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# The Impact of Reported β-Lactam Allergy on Clinical Outcomes and Antibiotic Use Among Solid Organ Transplant Recipients

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**Background.** Reported β-lactam allergies (BLAs) are common and frequently inaccurate, but there are limited data on the clinical implications of BLA among solid organ transplant (SOT) recipients. We examined the impact of BLA on clinical outcomes and antibiotic use among SOT recipients.

**Methods.** This retrospective cohort study included adult patients undergoing single-organ heart, kidney, liver, lung, or pancreas transplant at a United States academic medical center from 1 April 2017 to 31 December 2020. Demographic and clinical data were collected from the electronic health record. Multivariate median regression was performed to evaluate the association between BLA and days alive and out of the hospital in the first 180 days posttransplant (DAOH180). Multivariate logistic regression was performed to evaluate the association between BLA and antibiotic use.

**Results.** Among 1700 SOT recipients, 285 (16.8%) had a BLA at the time of transplant. BLA was not associated with DAOH180 (adjusted median difference, −0.8 days [95% confidence interval {CI}, −2.7 to 1.2]; $P = .43$). Patients with BLA were more likely to receive intravenous vancomycin (adjusted odds ratio [aOR], 1.8 [95% CI, 1.3–2.6]; $P < .001$), clindamycin (aOR, 9.9 [95% CI, 5.1–18.9]; $P < .001$), aztreonam (aOR, 19.6 [95% CI, 5.9–64.4]; $P < .001$), fluoroquinolones (aOR, 3.8 [95% CI, 2.8–5.0]; $P < .001$), or aminoglycosides (aOR, 3.9 [95% CI, 2.5–6.2]; $P < .001$).

**Conclusions.** BLA was associated with use of β-lactam alternative antibiotics but not DAOH180 among SOT recipients.

**Keywords.** antibiotic allergies; β-lactam allergies; solid organ transplant.

Self-reported allergies to β-lactam antibiotics are common, with approximately 8% of healthcare-seeking individuals in the general United States (US) population reporting a penicillin allergy and 1% reporting a cephalosporin allergy [1]. Among hospitalized patients, the prevalence of reported β-lactam allergy (BLA) has been reported to be as high as 19% [2–4]. However, the vast majority of these reported allergies are inaccurate, either due to misdiagnosis or resolution of the allergy with time; in fact, >90% of patients with a reported penicillin allergy are not truly allergic when tested and rechallenged [5, 6]. There is a growing body of evidence regarding the negative impact of

reported BLA, including greater risk of receiving non-first-line antibiotics, inferior clinical outcomes, infections due to multidrug-resistant organisms (MDROs) or *Clostridioides difficile*, longer hospital stays, and higher healthcare-related costs [2, 4, 7].

The impact of BLA among immunocompromised hosts, however, remains poorly characterized despite a high prevalence of BLA in this population, which ranges from 16% to 21.5% in various cohorts [8–11]. In particular, as organ transplantation becomes increasingly common in the US and worldwide, solid organ transplant (SOT) recipients represent an emerging cohort of patients at particularly high risk of developing serious bacterial infections due to surgical complications, indwelling lines and devices, receipt of immunosuppressive medications, and comorbid medical conditions [12, 13]. MDRO infections and *C difficile* infection are frequent complications of organ transplantation, reflecting frequent healthcare exposure and high rates of antibiotic use [14, 15]. These risks underscore the importance of offering first-line antibiotics when infectious complications arise, not only to optimize treatment effectiveness but also to minimize the risk of subsequent antibiotic-resistant colonization or infection, antibiotic-related adverse events, and toxicity. Despite the theoretical potential

for BLA to limit options for antibiotic therapy among SOT recipients, the few existing studies that have examined antibiotic allergy labels in this population have been limited by small sample sizes, broad cohorts that include non-SOT recipients, or short follow-up durations [9, 16]. Moreover, the impact of reported BLA on clinical outcomes specifically among SOT recipients still remains largely uncharacterized.

In this study, we evaluated the association between reported BLA and posttransplant clinical outcomes and antibiotic use among SOT recipients at a US academic transplant center.

