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29 Dear editor,

30 Patient-reported antibiotic allergies (so-called antibiotic allergy labels [AALs]) are associated with
31 suboptimal prescribing and inferior clinical outcomes, especially in the immunocompromised(1, 2).
32 The prevalence, type and impact of AALs in liver transplant recipients (LTRs) remains ill defined. We
33 report on AALs and their impact on a cohort of Australian LTRs.

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35 A retrospective matched cohort study was conducted over a 5-year period (2010-2015) at an
36 Australian liver transplant centre (Austin Health). Using a departmental liver transplant database,
37 LTRs with an AAL were identified (AAL). An equal number of matched controls (LTR without an
38 antibiotic allergy label; non-AAL) were randomly selected for comparison. AALs were evaluated and
39 classified as Type-A adverse drug reactions ([ADRs], non-immune mediated), Type-B ADRs (immune-
40 mediated) or unknown(3). Baseline demographics, transplant history and infection-related
41 admission data was collected. From time of transplant until 12-months post, antibiotics
42 administered during infection-related admissions were recorded: agent(s) and duration. Re-
43 admission, ICU-admission, *Clostridium difficile* infection (CDI), multi-drug resistant (MDR) organism
44 isolated and mortality rate were captured. An MDR organism defined as bacterium resistant to at
45 least one agent in three or more antibiotic classes(4).

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47 From 313 LTRs, 51 (16%) had ≥ 1 AALs. Females predominated in the AAL group (75% vs. 25%,
48 $p=0.003$) and there was no statistically significant difference in the rates of ICU admission and
49 mortality (**Supplementary Table 1**). Seventy-seven AALs were recorded: 23%(18/77) Type-A ADR,
50 66% Type-B ADR (51/77) and 10% (8/77) unknown. Of the Type-A ADRs, 72% (13/18) were
51 gastrointestinal upset and of Type-B 6% (3/51) were severe cutaneous adverse drug reactions
52 (SCAR), 55% (28/51) maculopapular exanthema (MPE), 35% (18/51)

53 anaphylaxis/urticaria/angioedema and 4% (2/51) other. The antibiotics implicated in AALs are
54 demonstrated in **Figure 1**.

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56 AAL patients were associated with higher cephalosporin (107/354 [30%] vs. 75/328 [23%], $p=0.03$),
57 nitroimidazole (34/354 [10%] vs. 15/328 [5%], $p=0.02$) and glycopeptide courses (78/354 [22%] vs.
58 76/328 [23%], $p=0.08$). When comparing the AAL and non-AAL groups there was a non-significant
59 reduction in penicillin V/G or aminopenicillin (26/354 [7%] vs. 36/328 [11%], $p=0.14$) and beta-
60 lactam/beta-lactamase inhibitor courses (43/354 [12%] vs. 49/328 [15%], $p=0.31$). There was also an
61 increasing trend in the number of MDR gram-negatives isolated (4/50 [8%] vs. 1/51 [2%] $p=0.20$)
62 and CDI (9 [18%] vs. 3[6%], $p=0.07$).

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64 Sixteen (31%) LTR in the AAL group had a trimethoprim-sulfamethoxazole (TMP-SMX) ADR history
65 noted, with the majority (11, 68%) classified as Type-B ADRs (7[43%] delayed, 4[25%] immediate),
66 and the remaining 2(13%) as Type-A ADRs and 3(19%) as unknown. In regards to *Pneumocystis*
67 *jiroveci* pneumonia (PJP) prophylaxis, aerosolised pentamidine (AP) was employed in 56%(9/16) of
68 these patients with a TMP-SMX ADR history immediately post-transplant. Only one patient received
69 dapsone, without ADR. 63% (10/16) of TMP-SMX ADR patients were toxoplasmosis IgG-positive, of
70 which 80% (8/10) received no directed toxoplasmosis prophylaxis. In relation to treatment doses,
71 there was a reduction in TMP-SMX usage as a proportion of total antibiotic courses in the AAL group
72 (0/354 vs. 9/328[3%], $p=0.001$).

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75 Although the conclusions are limited by the small cohort size, a high AAL prevalence in LTRs was
76 identified, predominately towards sulphonamides and beta-lactams. Significantly, a large proportion
77 of AALs were Type-A (23%), amendable to immediate 'de-labeling'. In LTRs with sulphonamide
78 allergy, TMP-SMX or dapsone may also have been unnecessarily avoided considering antibiotic
79 sulphonamide cross-reactivity is lower than previously thought(5), and TMP-SMX desensitisation or
80 rechallenge is often effective(6, 7).

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82 Comparable to non-transplant patients, where AALs was found to be associated with increased
83 microbiological resistance and CDI(8), a similar trend was also noted in our cohort. In light of recent
84 increasing cephalosporin resistance(9) and CDI in LTRs(10), and our data demonstrating both,
85 aggressive antibiotic allergy testing (AAT) and 'de-labeling' should be evaluated(11). Cephalosporin
86 and other broad spectrum antibiotic usage is often a common target for antimicrobial stewardship
87 programs (ASPs); the addition of AAT in high-risk antibiotic usage populations, such as transplant
88 recipients, is likely to support ASPs by enhancing use of first-line narrow spectrum agents(12). The
89 largest benefit of AAT is likely to be pre-transplantation, to effectively reduce AAL prevalence, and
90 improve antibiotic prescribing in this vulnerable cohort.

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94 **References**

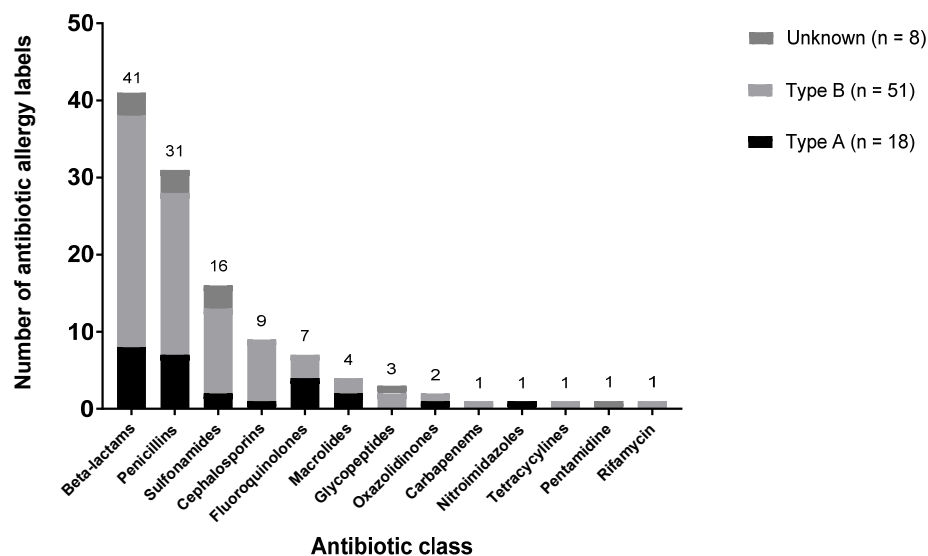
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Figure 1: Antibiotic allergy labels per antibiotic class (n = 77)



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