

ORIGINAL ARTICLE

The role of skin testing and extended antibiotic courses in assessment of children with penicillin allergy: An Australian experience

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Aim: To determine if skin testing (ST) in addition to extended oral provocation challenge (OPC) is necessary for beta-lactam allergy verification in an Australian paediatric population.

Methods: This was a retrospective study (176 children) that undertook assessments for beta-lactam allergy from 2006 to 2015 at a tertiary paediatric hospital. Patients either underwent direct OPC without ST or ST plus challenge if ST was negative.

Results: The analysis included children with a history of varying rash types/severity as well as angioedema and reported anaphylaxis. A direct OPC was undertaken in 73 children. Three children reacted with one anaphylaxis. A total of 103 children underwent ST, with 13 children (12.6%) reacting. Of the 90 who subsequently proceeded to OPC, 4 reacted. A total of 132 children were given an extended oral course of the culprit antibiotic, to which 6 children reacted.

Conclusions: A direct OPC with the culprit drug in Australian children can be safely performed, avoiding resource-intensive and painful ST. Our data demonstrate that a prior history of anaphylaxis does not necessarily predict IgE-mediated allergy, as detected by positive immediate ST or reactions to oral challenge. Such history should not detract from efforts to assess these children for antibiotic allergy. We suggest that extended courses of at least 5 days are important in paediatric antibiotic de-labelling as six children (4.5% of those who were prescribed the extended course) reacted in our study and even developed symptoms late in the extended course, from days 2 to 6.

Key words: beta-lactam allergy; penicillin allergy; skin testing.

What is already known on this topic

- 1 Parent-reported antibiotic allergy in children is a common problem; the majority of reactions to antibiotics reported are rashes.
- 2 According to international studies, the rate of true allergy in children with rashes is low.
- 3 Skin testing (ST) is time consuming, expensive and painful and is only available at specialist clinics.

What this paper adds

- 1 This first Australian paediatric study provides data to guide the management of reported antibiotic allergies in children and demonstrates that a prior history of anaphylaxis does not necessarily predict IgE-mediated allergy, as detected by positive immediate ST or reactions to oral challenge; thus, such history should not detract from efforts to assess these children for antibiotic allergy.
- 2 A direct oral provocation challenge with the culprit drug in Australian children can be safely performed, avoiding resource-intensive and painful ST.
- 3 Extended courses with the culprit drug are important in the assessment, allowing confirmation of delayed reactions, which were more frequently detected than immediate reactions.

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The ubiquitous use of beta-lactam antibiotics has led to an increase in antibiotic allergy labelling, while the rate of true allergy has been shown to be low.^{1–3}

Better evidence for guiding diagnostic and management strategies for paediatric antibiotic allergy is emerging.^{2,4,5} The most recent paediatric studies, including a systematic review, conclude that there is no rigorous evidence to support skin testing (ST) for the investigation of antibiotic allergy in children,⁶ and direct

progression to oral provocation challenge (OPC) with the culprit antibiotic in children with a rash can be safely performed.⁷ Australian data in this regard are currently missing. To date, there is also limited evidence on the assessment of children with more severe reactions than mild to moderate rashes and on the value or duration of an extended course as part of the OPC after the successful administration of an initial supervised dose.^{1,3,8} This may be relevant as many children present with ill-specified non-immediate reactions. The data gap in the literature highlights the need for further studies to elucidate the optimal approach for antibiotic de-labelling in children.

Here, we reviewed 176 children, aged 0–16 years, who underwent assessments for beta-lactam allergy, either by direct OPC without ST or ST plus OPC if ST was negative, over a 10-year period (2006–2015) at a tertiary paediatric hospital in Western Australia. The children were a typical referral cohort not prospectively recruited to the study. There were no children with a history of a severe cutaneous adverse reaction, severe organ involvement due to a presumed drug hypersensitivity or serum sickness. Data collection included demographics, initial reactions and suspected culprit antibiotic.