## METHODS

### Study Setting and Population
This retrospective cohort study was conducted at the University of Pennsylvania Health System (UPHS) in Philadelphia, Pennsylvania. Patients ≥18 years of age who underwent single-organ heart, kidney, liver, lung, or pancreas transplant between 1 April 2017 and 31 December 2020 and survived until at least postoperative day (POD) 1 were included. Among patients who underwent >1 transplant within the study period, only the first transplant episode was included. Institutional guidelines for transplant surgery perioperative antibiotic prophylaxis are summarized in Supplementary Table 1.

### Exposure
The primary study exposure was the presence of an allergy or intolerance label to ≥1 non-monobactam β-lactam antibiotic (ie, penicillins and penicillin derivatives, cephalosporins, cephamycins, and/or carbapenems) in the electronic health record on the day of index transplant surgery. BLA labels were manually verified by an infectious diseases–trained physician (H. L. Z.). Due to inconsistent documentation of the nature and/or severity of reported reactions in the medical record, patients with any documented reaction to a β-lactam antibiotic were included in the exposed group.

### Primary Outcome
The primary outcome was days alive and out of the hospital in the first 180 days posttransplant (DAOH180), defined as the number of days from POD1 through POD180 during which the patient was neither hospitalized in a UPHS hospital nor deceased. Only UPHS hospitalizations were considered because since SOT recipients are rarely hospitalized outside of their transplant center in the early posttransplant period, and in the rare circumstances in which they are hospitalized outside of their transplant center, they are routinely transferred to the transplant center for their care.

### Secondary Outcomes
Length of index hospitalization was evaluated from day of transplant surgery until hospital discharge, and rehospitalization was evaluated from POD1 through POD180.

Antibiotic use from POD1 through POD180 was analyzed in several ways:

1. Cumulative inpatient antibiotic days of therapy (DOT), defined as the aggregate sum of calendar days during which any dose of a specific systemic antibacterial antibiotic was administered to a patient. This measure excluded agents used for *Pneumocystis jirovecii* prophylaxis (trimethoprim-sulfamethoxazole, atovaquone, dapsone), azithromycin among lung transplant recipients due to routine prophylactic use, antimycobacterial agents due to typically prolonged courses, and oral vancomycin or fidaxomicin due to limited systemic exposure (Supplementary Table 2).
2. Total number of antibiotic classes received in the inpatient and/or outpatient setting.
3. Receipt of specific systemic antibacterial agents or classes (penicillin-class antibiotics, cephalosporin-class antibiotics, carbapenem-class antibiotics, intravenous vancomycin, clindamycin, aztreonam, fluoroquinolone-class antibiotics, and aminoglycoside-class antibiotics) in the inpatient and/or outpatient setting.

Other secondary outcomes were also evaluated POD1 through POD180: positive *C difficile* assay; incident MDRO acquisition; acute kidney injury (AKI), defined as an increase in serum creatinine ≥0.3 mg/dL within 48 hours or ≥50% above baseline within 7 days [17]; invasive candidiasis, defined as isolation of *Candida* species in culture from a sterile site such as blood, bone, pleural cavity, or peritoneal cavity; surgical site infection as ascertained by *International Classification of Diseases, Tenth Revision* (*ICD-10*) diagnosis codes; and all-cause mortality. Incident MDRO was defined as isolation of methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, extended-spectrum cephalosporin-resistant Enterobacterales (defined as Enterobacterales nonsusceptible to at least 1 of the following agents: cefepime, ceftriaxone, cefotaxime, ceftazidime, ceftolozane-tazobactam, or ceftazidime-avibactam), carbapenem-resistant Enterobacterales (defined as Enterobacterales resistant to at least 1 of the following agents: imipenem, meropenem, ertapenem, meropenem/vaborbactam, or imipenem/relebactam), or multidrug-resistant *Pseudomonas aeruginosa* (defined as *P aeruginosa* nonsusceptible to at least 1 agent in at least 3 of the following 5 classes: (1) extended-spectrum cephalosporins (cefepime, ceftazidime, ceftolozane-tazobactam, ceftazidime -avibactam); (2) fluoroquinolones (ciprofloxacin, levofloxacin); (3) aminoglycosides (amikacin, gentamicin, tobramycin); (4) carbapenems (imipenem, meropenem, doripenem); and (5) piperacillin-tazobactam, in a clinical culture from POD1 through POD180 without prior isolation in the 365 days preceding transplant surgery [18].

