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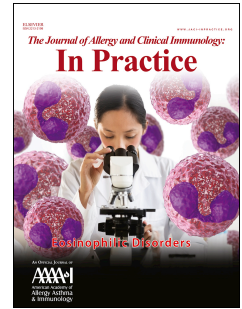
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Accepted Manuscript

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

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

2

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16

17 **Conflict of Interest**

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33

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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

60 Highlights box

61

62 1. What is already known about this topic?

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

66

67 2. What does this article add to our knowledge?

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

71

72 3. How does this study impact current management guidelines?

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

77

78 Keywords

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

81

82 Abbreviations

83	95% CI	95% Confidence Interval
84	AC	Amoxicillin-clavulanate
85	BL	Beta-lactam
86	BP	Benzylpenicillin
87	DPT	Drug provocation test
88	IDT	Intradermal test
89	NHS	National Health Service
90	NPV	Negative Predictive Value
91	MD	Minor determinant, Sodium Benzylpenilloate
92	PPL	Penzylpenicillinpolylysine
93	PT	Piperacillin-tazobactam
94	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}.

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

137

138 **Methods**

139 Data Collection

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

163 This study was conducted as part of an approved audit within the department. The
164 data were collected in a database that was then reviewed and checked for
165 inconsistencies by two independent investigators. Any discrepancies were then
166 discussed between the two independent investigators and unresolved discrepancies
167 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 reading⁶. 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 testing¹⁹. 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

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

222

223 Statistical Analysis

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

232

233 **Results**

234 Between July 2010 to December 2016, 1096 patients were referred for and
235 underwent BL allergy testing, 4 patients were excluded at this stage of the analysis
236 as these patients had an incongruence between their history of presentation and skin
237 test results and subsequently had a negative DPT. In the remaining 1092 patients
238 the male:female ratio was 1:3.1 (32%:68%) and the median age was 48 (range: 15-
239 95) years. Sixty-six percent of patients tested were of white ethnicity; while the
240 remaining patients tested were of Black, Middle Asian, East Asian, or mixed ethnicity.
241 The index drug was unknown in over half of patients (i.e most patients just reported a
242 suspected allergy to “an unknown penicillin” or BL class of antibiotic). Amoxicillin
243 (13.8%) and AC (13.4%) were the most commonly specifically implicated penicillin-
244 based/BL antibiotics (Table 1).

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

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

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

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

270 0.001) were 39 times more likely to have a type I BL allergy compared to those with
271 other symptoms, those with cutaneous symptoms only were not (OR 1.26, 95% CI
272 0.57 – 2.80, $p = 0.564$). Furthermore if a patient could recall what their index BL was
273 (apart from Meropenem) they were 4 to 15 times more likely to have a type I BL
274 allergy compared to those who could not recall their index BL (OR 3.97 – 14.78, $p <$
275 0.05). Patients with <1 year elapsed since index reaction were 2.5 times more likely
276 to have a type I BL allergy compared to those with >1 year elapsed since index
277 reaction (OR 2.69, 95% CI 1.38 – 5.23, $p = 0.004$).

278 An improved multivariate logistic regression model was constructed with the inclusion
279 of the variable history of reaction less than 1 year ago (Table 3, Model 2). In the final
280 model history of reaction ($p = 0.004$), index drug ($p = 0.001$) and history of reaction
281 less than 1 year ago ($p = 0.001$) were independently and significantly associated with
282 type I BL allergy. Patients with a history of anaphylaxis (OR 10.98, 95% CI 2.58 –
283 46.76, $p = 0.001$), those who could recall what their index BL was (apart from
284 Ampicillin and Meropenem, OR 3.51 – 12.43, $p < 0.05$), and a reaction <1 year ago,
285 particularly in patients with a history of anaphylaxis (OR 38.66, 95% CI 3.46 –
286 432.13, $p = 0.003$) was associated with increased odds of type I BL allergy.

