Beta Lactam and Other Antibiotic Allergies in Solid Organ and Hematopoietic Cell Transplant Recipients

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Abstract

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Background

Patients with reported beta lactam antibiotic allergies (BLA) are more likely to receive broad-spectrum antibiotics and experience adverse outcomes. Data on the burden of beta lactam and other antibiotic allergies among solid organ transplant (SOT) and hematopoietic cell transplant (HCT) recipients are limited.

Methods

We reviewed records of first-time adult SOT or allogeneic HCT recipients from 1/1/2013-12/31/2017 to characterize allergy labels at time of transplant. Days of hospitalization and inpatient antibiotic use for pre-specified antimicrobials were examined for the first 100 days post-transplant. Incidence rate ratios (IRR) comparing

antibiotic use in BLA and non-BLA groups were calculated using negative binomial models for two metrics: days of therapy (DOT)/1000 inpatient days and percentage of antibiotic exposure days, both adjusted for transplant type, age, and cystic fibrosis diagnosis.

Results

Among 2153 SOT (65%) and HCT (35%) recipients, 634 (29%) reported any antibiotic allergy and 347 (16%) reported BLAs. BLA patients had significantly higher DOT for vancomycin (IRR 1.4 [1.2 – 1.7], $p<0.001$), clindamycin (IRR 7.6 [2.2 – 32.4], $p=0.001$), aztreonam in HCT (IRR 9.7 [3.3 – 35.0], $p<0.001$), fluoroquinolones in SOT (IRR 2.9 [2.1 – 4.0], $p<0.001$) and lower DOT for ampicillin-sulbactam (IRR 0.1 [0.0 – 0.4], $p<0.001$) and piperacillin-tazobactam (IRR 0.4 [0.2 – 0.6], $p<0.001$) compared to non-BLA patients; these findings were consistent when using percentage of antibiotic exposure days.

Conclusions

Transplant recipients have a high burden of reported antibiotic allergies, and reported BLA was significantly associated with altered post-transplant antibiotic prescribing. Pre-transplant allergy evaluation may optimize antibiotic stewardship in this population.

Introduction:

Beta lactam allergies (BLA) are reported in up to 20% of hospitalized patients, but many of these allergy "labels" may be inaccurate as the rate of reported penicillin allergy is much higher than the rate of clinically significant reactions to penicillin [1-9]. A growing body of evidence suggests that BLA are associated with altered antibiotic prescribing and adverse clinical outcomes including increased length of hospital stay, hospital readmissions, higher rates of methicillin resistant *Staphylococcus aureus* (MRSA) infection, and mortality [4-6, 10, 11].

Antibiotic allergies documented in the electronic health record (EHR) directly influence selection of antibiotics for treatment or prevention of infection, and inaccurate assessment and documentation of allergies may lead to suboptimal antibiotic use. Patients who undergo solid organ transplantation (SOT) or allogeneic hematopoietic cell transplantation (HCT) are at high risk for post-transplant infections, including drug resistant organisms, and *Clostridioides difficile* infection (CDI); therefore, it is critical to develop strategies to optimize antibiotic use in this population [12, 13]. There are limited data on the burden of BLA among SOT and HCT recipients [14]. Given their frequent exposures to the healthcare system, antibiotics, and polypharmacy, transplant candidates may represent a population at increased risk for antibiotic allergy labeling and a group that could benefit from allergy evaluation prior to transplantation.

In this study, we describe the prevalence of antibiotic allergies, including BLA, and assess post-transplant antibiotic use and other clinical outcomes among SOT and HCT recipients with and without BLA labels.

Methods:

Study design

We retrospectively reviewed patients who were hospitalized for SOT or HCT at the Seattle Cancer Care Alliance and University of Washington Medical Center between 1/1/2013-12/31/2017. We characterized antibiotic allergies reported at time of transplant and evaluated the association of beta lactam allergies with antibiotic utilization and clinical outcomes during the 100-day period after transplantation.

Study subjects

Patients were included if they received a first-time allogeneic HCT or SOT as an inpatient at the University of Washington Medical Center and were ≥18 years old at the time of transplant. Exclusion criteria included recipients of dual organs (e.g. heart-kidney, liver-HCT), recipients of tandem autologous-allogeneic HCT, or recipients of first transplants who received a second transplant within the first 100 days post-transplant.

Data collection

Patients were identified and baseline demographic and clinical data were obtained from prospectively-maintained transplant center databases. Electronic data abstraction identified patients with an antibiotic allergy label entered into their EHR at any time. Chart review determined which allergy labels were present at the time of transplant and documented reactions using the allergy banner in the medical chart and admission notes in the electronic medical record. Antibiotic allergy labels that were removed prior to transplant or added following transplant were not included. Patients who had reported allergies to antibiotics in penicillin, cephalosporin, or carbapenem classes were categorized as having beta lactam allergy labels. We extracted electronically antibiotic use, CDI (defined by a positive PCR result (Xpert® *C. difficile*;

Cepheid), and hospitalizations in the first 100 days following transplant. This study was approved by the Fred Hutchinson Cancer Research Center Institutional Review Board.

Data analysis

We used two different patient-level metrics to assess inpatient antibiotic use for each of the following pre-specified antibiotics in the first 100 days post-transplant: IV vancomycin, fluoroquinolones, clindamycin, carbapenems, piperacillin-tazobactam, cefepime, ceftazidime, ceftriaxone, ampicillin-sulbactam/amoxicillin-clavulanate, and aztreonam. The first metric was days of therapy (DOT) per 1000 inpatient-days [15]. In order to account for potential group differences in overall antibiotic use, we computed a second metric defined as the percentage of total antibiotic exposure days (number of days at least one antibiotic was administered, excluding prophylaxis) that each individual antibiotic was administered among patients who received any non-prophylaxis antibiotic in the 100 days post-transplant. For example, the percentage of total antibiotic exposure days for vancomycin would be the number of days that vancomycin was given out of the total number of days that any non-prophylactic antibiotic was given, computed for each patient.

