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Title: The impact of antibiotic allergy testing in transplant patients

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To the Editor,

Patient reported antibiotic allergies, so-called antibiotic allergy labels (AAL) are highly prevalent amongst hospitalized patients globally¹. The highest prevalence of AALs has been found to be in immunocompromised patients, in particular transplant patients, with a large U.S. study reporting a prevalence of 29% amongst solid organ and stem cell transplant recipients². Whilst studies have demonstrated that AALs in transplant patients are associated with the use of broad-spectrum antibiotics², the impact of antibiotic allergy testing (AAT) on antibiotic use in this patient cohort remains ill defined.

Transplant patients, including solid organ and haematopoietic stem cell transplant patients, who were first reviewed at Austin Health between the period of April 2015 and February 2020 were identified from a prospective AAT database – including baseline demographics, immunosuppression, AAT results and AAL(s) data. Patients had undergone skin prick testing (SPT)/intradermal testing (IDT), patch testing (PT), direct oral challenge or oral challenge post skin testing, as per previously published protocols^{3,4}. Additional data relating to inpatient and outpatient antibiotic prescribing and infective episodes, for the periods 12 months pre-AAT and 12 months post-AAT, was collected from electronic medical record (EMR) and analyzed as per methods provided in **Supplementary materials**.

A total of 66 transplant patients were identified as having undergone AAT in the period between April 2015 and February 2020, details in **Supplementary Table S1**. 84.8% (56/66) of patients were immunosuppressed at the time of testing and the types of immunosuppression are showed in **Supplementary Figure S1**. 60.6% (40/66) of patients were post-transplant at the time of testing.

Amongst the 66 patients, there were 111 individual AALs identified prior to their AAT, with 62.1% (41/66) of patients having one AAL. The type of AALs are illustrated in **Supplementary Figure S2**. The classification and description of all AALs are illustrated in **Supplementary Figure S3**. 64 AALs (55.9%) were removed in total, as per the antibiotic classes demonstrated in **Supplementary Figure S4** (details regarding the remaining 47 AALs are discussed in eResults). 62% of all beta-lactam AALs and 75% of all penicillin AALs were removed post-AAT. 86.4% (57/66) of patients had at least one AAL removed whilst 6 patients (9.1%) reported a positive test without any systemic adverse events.

There was a total of 443 inpatient antibiotic courses identified in the period 12 months pre-AAT until 12 months post-AAT, amongst 50 patients. We noted a significant increase in narrow spectrum penicillin use in the 12 months post-AAT compared to 12 months pre-AAT [adjusted odds ratio 5.07 (1.22-21.13)] (**Table 1**). 84.6% (11/13) of the narrow spectrum penicillins prescribed post-AAT were in patients with a prior penicillin AAL which was subsequently delabelled. When evaluating both inpatient and outpatient antibiotic prescribing, we found similar patterns of prescribing post-AAT to that for inpatient use only (**Table 1**).

When analyzing health service outcomes, we found a reduction in hospital length of stay 12 months post-AAT compared to 12 months pre-AAT (12.23 days vs 10.90 days, $p=0.61$).

Despite the limitations of a single centre retrospective analysis, we have demonstrated for the first time, the safety and efficacy of AAT in solid organ and haematopoietic stem cell transplant recipients, using previously published testing criteria^{3,4}. We demonstrated, using an adjusted model, that AAT led to significantly increased utilisation of narrow spectrum penicillins and beta-lactam/beta-lactamase inhibitor combination antibiotics 12 months post-AAT compared to 12 months pre-AAT, without reported adverse effects when using previously labelled antibiotics (e.g. penicillin). These findings highlight the role of AAT in improving antibiotic usage in

this patient cohort, including patients with allergy phenotypes of all severities and underlying immunosuppression. Thus, widespread access to AAT in the pre-transplantation period could optimize the antibiotic therapy of infective complications throughout their transplant care.

Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *Transplant Infectious Diseases*.

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Author contributions

JT contributed to the study design. AY and SV participated in the analysis of the results. JT and AY contributed to the writing of the manuscript. KC, MR and SV were involved in reviewing the manuscript. All authors have read and approved the manuscript.

Table 1. Inpatient and outpatient prescribing outcomes for the 12 months pre-AAT versus 12 months post-AAT

Inpatient antibiotic prescribing				
Antibiotic classification	12 months pre-AAT n (%)	12 months post-AAT n (%)	Crude OR [†] (95% CI)	Adjusted OR [‡] (95% CI)
	N = 236	N = 207		
Narrow spectrum penicillin [§]	3 (1.3%)	13 (6.3%)	4.78 (1.22, 18.71) p=0.025	5.07 (1.22, 21.13) p=0.026
Narrow spectrum beta-lactam [§]	12 (5.1%)	17 (8.2%)	1.67 (0.62, 4.52) p=0.497	1.78 (0.68, 4.67) p=0.538
Beta-lactam/beta-lactamase inhibitor combination	18 (7.6%)	35 (16.9%)	2.38 (0.82, 6.94) p=0.112	2.71 (0.92, 7.98) p=0.070
Restricted antibiotic	103 (43.6%)	72 (34.8%)	0.69 (0.38, 1.25) p=0.221	0.72 (0.38, 1.33) p=0.291
Inpatient and outpatient antibiotic prescribing				
	N = 269	N = 254		
Narrow spectrum penicillin	4 (1.5%)	15 (5.9%)	4.16 (1.01, 17.11) p=0.048	4.71 (1.06, 20.96) p=0.042
Narrow spectrum beta lactam [§]	18 (6.7%)	22 (8.7%)	1.32 (0.51, 3.40) p=0.562	1.36 (0.55, 3.39) p=0.508
Beta-lactam/beta-lactamase inhibitor combination	22 (8.2%)	49 (19.3%)	2.68 (0.95, 7.56) p=0.062	2.98 (1.04, 8.50) p=0.042
Restricted antibiotic	117 (43.5%)	86 (33.9%)	0.67 (0.37, 1.19)	0.68 (0.37, 1.22)

			p=0.169	p=0.194
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[†]From univariable logistic regression models (with time period as the only predictor).

[‡]From multivariable logistic regression models, controlled for sex and age-adjusted Charlson comorbidity index and indication.

[§]Due to small sample size, adjusted only for sex and age-adjusted CCI

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