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# Long-term impacts of antibiotic allergy testing on patient perceptions and antibiotic utilization

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**Objectives:** To define the long-term impacts of antibiotic allergy testing (AAT) on patient allergy perception and antibiotic utilization.

**Methods:** Patients were identified from a prospective AAT database as having completed testing during a 15 month period beginning January 2017. Patients were contacted for a follow-up survey at least 12 months post-AAT. For those contacted, baseline demographics, antibiotic allergy label (AAL) history, age-adjusted Charlson comorbidity index, infection history, antibiotic de-labelling ($\geq$1 AAL removed following AAT) and antibiotic usage for 12 months prior to testing (pre-AAT) and 12 months following testing (post-AAT) were recorded for each patient.

**Results:** From the follow-up survey of 112 patients post-AAT, 95.2% (59/62) of patients with complete AAL removal expressed willingness to use 'de-labelled' antibiotics and 91.9% (57/62) were adherent to allergy label modification. Comparing antibiotic utilization 12 months pre-AAT versus 12 months post-AAT, AAT was associated with a significant increase in preferred antibiotic therapy [adjusted odds ratio (aOR) 3.29, 95% CI 1.56–6.92] and reduction in restricted antibiotic utilization (aOR 0.42, 95% CI 0.19–0.93).

**Conclusions:** An antimicrobial stewardship (AMS)-led AAT programme was safe and effective in the long term in the promotion of preferred and narrow-spectrum antibiotic usage, and favourable patient perception towards the AAT testing results was identified. This study further supports the routine incorporation of AAT into AMS programmes, confirming safety and durability of testing impacts on patients as well as increasing preferred antibiotic utilization.

## Introduction

The prevalence of patient-reported antibiotic allergies [so-called antibiotic allergy labels (AALs)] is reported in up to 24% of hospitalized inpatients receiving antibiotic therapy.[1] The short-term impacts of antibiotic allergy testing (AAT) are evident, including drug-cost savings and improved antibiotic appropriateness.[2–4] However, the available literature infrequently extends beyond the inpatient or acute post-discharge period.[5,6] Furthermore, there have been infrequent examinations of patient acceptance and recollection of their allergy label modifications (ALMs) and willingness to use 'de-labelled' antibiotics post-AAT. We evaluated the patient perception towards their AAL status post-AAT and willingness to utilize de-labelled antibiotics. Further, we examined the long-term impacts of AAT on inpatient antibiotic utilization.

## Patients and methods

A follow-up phone survey was undertaken of patients that underwent AAT as part of an antimicrobial stewardship (AMS)-led service at Austin Health (Melbourne, Australia) from 1 January 2017 to 1 March 2018. Participants were identified from the prospective AAT database, which contains patient baseline demographics, episodes of infections, immunosuppression, mental health history, AAT results and AAL(s) data. Patients had undergone skin prick/intradermal testing (SPT/IDT), patch testing and/or oral provocation (OP) as per previously published protocols.[2,7] Post-AAT, patients, treating

specialist clinicians and general practitioners are provided with a letter outlining the (i) AAT results; (ii) revised AAL; and (iii) recommendations for future antibiotic usage. The patient's revised AAL is also updated in the Austin Health electronic medical record (EMR).

All surveyed participants that underwent AAT during the study period had their survey results paired with clinical and antibiotic prescribing data extracted from the prospective patient database and EMR. Inpatient infective episode data and antibiotic prescriptions for the period 12 months prior to (pre-AAT) and 12 months post (post-AAT) testing were included.

A phone survey was undertaken as described in the Supplementary data (available at *JAC-AMR* Online). In brief, the structured survey asked for the participants' (i) reporting of their currently perceived allergy 'labels'; (ii) antibiotic utilization post-AAT; and (iii) willingness to use 'de-labelled' antibiotics. An antibiotic course (excluding prophylactic antibiotics) was defined as one or more doses of included antibiotics used in any inpatient admissions. Topical antibiotics and non-surgical prophylactic antibiotics were excluded. A narrow-spectrum penicillin was defined as amoxicillin, ampicillin, benzylpenicillin, dicloxacillin, flucloxacillin, phenoxymethylpenicillin, penicillin G or penicillin VK. Restricted antibiotics were defined as carbapenems, lincosamides, lipopeptide, fluoroquinolones, glycopeptides, piperacillin/tazobactam, oxazolidinone and third- or fourth-generation cephalosporins. Preferred antibiotic treatment for an infection episode was defined as first-line therapy recommended by Australian Therapeutic Guidelines: Antibiotic (Edition 15).[8] If there were no appropriate recommendations in the guidelines, a local guideline was utilized as a substitute. A patient was deemed to have avoided a preferred antibiotic if an alternative antibiotic was administered, irrespective of the patient's AAL (e.g. use of cefepime for febrile neutropenia in place of piperacillin/tazobactam).