Both antibiotic use metrics were compared between patients with and without reported BLA using negative binomial models including an offset to account for inpatient days (first metric) or antibiotic exposure days (second metric). Model estimates were presented as incidence rate ratios (IRR) with 95% confidence intervals (CI). In the HCT population, fluoroquinolone class antibiotics are more commonly used at our center for antibacterial prophylaxis among neutropenic patients than for treatment of infection so we analyzed fluoroquinolone use only among SOT recipients. Aztreonam use was minimal in SOT recipients and so this was only analyzed as an outcome in HCT recipients. Number of inpatients days was compared between BLA groups using a negative binomial model with an offset for number of days alive. Cox regression was used to compare BLA groups with respect to mortality and CDI diagnosis in the first 100 days post-transplant.

All multivariable models were adjusted for the following *a priori* hypothesized confounders: age, type of transplant and pre-transplant diagnosis of cystic fibrosis. Because cystic fibrosis was specific to lung transplant recipients, transplant type was coded as a categorical variable with the following six groups: allogeneic HCT, liver SOT, kidney SOT, heart SOT, lung SOT with pre-transplant diagnosis of cystic fibrosis, and lung SOT without pre-transplant diagnosis of cystic fibrosis. We used likelihood-based CIs and likelihood ratio testing to determine p-values and statistical significance, defined as a 2-sided p-value <0.05. We tested for interactions between reported BLA and transplant type (HCT vs. SOT) and presented separate models if the p-value for the interaction was <0.01.

Post-hoc analyses were conducted to assess the effect of adjusting for other demographic variables associated with BLA (gender, transplant-specific demographics) on estimates of BLA associations with our outcomes. All analyses were performed in R [R Core team (2017)].

Results:

Cohort Description

Our cohort of 2153 transplant recipients included 1410 (65%) SOT and 743 (35%) allogeneic HCT recipients. Baseline demographics and other transplant characteristics are summarized in Table 1.

Prevalence of antibiotic allergies and reactions to BLAs

Among 2153 transplant recipients, 634 (29%) reported ≥1 antibiotic allergy at time of transplant; 194 (9%) reported allergies to ≥ 2 classes of antibiotics. The most commonly reported allergies were to penicillins (40%), sulfa (29%), and cephalosporins (17%). Overall, 347 of 2153 (16%) patients reported a BLA (12% penicillin class, 5% cephalosporin class, and 1% carbapenem class).

Female gender and several transplant-specific characteristics were more common in the BLA vs non-BLA groups, including diagnosis of polycystic kidney disease (18% vs 10% of kidney transplant recipients), model for end-stage liver disease (MELD) score of ≥35 at time of liver transplant (34% vs 24% of liver transplant recipients), use of a ventricular assist device at time of heart transplant (79 vs 71% of heart transplant recipients), diagnosis of cystic fibrosis (27% vs 11% of lung transplant recipients), or diagnosis of acute myelogenous leukemia (55% vs 39% of allogeneic HCT recipients) (supplemental Tables 2-6).

Prevalence of BLA varied significantly by HCT/SOT group ($p=0.01$) and also by transplant type among the SOT recipients ($p<0.001$). BLA was most prevalent in allogeneic HCT and lung transplant recipients and least common in liver transplant recipients (Figure 1). Prevalence of reported allergy to other classes, such as cephalosporins, fluoroquinolones, and vancomycin, also varied by transplant type (Figure 1, Table 7).

Among patients with BLAs, the most frequently reported reaction were skin complaints (61%), including rash (42%), hives (18%) and itching (10%) (Table 8). Anaphylaxis or angioedema was reported by 9% of BLA patients. Allergies that were unknown/not recorded made up 18% of all reported reactions.

Post-transplant antibiotic use and clinical outcomes

Clinical outcomes and antibiotic DOT per 1000 inpatient-days for each antibiotic are shown in Table 9. Non-prophylactic antibiotics were used at least once in 94% (2020/2153) of patients and broad-spectrum antibiotic use was common. On average patients received ≥1 non-prophylactic antibiotic for 41% of inpatient days in their first 100 days post-transplant (IQR 16.7%, 62.5%). Vancomycin and fluoroquinolones were most commonly used; clindamycin and ampicillin-sulbactam/amoxicillin-clavulanic acid were used infrequently.

The mean percentage of total antibiotic exposure days for each antibiotic is shown in Figure 2. Patterns in antibiotic use by metric were similar to those captured by DOT per 1000 inpatient days; overall, fluoroquinolone (SOT) and vancomycin use was common (used for an average of 15% and 26% of antibiotic exposure days, respectively); clindamycin, aztreonam (HCT), and ampicillin-sulbactam/amoxicillin-clavulanic acid use were uncommon (all used for an average of <2% of antibiotic exposure days). Carbapenems, ceftazidime, and cefepime were given more commonly among HCT recipients, while ceftriaxone was more frequently administered among SOT recipients (Figure 3); variation was also noted across different solid organ transplant types.

Both measures of antibiotic use (DOT/1000 inpatient days and mean percentage use per antibiotic exposure days) depict consistent differences in antibiotic use between patients with and without reported BLA. In multivariable models that examined DOT/1000 inpatient-days (Figure 4A), patients with BLAs had significantly higher use of vancomycin (IRR 1.4 [95% CI 1.2, 1.7, p<0.001) and clindamycin than patients without BLAs (IRR 7.6 [95% CI 2.2, 32.4], p<0.001) and significantly lower use of ampicillin-sulbactam/amoxicillin-clavulanate (IRR 0.1 [95% CI 0.04, 0.4], p<0.001) and piperacillin-tazobactam (IRR 0.4 [95% CI 0.2, 0.6], p<0.001). 225 of 347 (65%) of patients with a listed BLA received a beta lactam as an inpatient in the 100 days after transplant (13% received a penicillin, 52% received a cephalosporin, 23% received a carbapenem) vs 1641 of 1806 (91%) patients without a reported BLA (27% received a penicillin, 86% received a cephalosporin, 17% received a carbapenem). Of the 30 patients with BLA who received ampicillin-sulbactam, amoxicillin-clavulanate, or piperacillin-tazobactam, 16 reported allergies to a non-penicillin beta lactam, 2 reported penicillin class allergies with reactions that were not recorded, and 1 received an allergy consultation prior to receiving the antibiotic. HCT recipients with BLAs had higher aztreonam use (IRR 9.7 [95% CI 3.3, 35.0], p<0.001) and SOT recipients with BLAs had higher fluoroquinolone use (IRR 2.9 [95% CI 2.1, 4.0], p<0.001). There were no significant differences in use of ceftriaxone, carbapenems, or cefepime; however there was a trend toward increased carbapenem use in patients with BLAs. Because the adjusted incidence rate ratio for ceftazidime use differed by SOT vs HCT group, separate model estimates are presented for each group; neither relationship was statistically significant.