Methods

Children were assessed by either ST followed by OPC (if ST was negative; Group 2) or direct OPC (Group 1). The children were not randomised to either group but assigned at the preference of the treating immunologists/allergists (retrospective chart review analysis).

Skin prick testing (SPT) was performed by using 1 mm metal lancets (Stallergenes, Paris, France). For intradermal testing (IDT), 0.02 mL of either allergen or control was injected using 26 gauge needles. Testing was performed with normal saline, histamine (10 mg/mL; SPT only), benzyl penicilloyl octa-L-lysine (penicilloyl-polylysine), sodium benzylpenicilloate (minor determinant) (Diater, Madrid, Spain), benzylpenicillin and the suspected culprit antibiotic. These were amoxicillin (70%), penicillin V (16%), cephalexin (10%), co-amoxiclav (2%) and flucloxacillin (2%). The ST was read 15 min after the application of reagents. A wheal at least 3 mm greater than the negative control was considered a positive SPT result, and for IDT, a wheal at least 3 mm greater than the control saline bleb was considered positive.

Where blood sampling was performed for specific IgE, a positive response was considered to be >0.35 kU/L of amoxicilloyl, penicilloyl G, penicilloyl V and ampicilloyl.

OPCs were performed with the suspected culprit antibiotic (amoxicillin 70%, penicillin 16%, cephalexin 10%, Augmentin 2% and flucloxacillin 2%) by administering one tenth and then a full dose of the antibiotic 30 min apart if there was no reaction to the first dose. Children were then observed for 1 h. Following successful OPC, children were discharged home on a 5-day extended course with the culprit antibiotic using standard dosing.

Retrospectively, the research team identified risk categories for all the patients included. We categorised patients as high risk or low risk according to their clinical history. This categorisation took into account both the timing of the original reaction and the clinical features. We assigned high risk to patients who had a reaction history with any systemic features of concern. Low-risk patients were those with remote rashes without systemic

features. Low-risk patients were deemed to have a negligible risk of reacting during assessment.

Statistical data analysis was performed using Mann–Whitney *U* test for continuous data and Fisher's exact test for categorical data.

Results

Cohort descriptors and characteristics

Table 1 is a summary of demographic data and history.

The majority of patients reviewed ($n = 128$, 72.7%) had been referred by their general practitioner to the clinical immunology service, with hospital wards and the emergency department each referring 19 patients (10.8%). The referral source for the remaining patients was not documented.

We also recorded information on any confounding illness (carer's interpretation of illness) at the time when the antibiotic was given. No confounding illnesses were recorded for 65 children (36.9%). Chest infection ($n = 26$, 14.7%), tonsillitis ($n = 24$, 13.6%), viral illness ($n = 16$, 9.0%) and ear infection ($n = 16$, 9.0%) were the most commonly recorded confounding conditions. Asthma was the most commonly recorded chronic illness amongst the patients reviewed ($n = 14$, 7.9%). Eczema was reported for eight patients (4.5%).

In terms of blood testing, there were no positive radioallergo-sorbent tests for the 156 patients tested.

The children were then analysed in two groups depending on whether or not their assessments included ST in addition to OPC (Figure 1). Group 1 ($n = 73$, 41.5%) included children who underwent a direct two-stage OPC. Group 2 ($n = 103$, 58.5%) included children who underwent ST (103 undergoing SPT, 92 undergoing IDT) followed by OPC if the ST was negative.

Using Fisher's exact test, we found statistically significant differences between Groups 1 and 2; children undergoing a direct challenge without ST (Group 1) were younger in age at reaction and age at challenge. Group 1 had a lower rate of children with an urticarial rash with angioedema and anaphylaxis in their past history (Table 1). Gender and coexisting allergies did not influence testing outcome for ST (Group 2), OPC or the 5-day course of antibiotic challenge (Group 1 and 2).

