression analysis was performed on the remaining cohort of 879 patients,
10 using Enter, Forward Stepwise and Backward Stepwise regression, with type I
11 hypersensitivity status as the dependent variable. The independent variables
12 entered into the regression were age, gender, ethnicity, time of reaction, history of
13 reaction and index drug. The reference used for gender was male and the history of
14 <1 year since reaction for time of reaction. Ethnicity was entered as a 6-category
15 variable (white, black, middle Asian, mixed, east Asian and unknown) with white as
16 the reference category. History of reaction was entered as a 3-category variable
17 (anaphylaxis, cutaneous symptoms only and other symptoms) with unknown as the
18 reference category. Index drug was entered as an 8-category variable (amoxicillin,
19 penicillin V/G, flucloxacillin, cephalosporin, piperacillin-tazobactam, ampicillin,
20 meropenem and unknown) with unknown as the reference category. For the history
21 of reaction, anaphylaxis was defined as 2 or more organ systems involved ^{E1},
22 cutaneous symptoms only was defined as either a non specific rash, maculopapular
23 rash or urticaria/angioedema, while other symptoms were defined as either
24 gastrointestinal, neurological, musculoskeletal symptoms or unknown symptoms.
25 Backward stepwise regression had the highest Nagelkerke R² value and was
26 selected as the regression method used.

27 The variables entered on step 1 of Model 1 were age, gender, ethnicity, time of
28 reaction (<1 year since reaction), history of reaction and index drug. The variables
29 age, gender, and ethnicity failed to reach statistical significance. This model despite
30 accounting for 46% of the variance of type I BL allergic status (Nagelkerke R² 0.460)
31 had a poor goodness of fit (Hosmer and Lemeshow test p = 0.035). To improve
32 goodness of fit the variable history of reaction less than 1 year ago was added to the
33 model, and was entered as a 2-category variable (history of anaphylaxis less than 1
34 year ago and cutaneous symptoms less than 1 year ago). The variables entered on
35 step 1 of Model 2 were age, gender, ethnicity, time of reaction (<1 year since
36 reaction), history of reaction, index drug, and history of reaction less than 1 year ago.
37 Backward stepwise regression was performed and this resulted in a model which

38 accounted for 48% of the variance of type I BL allergic status (Nagelkerke R^2 0.479)
39 with an acceptable goodness of fit (Hosmer and Lemeshow test $p = 0.062$).

40 Regression analysis including the following variables “index drug less than 1 year
41 ago”, “history of reaction due to an index drug” and “history of reaction due to an
42 index drug less than 1 year ago” were all not statistically significant and did not
43 improve goodness of fit (data not shown).

44 Data were summarised as percentages and frequencies where appropriate. Data
45 were compared using the Chi-squared test and statistical significance set at $p < 0.05$.
46 Edwards’ Venn diagram was generated using the web-based application jvenn ^{E2}.
47 Bootstrapping was performed and 95% confidence intervals are based on 1000
48 bootstrap samples.

49

50

Reference:

- E1. Simons FE, Arduzzo LR, Bilo MB, El-Gamal YM, Ledford DK, Ring J, et al. World allergy organization guidelines for the assessment and management of anaphylaxis. *World Allergy Organ J* 2011; 4:13-37.
- E2. Bardou P, Mariette J, Escudie F, Djemiel C, Klopp C. jvenn: an interactive Venn diagram viewer. *BMC Bioinformatics* 2014; 15:293.