Multivariable models that examined antibiotic use as the percentage of total antibiotic exposure days showed results consistent with the first metric (Figure 4B). Among SOT recipients, fluoroquinolone use by BLA group varied by SOT type: IRR adjusted for age was 6.49 among kidney recipients (95% CI 4.45, 9.51; p<0.001), 2.74 among liver recipients (95% CI 1.77, 4.30; p<0.001), 3.52 among heart recipients (95% CI 1.35, 10.93; p=0.01), and 1.27 among lung recipients, where the model was additionally adjusted for pre-transplant cystic fibrosis (95% CI 0.63, 2.73; p=0.52).

There were no significant differences by reported BLA in the number of inpatient days (unadjusted IRR 1.08 [95% CI 0.98, 1.18], p=0.11; adjusted IRR 1.03 [95% CI 0.96, 1.12], p=0.40) or diagnosis of CDI (unadjusted HR 1.16 [95% CI 0.77, 1.75], p=0.48); adjusted HR 1.10 [95% CI 0.73, 1.66], p=0.66). Mortality was significantly higher in patients with BLA in univariate analysis (HR 1.66 [95% CI 1.06, 2.60], p=0.035) but was no longer significant in the multivariable analysis although the trend remained (HR 1.52 [95% CI 0.97, 2.39], p=0.08).

Sensitivity Analyses:

To address whether notable differences in gender and transplant-specific characteristics (AML, polycystic kidney disease, VAD use, and MELD ≥35) between patients with and without reported BLA influenced our estimates of association between BLA group and outcomes, we evaluated models that adjusted for these additional covariates; additional adjustment did not result in significantly different estimates (data not shown).

Discussion:

To our knowledge, this is the one of the first studies to describe the burden of antibiotic allergies among solid organ and hematopoietic cell transplant recipients. We

found that nearly 30% of transplant recipients reported at least one antibiotic allergy at the time of transplant, with nearly 10% of patients reporting 2 or more antibiotic allergies. Beta lactam allergies were most commonly reported, and were present among 16% of all transplant recipients. We observed greater post-transplant use of selected broad-spectrum antibiotics among patients with a reported BLA.

The rate of reported antibiotic allergy (29%) was similar to previous reports of allergy prevalence in hospitalized patients [1, 5-7, 16]. The prevalence of penicillin and sulfa allergy in our study was 12% and 9%, respectively, which is similar to that reported in previous studies evaluating EHR-reported allergy [1, 16, 17]. However, reported allergies to cephalosporins (5%), fluoroquinolones (5%), and vancomycin (4%) were notably higher in our study compared to previous reports where reported allergies to these antibiotics ranged from 1.3-1.7%, 0.6-1.3%, and 0.7%, respectively. These differences likely reflect the wide breadth of antibiotic exposure that transplant candidates experience even before transplantation.

The prevalence of reported BLA varied significantly by type of transplant and was highest in HCT and lung transplant recipients. Specific pre-transplant comorbidities may be associated with greater antibiotic exposure prior to transplant and thus a higher risk of allergy labeling; another possibility is that some comorbidities could portend higher immunologic “reactivity” and thus higher risk of acquiring a “true” allergy label [18, 19]. Women were significantly more likely to report a BLA than men, an observation that has been noted previously for penicillin allergy [17, 20].

Among the patients with BLAs, the majority of patients (61%) reported a skin complaint and “rash”, not further specified, was the most common reported reaction (42%). Rash or other skin complaints could represent a wide range of both allergic and non-allergic syndromes. To appropriately assess the risk of severe immunologic reaction following antibiotics, more thorough documentation of antibiotic allergy history is necessary, either through a detailed narrative or through use of an allergy-focused questionnaire, as has been previously developed and validated [9, 21].

Nearly 20% of patients did not have a reaction specified, or specified that their reaction was remote or not known. A study of patients with an unknown or remote history of penicillin allergy had a low rate of positive skin testing similar to that among patients without a reported history of penicillin allergy (1.7% in both groups) [22]. Since the majority of reported BLAs in our study were to penicillin, we would anticipate that the group of patients with unknown reactions could have their allergy removed with an appropriate evaluation.

We used two metrics to evaluate antibiotic use in our study. The first, DOT/1000 inpatient-days, is a standard metric for reporting antimicrobial use [15], which allowed us to directly quantify use of selected antibiotics and evaluate the potential effect of BLA among all candidates presenting for transplant. The second, percentage of antibiotic exposure days, is a novel metric that was used to characterize relative use of selected antibiotics and thus may provide a proxy of antibiotic clinical decision-making among patients who received antibiotics during their post-transplant course. Examining individual antibiotic use when compared to overall antibiotic exposure days may also account for potential differences in sustained risk and severity of infection between BLA and non-BLA groups. Both metrics accounted for different lengths of observed time due

to mortality, which is important in patients with a high burden of illness, and should be considered for future studies in similar populations.

We observed significant differences in inpatient antibiotic use for both metrics among patients with reported BLA, specifically increased use of vancomycin and clindamycin, lower use of beta lactam/beta lactamase inhibitor combinations, and increased use of aztreonam (HCT) and fluoroquinolones (SOT). The greater use of non-beta lactam agents in patients with reported BLAs suggests opportunity for use of narrower-spectrum penicillin or cephalosporin antibiotics in cases where reported BLA does not represent a true BLA. Beta lactams are safe, well-tolerated, and highly efficacious; use of non-beta lactam alternatives has been associated with increased risks of colonization with antibiotic-resistant organisms [10, 23], adverse drug events [23, 24], and potential for lower antibacterial efficacy for some clinical syndromes [25-28]. These mechanisms are thought to explain reported links between penicillin or beta lactam allergies and adverse outcomes including increased length of hospital stay, ICU admission rates, readmission rates, mortality, hospital cost, and incidence of CDI, MRSA, and VRE infection [4-6, 10, 11]. In our study we did not see significant differences in inpatient days or CDI, however our study was underpowered to detect such differences.