We also looked at the age at reaction and the age at challenge of the 27 children with a self-reported anaphylaxis reaction; this group was not all necessarily assigned a high risk categorisation in our review. Of these 27 children, 3 failed at OPC, and 2 had been skin tested and had not reacted; 17 were assessed within 1 year of the initial reaction, with 4 children waiting more than 4 years for assessment following the initial reaction. Of the 10 children who were assessed more than a year after their initial reaction, 2 were assigned to Group 1 and were successful at OPC; 8 were assigned to Group 2, with none reacting to ST or OPC and one reacting on day 6 of the extended 5-day course.

Results of the ST (Group 2 only)

In Group 2, 103 skin prick tests were performed. IDT was also performed in 92 of these children. A total of 13 cases had a reaction to ST (12.6%). Of the 13 children, 4 were deemed high risk. Two children reacted to SPT alone and 11 to IDT alone. Both children

who reacted at SPT had wheals <5 mm. Of the 11 who reacted at IDT, 10 had wheals of >5 mm. The children with a positive skin test were deemed antibiotic allergic and did not proceed to the oral challenge. Of the 22 children with previously self-reported severe anaphylactic reactions, all had negative SPT. IDT was performed on 20 of these children, and 1 had a positive result.

Results of the oral provocation challenge (Groups 1 and 2)

A total of 163 OPC were performed; 7 children reacted, with 3 experiencing anaphylaxis (1 in Group 1, with a history of reported anaphylaxis, and 2 in Group 2). Of the 90 patients from Group 2 who passed ST, 4 were unsuccessful in the OPC, 2 of who experienced anaphylaxis at challenge, both with a history of a rash. In Group 1, 73 OPCs were performed, with 3 patients reacting during the challenge with one anaphylaxis. Of the 27 children who were referred with severe previous reactions (defined as anaphylaxis), 5 were assessed by OPC only (Group 1), with 4 of these having successful OPC and 1 having an unsuccessful challenge with anaphylaxis. In Group 2, there were 22 children with severe previous reactions, and 2 of these were unsuccessful at challenge but with minor reactions only. All reactions to OPC occurred after the full dose of antibiotics, and there were no reactions to one tenth of the dose.

Results for the extended oral course

A total of 132 children with a negative OPC were discharged home on a 5-day course with the culprit antibiotic. Six children reacted during the extended course, and all were from Group 2 (successful completion of ST and OPC prior to being discharged home on the 5-day extended course).

Analysis of patient data according to risk

In addition to our above analysis, we retrospectively allocated children as described above into the low and higher risk categories in terms of their expected risk of reaction during assessment. Low risk was assigned to 130 patients, with 46 assigned high risk status; the allocation of these categories was substantially different from the historical assignment of children to Group 1 (direct OPC) or Group 2 (prior ST) assessment pathways by the treating immunologist.

There was a significant difference observed between the children in the low and higher risk categories with regard to the assessment pathway, with 49.2% ($n = 64$) of low-risk patients undergoing direct OPC, whereas only 9 of 46 high risk patients (19.6%)s underwent direct OPC ($P = 0.0004$).

Of the 66 (50.8%) low-risk patients who underwent ST, all had SPT, and 56 children had IDT; 3 patients (4.5%) reacted to SPT, and 7 patients (12.5%) reacted to IDT. Considering both Group 1 and Group 2, 5 of 121 low-risk patients reacted immediately at challenge (4.1%), with a further 4 of the 102 patients reacting during the prescribed extended course (3.9%).

Of the nine high-risk patients who proceeded directly to challenge only (Group 1), one reacted at OPC (11.1%), and none reacted during the 5-day extended course. Of the 37 high-risk patients assigned to Group 2, none reacted to SPT, 4 (10.8%) reacted to IDT, 2 reacted at challenge, and 2 of 30 who were prescribed the extended course reacted during the 5 days.

Of the low-risk patients, 4 of 102 who were prescribed the extended course reacted. Two of the high-risk patients reacted during the 5-day extended course, and one reported a cough on day 6 (1 day after completion of the extended course). This self-resolved promptly at home, without necessitating anaphylaxis treatment or medical attendance. It is unclear if these respiratory symptoms were related to the completed antibiotic course.