### Statistics

Fisher's exact test was utilized for categorical variables and the Wilcoxon rank sum test for comparison of median values. We used a mixed-effects logistic regression model to quantify the association between study period pre- or post-AAT and use of restricted antibiotics, narrow-spectrum penicillins, narrow-spectrum β-lactams and preferred antibiotics, with separate models for each of these four outcomes. In each case we report an unadjusted model (with time period as the only predictor) and an adjusted model [accounting for *a priori* variables; age-adjusted Charlson comorbidity index (CCI), mental illness history, immunocompromised status and each inpatient length of stay]. As these analyses were performed at the level of each antibiotic prescription, we included patients as random effects to account for the fact that some patients had multiple antibiotic prescriptions. Regression analyses were performed with R, version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria), using the lme4 package.

### Ethics

This project was approved by the Austin Health Research Ethics Committee (CD17005) on 23 July 2018.

## Results

A total of 158 patients were identified in the 15 month period from January 2017 to March 2018. A follow-up survey was conducted from March 2019 to April 2019 with 112 of 158 patients successfully contacted. There were 8.2% (13/158) of patients who refused to participate in the study. The remaining 20.9% (33/158) of patients who were lost to follow-up had either incorrect contact information in the EMR or were not contactable after three attempts conducted across three different days at different times. Of these 20.9% (33/158) patients, 84.8% (28/33) did not have a follow-up admission with an antibiotic encounter and 6.1% (2/33) were deceased. Baseline demographics and characteristics of the 112 participants forming the study cohort are demonstrated in Table 1.

From the 112 participants, 178 AALs were identified pre-AAT (Figure S1), with a median AAL of 1.59 per patient (range 1–6). Of these participants, 67.0% (75/112) had one AAL, 17.0% (19/112) had two AALs and 16.1% (18/112) had three or more AALs. Patients post-AAT had 79 AALs listed in the EMR, with a median AAL of 0.71 per patient (range 1–4).

Of the 112 participants, 99.1% (111/112) underwent AAT: 90.2% (101/112) underwent SPT/IDT with 90.1% (91/101) undergoing OP post-SPT/IDT; 8.9% (10/112) of patients underwent direct OP. At least one AAL was removed in 83.9% (94/112) of the patients post-AAT, with complete removal of all reported AALs seen in 55.4% (62/112) of the cohort.

From the 112 participants there was a total of 163 inpatient antibiotic courses identified in the combined 12 month pre-AAT and 12 month post-AAT periods. There was no statistically significant difference in antibiotic indication or participant characteristics (sex, median age, immunocompromised status and age-adjusted CCI) in those utilizing antibiotics in the pre- and post-AAT periods ($P > 0.05$; Table 1). There was an increase in prescribing of guideline-preferred antibiotic therapies 12 months post-AAT compared with 12 months pre-AAT [56.4% (44/78) versus 34.1% (29/85), $P = 0.0048$]. A similar effect was seen with regard to narrow-spectrum penicillin utilization in the 12 months post-AAT versus 12 months pre-AAT period [23.1% (18/78) versus 8.2% (7/85), $P = 0.0096$]. Furthermore, a significant reduction in the use of restricted antibiotics was observed in the 12 months post-AAT period [17.9% (14/78) versus 32.9% (28/85), $P = 0.0325$]. Using the previously described linear regression model we examined antibiotic utilization regarding (i) restricted antibiotic; (ii) preferred antibiotic therapy; (iii) narrow-spectrum penicillins; and (iii) narrow-spectrum β-lactams. There was a significantly reduced odds of receiving a restricted antibiotic [adjusted odds ratio (aOR) 0.42, 95% CI 0.19–0.93] and increase in preferred antibiotic utilization (aOR 3.29, 95% CI 1.56–6.92; Table 2).