In addition to contributing to potential differences in antibiotic prescribing and clinical outcomes, the presence of BLA or other allergy label may lead to clinician confusion thereby delaying antibiotic decision-making. One study found that reported penicillin allergy was associated with prolonged time to effective antibiotic therapy among patients presenting to the emergency department with a diagnosis of pneumonia, urinary tract infection, bacteremia, and sepsis, resulting in an average delay of 50 minutes [29], which is potentially a clinically meaningful delay. Furthermore, in a survey of the Emerging Infections Network, 97% of respondents surveyed felt there were potential benefits of antibiotic allergy “label” removal and 93% thought it worthwhile to refer patients for antibiotic allergy testing [30], suggesting possible provider frustration with antibiotic allergy labeling.

Our results suggest that a comprehensive approach to allergy characterization and evaluation should be considered among transplant candidates. Several studies suggest that antibiotic allergy evaluation is effective at removing allergy labels and improving guideline-preferred antibiotic use, including in an immunocompromised population, although transplant recipients have not been specifically studied [11, 31-35]. The majority of studies focus on penicillin skin testing or oral challenge as a mechanism for possible allergy label removal since reported penicillin allergy is common and skin testing is validated and reliable. However, as our data illustrate, transplant candidates have a high prevalence of multiple antibiotic allergies and non-penicillin antibiotic allergy that may be relevant to post-transplant antibiotic management [6]. Given the breadth of reported allergies and medical complexity of some transplant candidates, a full assessment by an allergist prior to transplant may be warranted in these patients.

Our study had several limitations. It was retrospective and included only a single transplant center. However, our center performs a high number of both SOT and HCT and we had a large number of patients available for analysis during the five-year inclusion period. Given the large referral area of the medical center, it is unlikely that we were able to capture all post-transplant admissions, particularly among SOT recipients. However, as we focused our analysis on the immediate 100 days post-transplant, it is

likely that the majority of inpatient stays were captured. Due to difficulty accurately capturing outpatient antimicrobial use, we limited our focus to inpatient antibiotics. Lastly, it is possible that patients with a reported BLA had a higher pre-transplant burden of infections, had higher pre-transplant morbidity or that there was unmeasured confounding; however models that incorporated demographic differences or analyzed antibiotic use as a percentage of total duration of antibiotic exposure showed that our identified differences in antibiotic use were robust.

In summary, we found that there is a high prevalence of antibiotic allergy and BLA in transplant candidates, and the presence of a BLA is associated with substantial differences in post-transplant inpatient antibiotic prescribing, which has been associated with worse clinical outcomes. Our results highlight the need for increased attention to BLA and other antibiotic allergies prior to transplant and may inform the implementation of a pre-transplant allergy evaluation program to optimize antimicrobial stewardship and clinical outcomes in this population.

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Conflicts of Interest
S.A.P. is supported by a research grant from Global Life Technologies, and has participated in clinical trials with Chimerix. The remainder of authors have no disclosures.

References:

1. Lee CE, Zembower TR, Fotis MA, et al. The incidence of antimicrobial allergies in hospitalized patients: implications regarding prescribing patterns and emerging bacterial resistance. Archives of internal medicine **2000**; 160(18): 2819-22.
2. Drug allergy: an updated practice parameter. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology **2010**; 105(4): 259-73.
3. Macy E, Contreras R. Adverse reactions associated with oral and parenteral use of cephalosporins: A retrospective population-based analysis. The Journal of allergy and clinical immunology **2015**; 135(3): 745-52.e5.
4. Macy E, Contreras R. Health care use and serious infection prevalence associated with penicillin "allergy" in hospitalized patients: A cohort study. The Journal of allergy and clinical immunology **2014**; 133(3): 790-6.
5. MacFadden DR, LaDelfa A, Leen J, et al. Impact of Reported Beta-Lactam Allergy on Inpatient Outcomes: A Multicenter Prospective Cohort Study. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America **2016**; 63(7): 904-10.
6. Huang KG, Cluzet V, Hamilton K, Fadugba O. The Impact of Reported Beta-Lactam Allergy in Hospitalized Patients With Hematologic Malignancies Requiring Antibiotics. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America **2018**; 67(1): 27-33.
7. Mirakian R, Leech SC, Krishna MT, et al. Management of allergy to penicillins and other beta-lactams. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology **2015**; 45(2): 300-27.
8. Blumenthal KG, Peter JG, Trubiano JA, Phillips EJ. Antibiotic allergy. Lancet (London, England) **2019**; 393(10167): 183-98.
9. Shenoy ES, Macy E, Rowe T, Blumenthal KG. Evaluation and Management of Penicillin Allergy: A Review. Jama **2019**; 321(2): 188-99.
10. Blumenthal KG, Lu N, Zhang Y, Li Y, Walensky RP, Choi HK. Risk of meticillin resistant Staphylococcus aureus and Clostridium difficile in patients with a documented penicillin allergy: population based matched cohort study. BMJ (Clinical research ed) **2018**; 361: k2400.
11. Moran R, Devchand M, Smibert O, Trubiano JA. Antibiotic allergy labels in hospitalized and critically ill adults: A review of current impacts of inaccurate labelling. British journal of clinical pharmacology **2019**; 85(3): 492-500.
12. Abbo LM, Ariza-Heredia EJ. Antimicrobial stewardship in immunocompromised hosts. Infectious disease clinics of North America **2014**; 28(2): 263-79.
13. Kamboj M, Sheahan A, Sun J, et al. Transmission of Clostridium difficile During Hospitalization for Allogeneic Stem Cell Transplant. Infection control and hospital epidemiology **2016**; 37(1): 8-15.
14. Khumra S, Chan J, Urbancic K, et al. Antibiotic Allergy Labels in a Liver Transplant Recipient Study. Antimicrobial agents and chemotherapy **2017**; 61(5).
15. Barlam TF, Cosgrove SE, Abbo LM, et al. Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America **2016**; 62(10): e51-77.
16. Zhou L, Dhopeshwarkar N, Blumenthal KG, et al. Drug allergies documented in electronic health records of a large healthcare system. Allergy **2016**; 71(9): 1305-13.