### Data Collection

All data were extracted from the electronic health record via the Epic Clarity database. Comorbidities at time of transplant were ascertained using *ICD-10* codes. Pretransplant hospitalization status (ambulatory, inpatient non–intensive care, or intensive care unit) was assessed on the calendar day preceding transplant surgery, with patients newly admitted to the hospital on the day prior to surgery (ie, scheduled admissions in preparation for surgery) considered to be ambulatory.

### Statistical Analyses

Data were analyzed in Stata version 16.1 software (StataCorp, College Station, Texas). Baseline characteristics were compared using Wilcoxon rank-sum test for continuous variables and $\chi^2$ test for categorical variables. Univariate and multivariate median regression was performed to evaluate the association between BLA and DAOH180, the association between BLA and length of index hospitalization, and the association between BLA and inpatient antibiotic DOT. An evaluation for an interaction effect between BLA and transplanted organ on DAOH180 was performed on the fully adjusted model using Wald test for joint significance. Preplanned subgroup analyses of the association between BLA and DAOH180 were performed excluding patients with non–β-lactam antibiotic allergies from both exposed and unexposed groups, comparing patients with cephalosporin class–only allergy to those with penicillin class–only allergy, and excluding patients undergoing retransplantation. Poisson regression was performed to evaluate the association between BLA and number of antibiotic classes received, and logistic regression was performed to evaluate the association between BLA and odds of rehospitalization within the first 180 days posttransplant, receipt of specific antibiotic agents or classes, incident MDRO acquisition, positive *C difficile* assay, invasive candidiasis, AKI, and surgical site infection. For all multivariate models, the following covariates were selected a priori for inclusion based on clinical justification: transplanted organ, recipient age, sex, diabetes mellitus at time of transplant, pretransplant hospitalization status, receipt of induction therapy, and initial antimetabolite drug. Due to low event counts, all-cause mortality was examined using unadjusted analysis only.

An α of .05 was used, and 2-tailed *P* values are reported. No adjustments were made for multiple comparisons.

## RESULTS

### Cohort Characteristics

Among 1700 patients, 285 (16.8%) had a BLA at the time of transplant. Among those with BLA, penicillin-class allergy was reported among 245 (86.0%), cephalosporin allergy among 61 (21.4%), and carbapenem allergy among 4 (1.4%), with 25 (8.8%) patients reporting allergies to ≥2 β-lactam classes. Patients with BLA were more likely to be female (52.3% vs

34.6%, *P* < .001), report a non-β-lactam antibiotic allergy (33.0% vs 12.2%, *P* < .001), or have cystic fibrosis (3.5% vs 0.9%, *P* < .001). Thirteen (4.6%) patients with BLA had an outpatient allergy/immunology encounter in the 90 days preceding transplant. Baseline characteristics are summarized in Table 1.

### Association Between BLA and Days Alive and Out of the Hospital

Median DAOH180 was 169 (interquartile range [IQR], 156–175) days among patients without BLA and 168 (IQR, 154–174) days among those with BLA (Figure 1). There was no significant association between BLA and DAOH180 in either unadjusted (median difference, –1.0 days [95% confidence interval {CI}, –3.0 to 1.0]; *P* = .32) or adjusted (adjusted median difference, –0.8 days [95% CI, –2.7 to 1.2]; *P* = .43) analyses (Table 2). There was not a significant interaction between BLA and transplanted organ on DAOH180 (*P* = .47). Similar findings were observed in subgroup analyses excluding patients with non-β-lactam antibiotic allergy (adjusted median difference, –0.5 days [95% CI, –2.7 to 1.6]; *P* = .62), comparing patients with cephalosporin class–only allergy to those with penicillin class–only allergy (adjusted median difference, –1.3 days [95% CI, –8.7 to 6.2]; *P* = .74), and excluding patients undergoing retransplantation (adjusted median difference, –0.7 days [95% CI, –2.7 to 1.2]; *P* = .46). There was no significant difference in length of index hospitalization following transplant surgery (adjusted median difference, 0.04 days [95% CI, –.8 to .9]; *P* = .92) or in odds of rehospitalization within the first