From the follow-up phone survey 73.2% (82/112) of participants were willing to use a previously labelled allergic antibiotic (Table 3). This was particularly evident in patients who had at least one AAL removed ($n = 94$) and those with complete AAL removal ($n = 62$), in 85.1% (80/94) and 95.2% (59/62), respectively. In those patients who were not willing to utilize the de-labelled antibiotic, 53.3% (16/30) were patients who were not 'de-labelled' post-AAT.

We compared patient-reported AALs at phone follow-up with the written revised AAL record provided to patients and providers post-AAT. Patient adherence with their revised recorded AAL post-AAT (ALM) was seen in 78.6% (88/112) of all patients, and 91.9% (57/62) in patients with complete AAL removal. The median age of patients who were not adherent to their ALM was 66 years (IQR 48.75–73), with no significant differences between sexes, histories of mental illness or immunocompromised statuses in those that were adherent to ALM and those that were not ($P > 0.05$).

Utilizing participant survey responses regarding antibiotic utilization (Table 3) and inpatient EMR prescribing data from the 112 patients, 68.8% (77/112) reported utilizing any antibiotic post-AAT. Of the 77 patients who utilized antibiotics post-AAT, 31.2% (24/77) took a previously labelled antibiotic. Amongst the patients who used any antibiotics post-AAT, 5.2% (4/77) reported an antibiotic-associated adverse drug reaction (ADR): two cases of urticaria,

one case of delayed rash and one case of isolated pruritus. Three of these cases were ADR to an unrelated antibiotic while one patient who took a previously labelled allergic antibiotic reported developing urticaria consistent with the pre-AAT index reaction. Of the patients who took a previously labelled allergic antibiotic, 95.8% (23/24) did not experience an ADR. The study identified eight patients who reported no allergies despite having AALs post-AAT; as the median age was 66.5 years in this cohort, clinicians may need to provide additional written and verbal cues to older patients and family members post-AAT to ensure ALM adherence.

**Table 1.** Characteristics of the 112 patients in the AAT cohort who completed telephone follow-up

| Demographic | Value |
|---|---|
| Age, years, median (IQR) | 62.5 (48–72) |
| Sex, female | 68 (60.7) |
| Age-adjusted CCI, median (IQR) | 3 (1–4) |
| Race | |
| white | 104 (92.9) |
| Asian | 8 (7.1) |
| Immunocompromised[a] | 23 (20.5) |
| psychiatric history[b] | 18 (16.0) |
| infective syndromes ($n=163$)[c] | |
| gastrointestinal infection | 29 (17.8) |
| bacteraemia | 11 (6.8) |
| febrile neutropenia | 6 (3.7) |
| urinary system infection | 3 (1.8) |
| lower/upper respiratory tract infection, including pneumonia | 41 (25.2) |
| skin, soft tissue, bone and joint | 38 (23.3) |
| other[d] | 35 (21.5) |
| Total admissions with infective diagnosis | 76 |
| pre[e] | 39 |
| post[f] | 37 |

Results are expressed as *n* (%) unless specified otherwise.
[a]Haematological malignancy, oncological malignancy, solid organ or stem cell transplant recipient, autoimmune disease, condition requiring >15 mg steroid (prednisolone equivalent) daily for 1 month.
[b]History of depression, anxiety or mood disorder.
[c]Infective episodes encountered 12 months pre- and post-AAT.
[d]Includes prophylaxis (17), infected mesh site (6), pyrexia of unknown origin (5), psoas abscess (3), infective endocarditis (2), post-liver transplant sepsis (2).
[e]Admissions by patients up to 12 months prior to AAT.
[f]Admissions by patients up to 12 months following AAT.

## Discussion

This study demonstrates the benefits of AAT that persist up to 12 months following testing, specifically regarding utilization of preferred antibiotic therapies and narrow-spectrum penicillins.[2] Importantly, this study highlights a patient's willingness to use previously labelled antibiotics and adherence with their revised AAL record post-AAT, especially in those with complete de-labelling.

In regard to patient willingness to utilize de-labelled antibiotics, we found that that an overwhelming majority (95.2%) were willing do so if they had a complete AAL removal. Only one patient who received a de-labelled antibiotic reported a mild adverse reaction at follow-up, a low rate consistent with previous studies.[5,9] Our AMS-led AAT programme and post de-labelling approach of verbal and written advice (AAT letter) to treating hospital clinicians and primary caregivers appears to be a successful strategy in ensuring patients take a de-labelled antibiotic, and the majority of 'unwilling' patients in fact had a confirmed hypersensitivity.