17. Macy E, Poon KYT. Self-reported antibiotic allergy incidence and prevalence: age and sex effects. The American journal of medicine **2009**; 122(8): 778.e1-7.
18. Colombo G, Yacoub MR, Burastero SE, et al. Multiple drug hypersensivity: insight into the underlying mechanism and correlation with autoimmune diseases. European annals of allergy and clinical immunology **2009**; 41(2): 50-5.
19. Cameron SJ, Richmond J. Ampicillin hypersensitivity in lymphatic leukaemia. Scottish medical journal **1971**; 16(10): 425-7.
20. Macy E, Schatz M, Lin C, Poon KY. The falling rate of positive penicillin skin tests from 1995 to 2007. The Permanente journal **2009**; 13(2): 12-8.
21. Devchand M, Urbancic KF, Khumra S, et al. Pathways to improved antibiotic allergy and antimicrobial stewardship practice: The validation of a beta-lactam antibiotic allergy assessment tool. The journal of allergy and clinical immunology In practice **2019**; 7(3): 1063-5.e5.
22. Gadde J, Spence M, Wheeler B, Adkinson NF, Jr. Clinical experience with penicillin skin testing in a large inner-city STD clinic. Jama **1993**; 270(20): 2456-63.
23. FDA updates warnings for fluoroquinolone antibiotics on risks of mental health and low blood sugar adverse reactions. **2018**.
24. van Hal SJ, Paterson DL, Lodise TP. Systematic review and meta-analysis of vancomycin-induced nephrotoxicity associated with dosing schedules that maintain troughs between 15 and 20 milligrams per liter. Antimicrobial agents and chemotherapy **2013**; 57(2): 734-44.
25. Blumenthal KG, Ryan EE, Li Y, Lee H, Kuhlen JL, Shenoy ES. The Impact of a Reported Penicillin Allergy on Surgical Site Infection Risk. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America **2018**; 66(3): 329-36.
26. McDanel JS, Perencevich EN, Diekema DJ, et al. Comparative effectiveness of beta-lactams versus vancomycin for treatment of methicillin-susceptible Staphylococcus aureus bloodstream infections among 122 hospitals. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America **2015**; 61(3): 361-7.
27. Chang FY, Peacock JE, Jr., Musher DM, et al. Staphylococcus aureus bacteremia: recurrence and the impact of antibiotic treatment in a prospective multicenter study. Medicine **2003**; 82(5): 333-9.
28. Jeffres MN, Narayanan PP, Shuster JE, Schramm GE. Consequences of avoiding beta-lactams in patients with beta-lactam allergies. The Journal of allergy and clinical immunology **2016**; 137(4): 1148-53.
29. Conway EL, Lin K, Sellick JA, et al. Impact of Penicillin Allergy on Time to First Dose of Antimicrobial Therapy and Clinical Outcomes. Clinical therapeutics **2017**; 39(11): 2276-83.
30. Trubiano JA, Beekmann SE, Worth LJ, et al. Improving Antimicrobial Stewardship by Antibiotic Allergy Delabeling: Evaluation of Knowledge, Attitude, and Practices Throughout the Emerging Infections Network. Open forum infectious diseases **2016**; 3(3): ofw153.
31. Trubiano JA, Thursky KA, Stewardson AJ, et al. Impact of an Integrated Antibiotic Allergy Testing Program on Antimicrobial Stewardship: A Multicenter Evaluation. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America **2017**; 65(1): 166-74.
32. Trubiano JA, Smibert O, Douglas A, et al. The Safety and Efficacy of an Oral Penicillin Challenge Program in Cancer Patients: A Multicenter Pilot Study. Open forum infectious diseases **2018**; 5(12): ofy306.

33. Trubiano JA, Chen C, Cheng AC, Grayson ML, Slavin MA, Thursky KA. Antimicrobial allergy 'labels' drive inappropriate antimicrobial prescribing: lessons for stewardship. The Journal of antimicrobial chemotherapy **2016**; 71(6): 1715-22.
34. Devchand M, Kirkpatrick CMJ, Stevenson W, et al. Evaluation of a pharmacist-led penicillin allergy de-labelling ward round: a novel antimicrobial stewardship intervention. The Journal of antimicrobial chemotherapy **2019**; 74(6): 1725-30.
35. Vyles D, Chiu A, Routes J, et al. Antibiotic Use After Removal of Penicillin Allergy Label. Pediatrics **2018**; 141(5).

Tables and Figures

Table 1. Demographics of transplant recipients with and without beta lactam allergy label[a]:

	Total n=2153	Beta lactam allergy label n=347	No beta lactam allergy label n=1806
Age groups			
18-44	552 (26)	89 (26)	463 (26)
45-64	1119 (52)	194 (56)	925 (51)
65+	482 (22)	64 (18)	418 (23)
Gender			
Male	1300 (60)	156 (45)	1144 (63)
Patient-reported Race/ethnicity[b]			
White	1631 (76)	281 (81)	1350 (75)
Hispanic or Latino/a	158 (7)	10 (3)	148 (8)
Asian	219 (10)	37 (11)	182 (10)
Black or African-American	131 (6)	8 (2)	123 (7)
Other	172 (8)	21 (6)	151 (8)
Type of transplant			
SOT			--
Kidney	560 (26)	89 (26)	471 (26)
Liver	378 (18)	35 (10)	343 (19)
Heart	224 (10)	28 (8)	196 (11)
Lung	248 (12)	55 (16)	193 (11)
HCT			--
Allogeneic	743 (35)	140 (40)	603 (33)
Admitted prior to day of transplant[c]	879 (41)	156 (45)	723 (40)