If we consider only Group 1 (direct OPC), there were 64 low-risk patients and 9 high-risk patients. Of the 3 patients from

Table 1 Summary of demographic data and background history (where known)

	Group 1: OPC only	Group 2: Skin testing and OPC	Statistical analysis
<i>n</i>	73	103	—
Gender (male), <i>n</i> (%)	41 (56.2)	55 (53.4)	NS
Age at reaction, years, median (min–max)	2 (0.5–13)	5 (0.3–14)	$P < 0.0001^*$ $U = 1810.5$
Age at challenge, years, median (min–max)	6 (1–16)	9 (1–16)	$P < 0.0001^*$ $U = 2345$
Number with previous reactions where known, <i>n</i> (%)	69 (94.5)	99 (96.1)	—
Previous self-reported mild reaction, <i>n</i> (%)	3 (4.3)	3 (3)	NS
Previous self-reported moderate reaction, <i>n</i> (%)‡	61 (88.4)	74 (77.1)	$P = 0.03^*$
Previous self-reported severe reaction, <i>n</i> (%)§	5 (7.2)	22 (22.2)	$P = 0.01^*$
Number with known rash types, <i>n</i> (%)	61 (83.6)	74 (71.8)	—
Urticarial rash, <i>n</i> (%)	29 (47.5)	32 (43.2)	NS
Urticarial + angioedema, <i>n</i> (%)	2 (3.3)	12 (16.2)	$P = 0.02^*$
Macular papular, <i>n</i> (%)	14 (22.9)	6 (8.1)	$P = 0.027^*$
Angioedema, <i>n</i> (%)	2 (3.3)	3 (4.1)	NS
Unspecified, <i>n</i> (%)	14 (22.9)	21 (28.4)	NS

*Statistically significant results where $P < 0.05$. †Mild reactions included reported non-specific symptoms or not further defined symptoms such as mild gastroenteritis, for example, nausea. ‡Rashes were classified as moderate reactions. Rash types were further detailed as given in the table above. §Severe reactions (anaphylaxis) included life-threatening allergic reactions with respiratory or cardiovascular compromise. Patients with a history of severe cutaneous adverse reactions or serum sickness were excluded from the study. NS, not significant; OPC, oral provocation challenge.