Our study demonstrated overall 78.6% of our patients were adherent to their ALM (91.9% in those with complete de-labelling), consistent with that reported previously by Bourke *et al.*[9] (75.3% overall ALM adherence). In patients with complex AALs post-testing where adherence was poorer, their recall of the exact details at phone follow-up may have been improved if asked to refer to their written record. To our knowledge, this is the first study to examine long-term patient acceptance of their revised allergy record in patients with penicillin and non-penicillin allergies with diverse allergy phenotypes. In patients with complex AALs or of an older cohort (>65 years), increased care is required post-AAT to ensure the ALM is understood by the patient.

This study has limitations, in particular its single-centre nature; in addition, patients were lost to follow-up, and there was an absence of outpatient prescribing data, potential selection bias towards patients with a recently encountered infection, and recall bias in those surveyed.

Nonetheless, this study clearly demonstrates significant positive long-term impacts of an AMS-led AAT programme on patient

**Table 2.** Inpatient antibiotic prescribing outcomes for the 12 months pre-AAT versus 12 months post-AAT for the investigated cohort ($n=112$)

| Antibiotic course | Pre-intervention ($n=85$) | Post-intervention ($n=78$) | Univariable model, OR (95% CI) | Multivariable model[a], aOR (95% CI) |
|---|---|---|---|---|
| Restricted | 28 (17.2%) | 14 (8.6%) | 0.45 (0.21–0.93) | 0.42 (0.19–0.93) |
| Narrow-spectrum penicillin | 7 (4.3%) | 18 (11.0%) | 4.05 (1.14–14.9) | 2.93 (0.80–10.7) |
| Preferred | 29 (17.8%) | 44 (27%) | 2.70 (1.26–5.79) | 3.29 (1.56–6.92) |

[a]Mixed effects logistic regression model utilized to quantify the association between the study period and named antibiotic groups, with separate models for each. In each case we report an unadjusted model (with time period as the only predictor) and an adjusted model (accounting for age-adjusted CCI, mental illness history, immunocompromised status and length of stay). As these analyses were performed at the level of each antibiotic prescription, we included patients as random effects to account for the fact that some patients had multiple antibiotic prescriptions.

**Table 3.** Survey responses from the 112 post-AAT patients contacted for phone follow-up

| Parameter | *n* (%) |
|---|---|
| Patients with complete AAL de-labelling | 62 |
| Willingness to have an antibiotic previously labelled as allergic | 59 (95.2) |
| ALM[a] adherence | 57 (91.9) |
| All patients surveyed, irrespective of AAL de-labelling ($n = 112$) | |
| willingness to have an antibiotic previously labelled as allergic | 82 (73.2) |
| Reasons for patients who refused ($n = 30$) | |
| believed they were allergic[b] | 25 (83.3) |
| wanted to be cautious[c] | 5 (16.7) |
| ALM[a] adherence | 88 (78.6) |
| Reporting characteristics of patients who did not adhere to ALM ($n = 24$) | |
| the same AAL pre-AAT | 7 (29.1) |
| part of pre-AAT AAL reported[d] | 9 (37.5) |
| 'self de-labelling'[e] | 8 (33.3) |

[a]ALM was defined as a revision or removal of existing AAL after AAT. Patient adherence to their AAL was determined through comparison of their AAL reported during the phone survey and the AAL recorded in their EMR post-AAT.
[b]Patient responded with a reasoning which was consistent with the belief that they were allergic to the antibiotic still.
[c]Patient responded with a reasoning that had a cautious approach to taking de-labelled antibiotics.
[d]These individuals reported being allergic to some parts of their pre-AAT AAL despite having a revision post-AAT.
[e]These patients reported having no allergy despite having AAL post-AAT, effectively 'self de-labelling'.

AAL perception, safety of utilizing de-labelled antibiotics and preferred antibiotic utilization. Future work must focus on integration of similar AAT programmes into other health services and enhanced processes that sustain patient and clinician acceptance of AAL revision and encourage utilization of de-labelled antibiotics post-AAT.

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## Transparency declarations

None to declare.

## Supplementary data

Figure S1, the telephone interview script and the Reviewer reports are available as Supplementary data at *JAC-AMR* Online.

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