[a]Numbers in table represent the number of patients (percentage) unless otherwise indicated. SOT, Solid organ transplant; HCT, hematopoietic cell transplant.
[b]Categories may be overlapping. Other includes: American Indian or Alaskan Native (n=52), Multiple Races (n=2), Native Hawaiian or Other Pacific Islander (n=46), Unavailable, unknown, or declined to answer (n=69).
[c]As defined by inpatient stay 48 hours prior to day of transplant

Table 2. Clinical characteristics of kidney transplant recipients[a]

	Kidney transplant recipients n=560	BLA n=89	No BLA n=471
Age, median (IQR)	55 (41 – 64)	56 (45 – 64)	55 (41 – 64)
Male	331 (59)	39 (44)	292 (62)
Source of transplant			
Living related	52 (9)	5 (5)	47 (10)
Deceased donor	443 (79)	76 (85)	367 (78)
Living unrelated	65 (12)	8 (9)	57 (12)
Reason for transplant			
Glomerular[b]	172 (31)	24 (27)	148 (31)
Congenital, Rare Familial, or Metabolic[c]	7 (1)	1 (1)	6 (1)
Hypertension	72 (13)	11 (12)	61 (13)
Malignant	4 (1)	0	4 (1)
Polycystic kidney disease	64 (11)	16 (18)	48 (10)
Tubular/interstitial[d]	28 (5)	6 (7)	22 (5)
Vascular[e]	6 (1)	2 (2)	4 (1)
Other, including unknown cause	72 (13)	13 (15)	59 (13)
ATG Induction [f]	459 (82)	76 (85)	383 (81)
CPRA[g]			
<20%	446 (80)	69 (78)	377 (80)
20-<80%	62 (11)	10 (11)	52 (11)
80-<100%	30 (5)	7 (8)	23 (5)
Allograft failure within 100 days post-transplant[h]	3 (1)	1 (1)	2 (0.4)
100 day survival	559 (99.8)	89 (100)	470 (99.8)

[a]Numbers in table represent the number of patients (percentage) unless otherwise indicated. BLA, beta lactam allergies; IQR, Inter-quartile range; ATG, Anti-thymocyte globulin; CPRA, Calculated panel reactive antibodies

[b]Includes: Membranous glomerulonephritis (n=5), IgA Nephropathy (n=48), Anti-GBM (n=2), Focal Glomerular Sclerosis (n=51), Amyloidosis (n=2), Systemic Lupus Erythematosis (n=11), Hemolytic Uremic Syndrome (n=1), Alport's syndrome (n=6), Goodpasture's syndrome (n=2), Henoch Schoenlein purpura (n=2), Chronic glomerulonephritis, otherwise unspecified (n=6), Granulomatosis with polyangiitis (n=6), Rapid progressive glomerulosclerosis (n=2), HIV nephropathy (n=1)

[c]Includes: Cystinosis (n=1), Hypoplasia/dysplasia/dysgenesis/agenesis (n=1), Medullary cystic disease (n=2), Congenital obstructive uropathy (n=3)

[d]Includes: Chronic pyelonephritis/reflux nephropathy (n=7), Oxalate nephropathy (n=1), Nephritis (n=2), Acquired obstructive nephropathy (n=4), Analgesic nephropathy (n=1), Calcineurin inhibitor nephropathy (n=7), Nephrolithiasis (n=1), Drug related interstitial nephritis (n=2), Lithium toxicity (n=3)

[e]Includes: Chronic nephrosclerosis (n=6)

[f]Patients not given ATG received basiliximab

[g]Information about CPRA was missing in 3 BLA and 19 non-BLA patients

[h]Graft failure occurred at days 0, 1, and 96

Table 3. Demographics of liver transplant recipients[a]

	Liver transplant recipients n=378	BLA n=35	No BLA n=343
Age, median (IQR)	58 (50 – 63)	58 (52 – 62.5)	58 (50 – 63)
Male	253 (67)	15 (43)	238 (69)
Reason for transplant			
Acute hepatic necrosis	11 (3)	1 (3)	10 (3)
Cholestatic cirrhosis[b]	29 (8)	2 (6)	27 (8)
Cirrhosis[c]	293 (78)	31 (89)	262 (76)
Hepatocellular carcinoma	6 (2)	0	6 (2)
Metabolic disorder	9 (2)	1 (3)	8 (2)
Other	4 (1)	0	4 (1)
ATG Induction)[d]	245 (65)	25 (71)	220 (64)
MELD at transplant			
<35	284 (75)	23 (66)	261 (76)
≥35	94 (25)	12 (34)	82 (24)
100 day survival	369 (98)	35 (100)	334 (97)

[a]Numbers in table represent the number of patients (percentage) unless otherwise indicated. BLA, beta lactam allergies; IQR, inter-quartile range; ATG, anti-thymocyte globulin; MELD, model for end-stage liver disease

[b]Includes: Primary biliary cirrhosis (n=6), Primary sclerosing cholangitis (n-21), Polycystic kidney disease (n=1), Congenital biliary disease (n=1)

[c]Includes: Alcoholic (n=66), autoimmune (n=15), cryptogenic (n=33), hepatitis B (n=16), hepatitis B and C (n=2), hepatitis B and D (n=1), hepatitis C (n=141), hepatitis C and alcoholic (n=7), NASH (n=38)

[d]Patients who were not given ATG received basiliximab (n=132) or methylprednisolone (n=1)

Table 4. Demographics of heart transplant recipients[a]

	Heart transplant recipients n=224	BLA n=28	No BLA n=196
Age, median (IQR)	55 (45 – 63)	55 (50 – 63)	56 (44 – 64)
Male	158 (71)	14 (50)	144 (73)
Reason for transplant			
Ischemic cardiomyopathy	102 (46)	14 (50)	88 (45)
Other cardiomyopathy[b]	108 (48)	14 (50)	94 (48)
Congenital Heart Disease	10 (4)	0	10 (5)
Valvular Heart Disease	3 (1)	0	3 (2)
Other[c]	1 (0.4)	0	1 (1)
Listing status at time of transplant[d]			
Status 1A	99 (44)	10 (36)	89 (45)
Status 1B	98 (44)	16 (57)	82 (42)
Status 2	20 (9)	2 (7)	18 (9)
CPRA[e]			
<20%	168 (75)	14 (50)	154 (79)
20-<80%	18 (8)	5 (18)	13 (7)
80-<100%	5 (2)	2 (7)	3 (2)
On ventricular assist device at time of transplant	161 (72)	22 (79)	139 (71)
ATG Induction	212 (95)	27 (96)	185 (94)
100 day survival	212 (95)	24 (86)	188 (96)