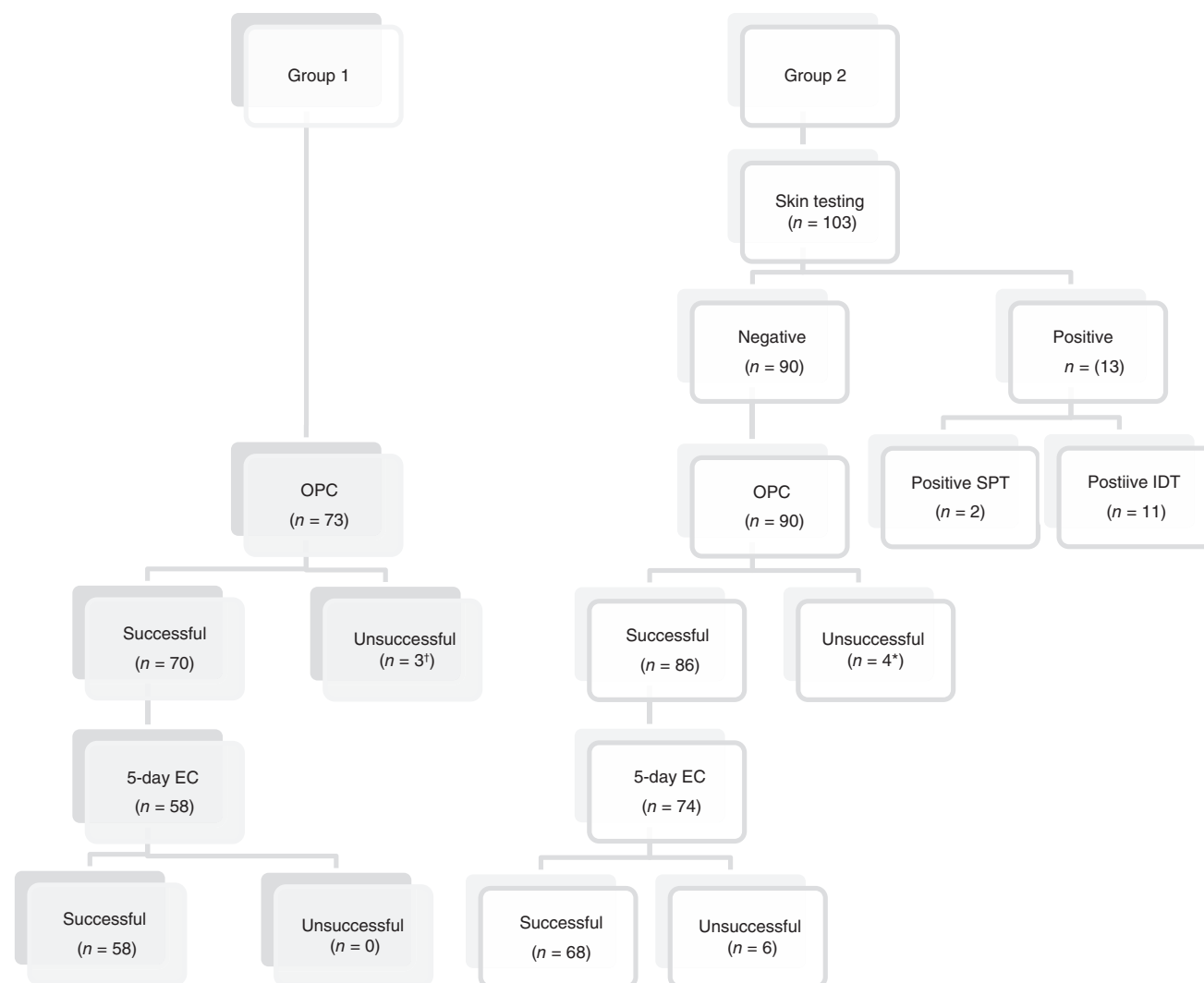


Fig. 1 Progression of children through individual assessment and subsequent EC of the culprit antibiotic for 5 days. Children who were unsuccessful at any stage were deemed allergic and did not undergo further testing. †Anaphylaxis reactions: Group 1 – One anaphylaxis at OPC; Group 2 – Two patients experienced anaphylaxis at OPC and one after completion of 5 of 7 extended course. EC, extended course; IDT, intradermal testing; OPC, oral provocation challenge; SPT, skin prick testing.

73 challenged in Group 1 who were unsuccessful, 2 were low risk, and 1 was high risk. No patient from Group 1, whether assigned low- or high-risk status, reacted during the extended 5-day course.

Group 2 patients ($n = 103$), of whom 66 were low risk and 37 were high risk, proceeded to OPC if ST was negative. Within this group, 6% of low-risk patients ($n = 9$) and 10.8% of high-risk patients ($n = 4$) were unsuccessful at ST. Subsequently, there were four patients who reacted immediately at OPC; three were low-risk patients (5.3% of low-risk patients in Group 2 who underwent OPC), and one was high risk (3.03% of high-risk patients in Group 2 who underwent OPC). There were six patients in Group 2 who reacted during the 5-day extended course, of whom four were low-risk patients and two high-risk patients.

Discussion

There has been a dramatic rise of allergies world-wide. Data regarding antibiotic allergy labelling in children is sparse. We performed the first Australian study in children to evaluate the role of ST, oral provocation and extended antibiotic courses in the confirmation of parent-reported beta-lactam antibiotic allergies.