287 We characterised a “low risk” cohort which had all of the following features in the
288 patient history: “no history of anaphylaxis to BL”, “a reaction to a BL more than 1 year
289 prior to referral” and “patients who could not recall what the index drug was”. The
290 NPV of the history at presentation for a type I hypersensitivity reaction with the 3
291 characteristic traits of the “low risk” cohort was 98.4% ($n = 493$, 95% CI 97.2% –
292 99.4%) which is similar to the NPV of skin testing for a type I hypersensitivity reaction
293 in the whole cohort of 98.9% (95% CI 98.1 – 99.5%). Of note the NPV of the history
294 for BL allergy in the cohort of patients classified as not “low risk” (i.e. the entire cohort
295 excluding the “low risk” cohort) was 80.6% (95% CI 76.9 – 84.6%). For the low risk
296 cohort, 1% (95% CI 0.2% – 1.9%) of patients had a positive immediate skin test
297 reading, 1.6% (95% CI 0.6% – 2.8%) of patients had a positive delayed skin test
298 reading, 0.6% (95% CI 0.0% – 1.4%) of patients had a positive immediate DPT, while
299 1.8% (95% CI 0.8% – 3.2%) of patients had a positive delayed DPT.

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

306 Of 74 patients who had an immediate reaction on skin testing, 80% of patients tested
307 positive to amoxicillin. Almost half (48%) of patients were monosensitized to
308 amoxicillin while 70% of patients had a negative skin test to both PPL and MD. The
309 diagnosis of immediate hypersensitivity by skin testing could be made in 92% of
310 patients with the utilization of only BP + amoxicillin \pm index BL (i.e. without the need
311 for PPL and MD). The utilization of only BP + amoxicillin \pm index BL for skin testing is
312 estimated to have a NPV for a type I hypersensitivity reaction of 98.1% (95% CI
313 97.1% – 99.0%), a reduction of approximately 1% when compared to the NPV for
314 skin testing with PPL + MD + BP + amoxicillin \pm index BL which is 98.9% (95% CI
315 98.1 – 99.5%).

316

ACCEPTED MANUSCRIPT

317 **Discussion**

318 In our cohort we identified that a historical reaction of anaphylaxis, knowing the index
319 drug and a reaction <1 year ago, particularly in patients with a history of anaphylaxis,
320 were associated with a type I beta-lactam hypersensitivity. Furthermore, in patients
321 who have no history of anaphylaxis, and a reaction of > 1 year from presentation,
322 who are unable to recall the index drug, the NPV of the history is similar to that of
323 skin testing, with 1% of these patients having a positive immediate skin tests and
324 0.6% having a positive immediate DPT in this “low risk” cohort. We also found in our
325 cohort that including the penicillin allergenic determinants (PPL and MD) for skin
326 testing, in comparison to the use of BP + amoxicillin ± index BL did not significantly
327 affect the NPV of skin testing for our cohort.

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

355 We found that only 4%, 1% and 3% of our BL allergic patients were solely sensitized
356 to PPL, MD and PPL+MD, respectively. Almost half (48%) of patients with positive
357 skin tests were monosensitized to amoxicillin (Figure 2). This low level of
358 sensitization to PPL and MD is similar to previous reports from smaller European
359 cohorts ^{12, 21, 22}. These findings likely reflect the specific prescribing practices in the
360 UK, with amoxicillin and AC being the most commonly prescribed BL in England
361 between 2006 to 2016, with around 13-17 million prescriptions per year
362 (approximately 6 times that for BP and 4 times that for flucloxacillin) ²³. Our results
363 are comparable to previous studies showing a very high positive aminopenicillin
364 allergy testing rate in Europe, where amoxicillin use is higher, ^{2, 24, 25} suggesting
365 regional/geographic differences in pattern of sensitivity to the major and minor
366 determinants compared to the United States of America. This regional variability in
367 response rates to penicillins other than the minor and major determinants has also
368 be highlighted in studies in Kuwait and Canada ²⁶⁻²⁸. We postulate that most of our
369 BL allergic patients were sensitized to amoxicillin, rather than natural penicillins,
370 leading to a lower rate of sensitization to PPL and MD. However, as amoxicillin skin
371 test/DPT positive patients did not undergo DPT with other BL, the role of side chain
372 sensitization remains to be further investigated.