[a]Numbers in table represent the number of patients (percentage) unless otherwise indicated. BLA, beta lactam allergies; IQR, inter-quartile range; CPRA, Calculated panel reactive antibodies; ATG, Anti-thymocyte globulin

[b]Includes: Adriamycin-induced cardiomyopathy (n=1), familial (n=11), hypertrophic (n=4), myocarditis (n=1), postpartum (n=4), viral (n=5), amyloidosis (n=4), Sarcoidosis (n=1), radiation/chemotherapy-induced cardiomyopathy (n=1), idiopathic (n=104)

[c]Includes: endocarditis (n=1)

[d]Status missing for 2 patients. 5 patients in non-BLA group were listed as status 7. Status 1A includes 1Ae and status 1B includes 1Be.

[e]Information about CPRA was missing in 7 BLA 26 non-BLA patients

Table 5. Demographics of lung transplant recipients[a]

	Lung transplant recipients n=248	BLA n=55	No BLA n=193
Age, median (IQR)	62 (55 – 66)	56 (33 – 63)	63 (57 – 67)
Male	150 (60)	26 (47)	124 (64)
Single lung transplant	33 (13)	6 (11)	27 (14)
Bilateral lung transplant	215 (87)	49 (89)	166 (86)
Diagnosis group			
Obstructive lung disease[b]	85 (34)	21 (38)	64 (33)
Pulmonary vascular disease[c]	8 (3)	3 (5)	5 (3)
Cystic fibrosis	36 (15)	15 (27)	21 (11)
Restrictive lung diseases[d]	119 (48)	16 (29)	103 (53)
CPRA[e]			
<20%	171 (69)	38 (69)	133 (69)
20-<80%	7 (3)	2 (4)	5 (3)
80-<100%	2 (1)	0	2 (1)
Basiliximab Induction	247 (99.6)	54 (98)	193 (100)
100 day survival	235 (95)	53 (96)	182 (94)

[a]Numbers in table represent the number of patients (percentage) unless otherwise indicated. BLA, beta lactam allergies; IQR, Inter-quartile range; CPRA, Calculated panel reactive antibodies

[b]Includes: Alpha-1-antitrypsin deficiency (n=16), bronchiectasis (n=3), chronic obstructive pulmonary disease/emphysema (n=62), lymphangioleiomyomatosis (n=2), sarcoidosis (n=2).

[c]Includes: primary pulmonary hypertension (n=6), pulmonary veno-occlusive disease (n=1), pulmonary hypertension related to scleroderma/CREST (n=1)

[d]Includes: Idiopathic pulmonary fibrosis (n=41), constrictive bronchiolitis (n=2), sarcoidosis (n=3), hypersensitivity pneumonitis (n=11), idiopathic interstitial pneumonia (n=35), mixed connective tissue disease (n=3), other cause of pulmonary fibrosis (n=14), rheumatoid disease (n=7), scleroderma (n=1), silicosis (n=1), granulomatosis with polyangiitis (n=1)

[e]Information about CPRA was missing in 15 BLA patients and 53 non-BLA patients

Table 6. Demographics of allogeneic transplant recipients[a]

	Allogeneic transplant recipients n=743	BLA n=140	Non-BLA n=603
Age, median (IQR)	53.2 (40 – 62.2)	53 (39.7 – 30.2)	53.3 (40.2 – 62.6)
Male	408 (55)	62 (44)	346 (57)
Reason for transplant			
AML	314 (42)	77 (55)	237 (39)
ALL	116 (16)	16 (11)	100 (17)
CML/CLL	44 (6)	5 (4)	39 (7)
Lymphoma	22 (3)	1 (1)	21 (3)
MDS/MPN	200 (27)	30 (21)	170 (28)
Other[b]	47 (6)	11 (8)	36 (6)
Type of transplant			
PBSC	587 (79)	114 (81)	473 (78)
CORD	100 (13)	15 (11)	85 (14)
BM	56 (7)	11 (8)	45 (7)
Transplant match			
Matched related	145 (20)	27 (19)	118 (20)
Matched unrelated	385 (52)	79 (56)	306 (51)
Mismatched	185 (25)	30 (21)	155 (26)
Haploidentical	28 (4)	4 (3)	24 (4)
Myeloablative conditioning	154 (21)	28 (20)	126 (21)
Relapse within 100 days	92 (12)	27 (19)	65 (11)
Any GVHD within 100 days	559 (75)	105 (75)	454 (75)
Grade 1-2	474 (64)	87 (62)	387 (64)
Grade 3-4	84 (11)	18 (13)	66 (11)
Skin GVHD within 100 days			
Grade 1-2	127 (17)	28 (20)	99 (16)
Grade 3-4	146 (20)	28 (20)	118 (20)
Gut GVHD within 100 days			
Grade 1-2	420 (56)	77 (55)	343 (57)
Grade 3-4	43 (6)	10 (7)	33 (5)
Liver GVHD within 100 days			
Grade 1-2	31 (4)	3 (2)	28 (5)
Grade 3-4	10 (2)	3 (2)	7 (1)
100 day survival	674 (91)	121 (86)	553 (92)

[a]Numbers in table represent the number of patients (percentage) unless otherwise indicated. BLA, beta lactam allergies; IQR, Inter-quartile range; AML, Acute myeloid leukemia; ALL, Acute lymphoblastic leukemia; CML, Chronic myeloid leukemia; CLL, Chronic lymphocytic leukemia; MDS, Myelodysplastic syndrome; MPN, Myeloproliferative neoplasm; PBSC, Peripheral blood stem cell transplant; CORD, Umbilical cord blood transplant; BM, Bone marrow transplant; GVHD, Graft-versus-host disease