**Table 1. Characteristics of Solid Organ Transplant Recipients With and Without β-Lactam Allergy Label, University of Pennsylvania Health System, April 2017–December 2020**

| Characteristic | No β-Lactam Allergy (n = 1415) | β-Lactam Allergy (n = 285) | *P* Value |
|---|---|---|---|
| Age, y, median (IQR) | 57 (47–64) | 57 (44–64) | .37 |
| Female sex, No. (%) | 490 (34.6) | 149 (52.3) | <.001 |
| Self-identified race, No. (%) | | | .36 |
| White | 939 (67.3) | 204 (71.6) | |
| Black or African American | 347 (24.9) | 62 (21.8) | |
| Other | 110 (7.9) | 19 (6.7) | |
| Not reported | 19 (…) | 0 (…) | |
| Self-identified ethnicity, No. (%) | | | |
| Non-Hispanic/non-Latino | 1306 (93.8) | 269 (94.4) | .72 |
| Hispanic or Latino | 86 (6.2) | 16 (5.6) | |
| Not reported | 23 (…) | 0 (…) | |
| Non β-lactam antibiotic allergy, No. (%) | 173 (12.2) | 94 (33.0) | <.001 |
| Transplanted organ, No. (%) | | | .19 |
| Kidney | 633 (44.7) | 124 (43.5) | |
| Liver | 375 (26.5) | 70 (24.6) | |
| Lung | 259 (18.3) | 50 (17.5) | |
| Heart | 146 (10.3) | 39 (13.7) | |
| Pancreas | 2 (0.1) | 2 (0.7) | |
| Retransplantation, No. (%) | 50 (3.6) | 11 (3.9) | .80 |

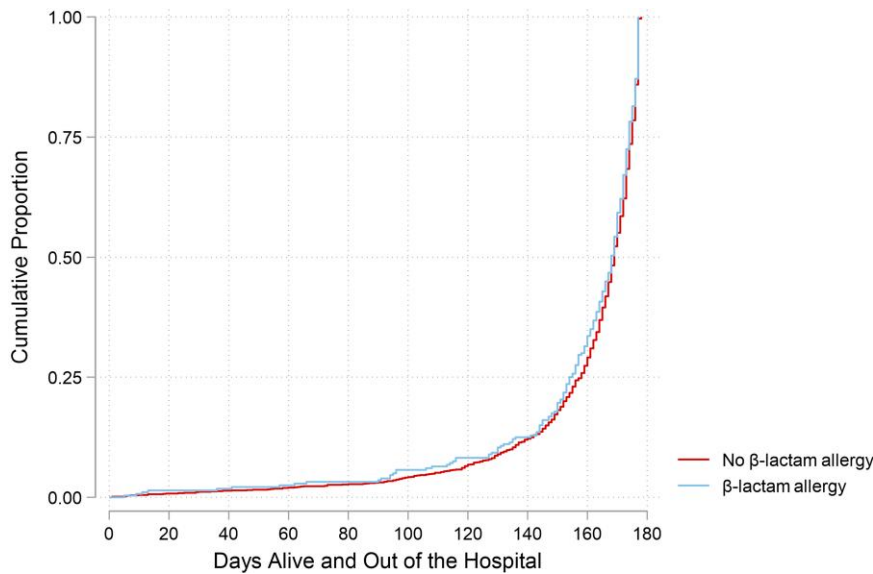Abbreviation, IQR, interquartile range.

**Figure 1.** Cumulative days alive and out of the hospital in the first 180 days among solid organ transplant recipients with and without β-lactam allergy label.

**Table 2.** Multivariate Median Regression of Association Between β-Lactam Allergy Label and Days Alive and Out of the Hospital in the First 180 Days Post–Organ Transplant

| Characteristic | Coefficient | (95% CI) | P Value |
|---|---|---|---|
| β-lactam allergy | −.79 | (−2.74 to 1.16) | .43 |
| Organ transplant type | … | … | |
|   Heart | ref | … | |
|   Kidney | 16.21 | (12.90–19.51) | <.001 |
|   Liver | 9.79 | (4.38–15.21) | <.001 |
|   Lung | −7.71 | (−11.16 to −4.25) | <.001 |
|   Pancreas | 2.91 | (−12.38 to 18.21) | .71 |
| Age (per additional year) | −0.03 | (−.09 to .03) | .32 |
| Female sex | −0.26 | (−1.78 to 1.25) | .73 |
| Diabetes mellitus | −1.03 | (−3.58 to 1.52) | .43 |
| Pretransplant hospitalization status | | | |
|   Ambulatory | ref | … | |
|   Inpatient, non-ICU | −2.38 | (−4.90 to .14) | .064 |
|   Inpatient, ICU | −16.15 | (−19.49 to −12.81) | <.001 |
| Receipt of induction immunosuppression | 1.12 | (−2.80 to 5.04) | .58 |
| Initial receipt of mycophenolate | −2.50 | (−7.32 to 2.32) | .31 |
| Initial receipt of azathioprine | −1.65 | (−4.47 to 1.18) | .25 |