The patients included in our retrospective review were found to be assessed by one of two pathways: either direct OPC (Group 1) or ST followed by OPC when ST was successfully completed (Group 2). We observed a statistically significant difference between the groups, with 49.2% of low-risk patients undergoing direct OPC, whereas only 9 of 46 high-risk patients (19.6%)s undergoing direct OPC ($P = 0.0004$). It is also to be expected that clinicians would tend to perform ST in children with a history

suggestive of an IgE-mediated reaction (e.g. urticarial rashes with angioedema and anaphylaxis).

ST was more likely to be omitted in children who were younger. It is not surprising that clinicians may favour omitting painful ST in younger children.

In our cohort, 26 of 176 children reacted to either ST, OPC or a 5-day extended course of antibiotic. This equates to a total of 15% of children being confirmed as antibiotic allergic. The rate of a positive reaction in Group 2 (ST and/or OPC) was higher, with 12.6% reacting to ST alone and a total of 19.4% of children found to be allergic. In Group 1, which had not undergone ST, 4.1% children were antibiotic allergic. The reaction rate to OPC of children in Group 1 is similar to data from Mill *et al.*⁷ These authors reported that 94.1% of children with amoxicillin allergy tolerated direct OPC. This is also comparable to the 3.4% of children who reacted with rash during the challenge in a study by Vezir *et al.*²

Considering direct challenge assessment, only 3.1% of low-risk children ($n = 2$) and 11.1% of high-risk children were allergic. When children were assessed by ST prior to OPC, the rate of positive reactions was higher for both the low- and high-risk groups: 24% of low-risk children and 18.9% of high-risk children. This raises the question of whether ST may lead to an overestimate of true allergy.

The use of an extended course during assessment of the antibiotic challenge in our cohort verified the antibiotic allergy status of an additional six children who had successfully completed ST and OPC.

A recent review⁸ by the European Academy of Allergy and Clinical Immunology Drug Allergy Interest Group considered the duration of an extended course as part of the provocation challenge. It was concluded that, while the risk of future reactions can be further reduced by an extended course, exposure to a full single therapeutic dose is sufficient for most cases (based on very limited evidence). Of note, a study on paediatric beta-lactam allergies with an extended course of 5 days reported only 1 child from 119 who reacted during the extended course, on day 4.² Another study⁴ of 88 children with possible beta-lactam allergy included a 48-h extended course and detected five delayed reactions to OPC/extended course. These had a range of 7–12 h after the dose was administered. It is not clear if these reactions occurred during the extended course or initial OPC. The latter study involved patch testing after a 48-h extended course to detect non-immediate reactions, which were negative in all patients including the six patients with positive OPC. The largest study³ challenged 818 children with 31 developing non-immediate reactions, all of which were mild. The median time to non-immediate reaction was 12 h, and 9 of the 31 children reacted more than 24 h after OPC.

Our data suggest that extended courses of at least 5 days with the culprit drug should be considered as the six children who reacted in our study developed symptoms from days 2–6. It is

unclear if the respiratory symptoms of the child reacting on day 6 were related to the completed antibiotic course. Given the retrospective nature of our study, we did not have a comparator group that was not given extended antibiotic courses to see if these reactions would have occurred anyway. However, based on published data so far, no studies have reported delayed rashes (after 48 h) after a once-off challenge in children.

Conclusions

This retrospective study allowed us to observe the role of ST in children with a history of a more severe reaction, even including cases of anaphylaxis. Our review showed that ST was not helpful in the assessment of antibiotic allergy even in children with a history of suspected anaphylaxis in the distant past. Our data also demonstrate that a prior history of anaphylaxis does not necessarily predict IgE-mediated allergy with a positive result to ST or an immediate reaction to the oral challenge. Thus, such history should not detract from efforts to assess these children for antibiotic allergy.

Limitations of our study include that is a retrospective review, and consequently, the allocation of patients to either group was not randomised. Future studies to challenge all patients regardless of ST result would further clarify the role of ST in the assessment of antibiotic allergy in children.

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