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

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

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

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

416 The main limitations of this retrospective study stem from the limitation of medical
417 records review. Certain variables such as demographics, duration since reaction and
418 index reactions were not available for every patient. Following a negative skin test,
419 199 declined DPT despite invitation and therefore allergy could not confidently
420 excluded. Retrospective data collection also includes potential referral or selection
421 bias; for example, referring clinicians may tend to refer patients with more severe
422 reactions or not refer patients with clear-cut histories of genuine BL allergies.
423 Furthermore, patients who defaulted their clinic appointments or declined skin testing
424 were not included. The variable "time of reaction" could only be categorized into <1
425 year or ≥ 1 year due to limitations of medical records. This highlights the necessity of
426 future prospective studies. Furthermore, patients with skin tests showing
427 monosensitization to amoxicillin did not undergo DPT and we could not ascertain if
428 they were genuine selective responders to amoxicillin (rather than false negative
429 results with other reagents). We are planning future studies into this selective cohort
430 of patients. More importantly, results from our cohort are region-specific and likely

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

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

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459

460 Contributor Statement

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

468

469 Conflict of Interest

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474

475

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- 569
570

	Whole cohort n (%)	Allergic Type I n (%)	Allergic 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

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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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582 **Figure Legends**

583

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

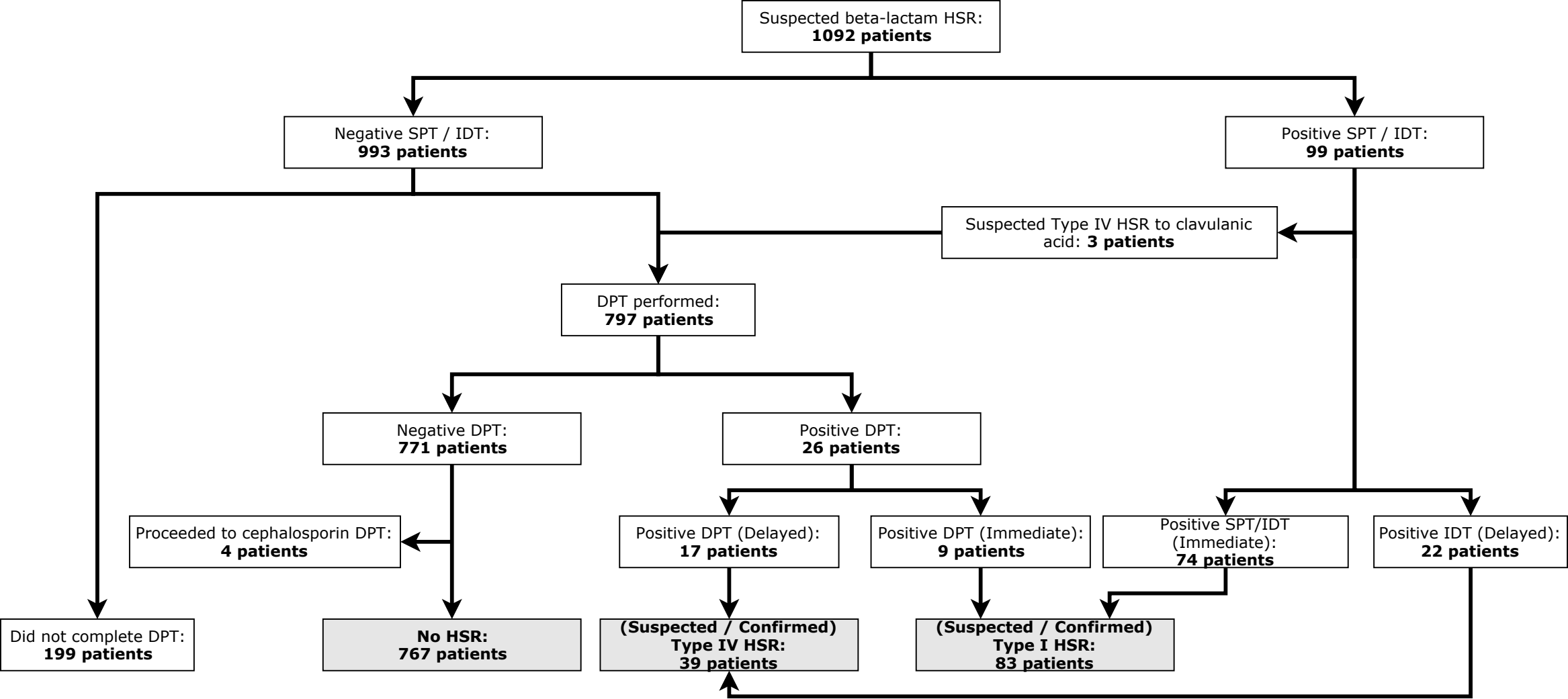
586

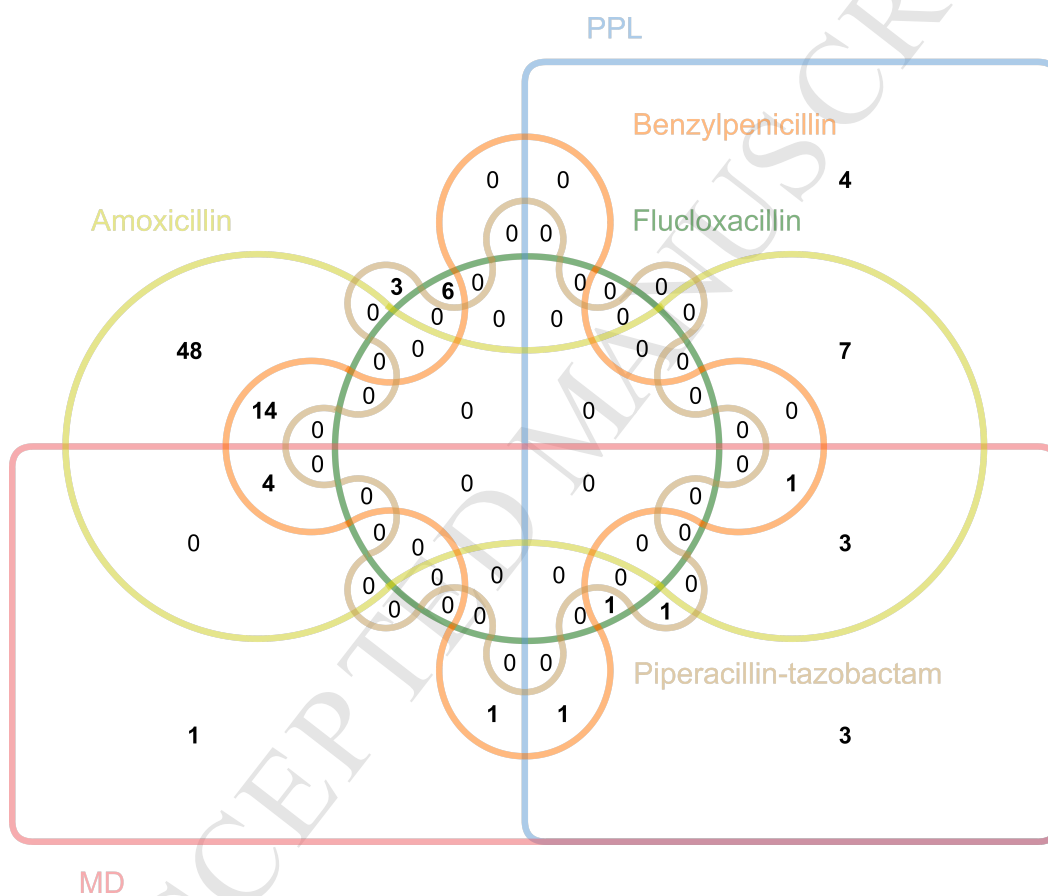
587 Figure 2: Edward-Venn diagram showing distribution sensitization pattern in positive
588 skin tests. Values represent percentages. PPL – benzylpenicillinpolylysine, MD -
589 minor determinant (MD).

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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

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