Abbreviations: CI, confidence interval; ICU, intensive care unit; ref, reference category.

180 days posttransplant (adjusted odds ratio [aOR], 1.2 [95% CI, .9–1.5]; $P = .20$) among patients with BLA compared to those without BLA.

**Association Between BLA and Antibiotic Use**

The median percentage of inpatient days during which patients received antibiotics was 33.3% (IQR, 16.7%–63.2%). BLA was not associated with inpatient antibiotic DOT in the first 180 days posttransplant in unadjusted (median difference, 0.0 days [95% CI, −2.0 to 2.0]; $P > .99$) or adjusted

(adjusted median difference, 0.0 days [95% CI, −1.7 to 1.7]; $P > .99$) analyses. However, BLA was associated with an increased number of antibiotic classes received (adjusted incidence rate ratio, 1.10 [95% CI, 1.0–1.2]; $P = .02$) as well as increased odds of receiving intravenous vancomycin, clindamycin, aztreonam, fluoroquinolones, and aminoglycosides (Table 3). Among patients with BLA, 68 (23.9%) still received penicillin-class antibiotics, 166 (58.3%) received cephalosporin-class antibiotics, and 42 (14.7%) received carbapenem-class antibiotics in the first 180 days posttransplant.

**Table 3.** Association Between β-Lactam Allergy Label and Odds of Receiving Specific Antibiotics or Antibiotic Classes in the First 180 Days Post–Organ Transplant

| Antibiotic Agent/Class | Unadjusted | | | Adjusted | | |
| --- | --- | --- | --- | --- | --- | --- |
| | OR | (95% CI) | P Value | aOR | (95% CI) | P Value |
| Aminoglycosides | 4.0 | (2.6–6.2) | <.001 | 3.9 | (2.5–6.2) | <.001 |
| Aztreonam | 16.9 | (5.5–52.1) | <.001 | 19.6 | (5.9–64.4) | <.001 |
| Carbapenems | 1.1 | (.8–1.6) | .51 | 1.1 | (.7–1.6) | .68 |
| Cephalosporins | 0.4 | (.3–.5) | <.001 | 0.2 | (.1–.3) | <.001 |
| Clindamycin | 9.2 | (4.9–17.2) | <.001 | 9.9 | (5.1–18.9) | <.001 |
| Fluoroquinolones | 3.4 | (2.6–4.5) | <.001 | 3.8 | (2.8–5.0) | <.001 |
| Penicillins | 0.3 | (.3–.5) | <.001 | 0.2 | (.1–.3) | <.001 |
| Vancomycin (IV) | 1.5 | (1.1–1.9) | .003 | 1.8 | (1.3–2.6) | <.001 |

OR refers to association between β-lactam allergy and odds of receiving antibiotic class listed in each row.

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; IV, intravenous; OR, odds ratio.

### Association Between BLA and Adverse Events

BLA was not significantly associated with a positive *C difficile* assay (aOR, 1.2 [95% CI, .7–2.1]; *P* = .56), incident MDRO acquisition (aOR, 1.0 [95% CI, .7–1.6]; *P* = .83) (Supplementary Table 3), AKI (aOR, 0.9 [95% CI, .7–1.2]; *P* = .51), invasive candidiasis (aOR, 1.3 [95% CI, .5–3.2]; *P* = .57), or surgical site infection (aOR, 0.7 [95% CI, .4–1.4]; *P* = .34). Deaths within 180 days of transplant occurred among 13 (4.6%) patients with BLA and 48 (3.4%) without BLA (unadjusted OR, 1.4 [95% CI, .7–2.5]; *P* = .34).

### DISCUSSION

In this study, we found that reported BLA was highly prevalent among SOT recipients. Furthermore, the presence of a BLA label at the time of transplant was associated with increased use of β-lactam-alternative antibiotics in the early posttransplant period, though we did not observe a significant association between BLA and clinical outcomes in this cohort.

Few other studies have examined antibiotic allergy labels among SOT recipients, and ours is the first of our knowledge to evaluate the impact of BLAs on clinical outcomes exclusively within this patient population [9, 16]. The prevalence of reported BLA in our cohort was much greater than that of the general population, in which an estimated 8% and 1% of healthcare-seeking adults report penicillin and cephalosporin allergies, respectively, though similar to those of other studies of immunocompromised patient populations in the US [1, 9, 10]. This high prevalence likely reflects the burden of antibiotic exposure experienced by patients who ultimately undergo organ transplantation. Despite the high prevalence of these labels, <5% of patients with BLA were connected to care with an allergist in the pretransplant period, representing a significant missed opportunity to evaluate and de-label incorrectly documented antibiotic allergies. In addition to a robust body of literature supporting the safety and efficacy of penicillin skin testing and direct challenges among immunocompetent hosts [5, 19–22],

BLA evaluation and de-labeling interventions targeting surgical patient populations have been demonstrated to be associated with increased use of first-line perioperative antibiotics [23–25]. Furthermore, data regarding the safe use of penicillin skin testing among immunocompromised hosts and transplant candidates have begun to accumulate in recent years [26–29]. As a result, considering the high proportion of SOT recipients with a BLA and the certainty that their posttransplant course will involve antibiotic exposures, pretransplant evaluation of BLAs should be a priority for this population.

There was a strong association between BLA and exposure to intravenous vancomycin, clindamycin, aztreonam, fluoroquinolones, and aminoglycosides in the posttransplant period, consistent with prior studies of the general adult inpatient and perioperative patient populations as well as Imlay and colleagues' study of solid organ and hematopoietic stem cell transplant recipients [7, 9]. These findings are of significance given the established associations between some of these β-lactam-alternative antibiotics and adverse events, including increased risk of *C difficile* with fluoroquinolone use and aminoglycoside-associated nephrotoxicity [30–33]. Additionally, use of β-lactam alternative agents are associated with lower effectiveness of therapy in certain clinical scenarios; for example, inferior survival outcomes have been observed in methicillin-susceptible *S aureus* infections when vancomycin rather than an anti-staphylococcal β-lactam antibiotic is used as definitive therapy [34]. However, in this study we did not observe a significant association between BLA and adverse clinical outcomes in the early posttransplant period. This lack of observed association could potentially be explained by the overall high utilization of broad-spectrum antibiotics in this patient population regardless of BLA status, with approximately 25% and 14% of our overall cohort receiving fluoroquinolones and carbapenems, respectively, in the first 180 days posttransplant. Furthermore, it is possible that the detrimental impact of BLA manifests beyond the first 180 days posttransplant, after several courses of non-first-line antibiotic exposures. Future studies should therefore evaluate the

association between BLA and adverse outcomes later in the posttransplant period. Nevertheless, the high prevalence of BLA in our cohort and its substantial impact on antibiotic use in the early posttransplant period still provide strong justification for the prioritization of SOT candidates in allergy de-labeling interventions.

Our study has several limitations. As all data were collected retrospectively from the electronic health record of a single health system, it is possible that posttransplant hospitalizations outside of UPHS were missed. This is unlikely to be significant, however, since patients receiving transplants at our center are followed almost exclusively within our health system during the first year posttransplant. Misclassification could also have occurred from underascertainment of comorbidities based on *ICD-10* code documentation or overascertainment of outpatient antibiotic use from drug prescription data. Bias due to unmeasured confounding from variables such as socioeconomic status and pretransplant infections is also possible. Additionally, the single-center nature of the study limits its generalizability. Last, the study had limited statistical power to detect clinically meaningful differences for some secondary outcomes, in particular *C difficile* and MDRO acquisition, for which our findings should be considered exploratory.

## CONCLUSIONS

Among SOT recipients, BLA was highly prevalent and associated with increased use of β-lactam-alternative antibiotics but not with clinical outcomes. Future studies should validate these findings in other cohorts as well as evaluate the feasibility, safety, and impact of antibiotic allergy interventions targeting SOT candidates.

### Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

### Notes

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