[b]Other includes Crohn's Disease (n=2), Hemophagocytic lymphohistiocytosis (n=2), Aplastic anemia (n=23), Immune deficiency disorder NOS (n=3), Multiple myeloma (n=2), Paroxysmal nocturnal hemoglobinuria (n=1), Erythropoietic protoporphyria (n=1), Sickle Cell Anemia (n=2), IgA Nephropathy (n=1), Multiple Sclerosis (n=1), Biphenotypic Leukemia (n=5), Prolymphocytic leukemia (n=3), and Plasma Cell Leukemia (n=1)

Figure 1. Prevalence of antibiotic allergy labels among SOT/HCT recipients by type of transplant[a,b,c]:
*Computed using Fisher's exact test, remainder tested by chi-square test
[a]Patients with antibiotic allergy labels to more than one class are counted in both classes. There were 634/2153 (29%) patients who had at least one allergy label. Of those patients, 129/634 (20%) patients had antibiotic allergy labels to two different classes, 48/634 (8%) patients had labels to three classes, 14/634 (2%) patients had labels to four classes, 2/634 (0.3%) patients had labels to five classes, and 1/634 (0.1%) patient had labels to 7 classes of antibiotics.
[b]In Figure 1A, Patients who had multiple beta lactam drug allergies were counted only once. 26/347 (7%) had both a penicillin and cephalosporin allergy label, 1 (0.2%) had both a cephalosporin and carbapenem allergy label, 2 (0.6%) had penicillin and carbapenem labels, and 1 (0.3%) had labels to all three classes.
[c]Other allergy classes were not reported due to low numbers (see Table 7 for full results): carbapenems (n=16), tetracyclines (n=37), aminoglycosides (n=10), macrolides (n=56), clindamycin (n=20), linezolid (n=2), metronidazole (n=8), nitrofurantoin (n=16), rifamycins (n=3), daptomycin (n=2), trimethoprim (n=1), aztreonam (n=5), polymyxins (n=5), telavancin (n=1).

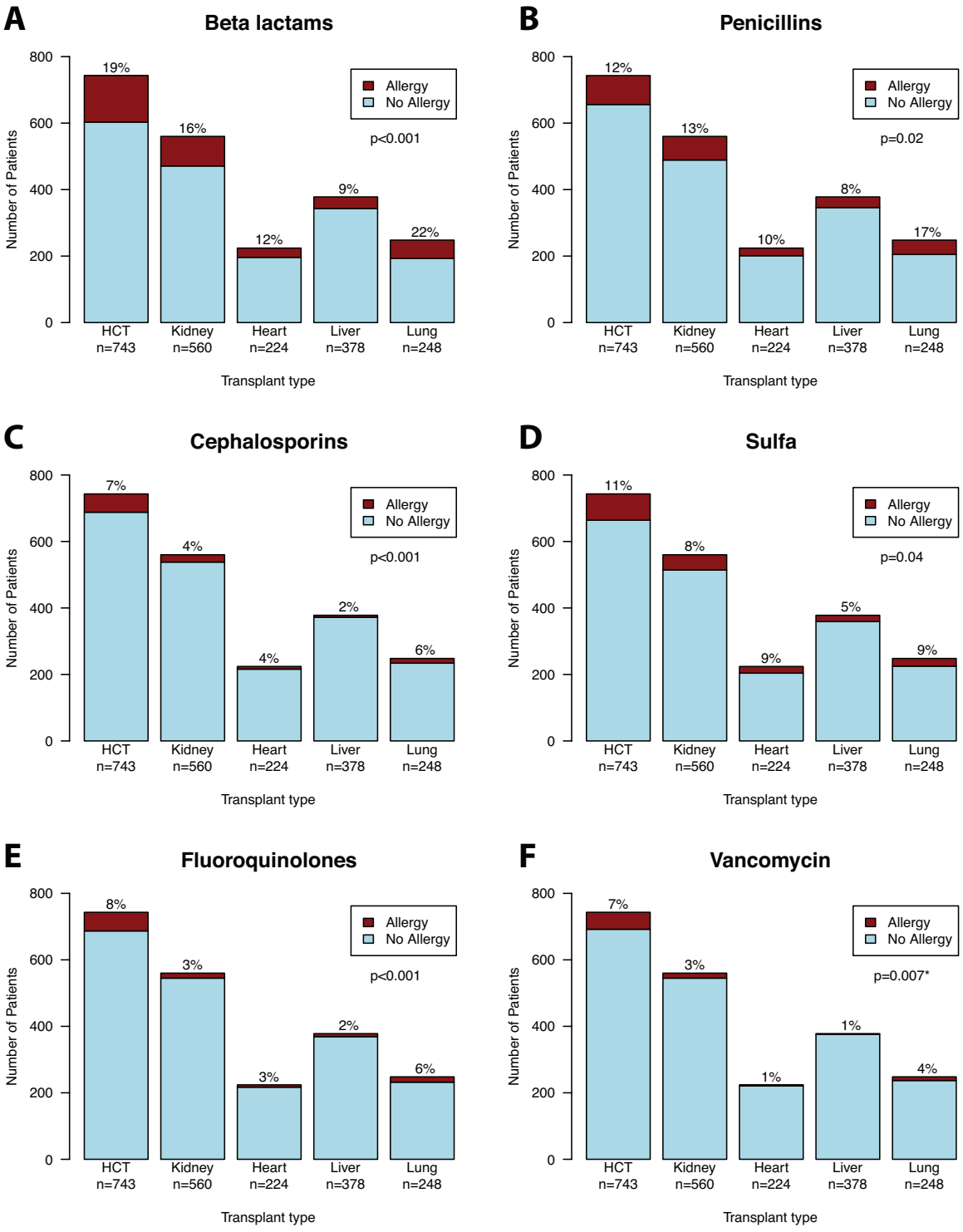
A
Beta lactams
Number of Patients
800
600
400
200
0
19%
16%
12%
9%
22%
Allergy
No Allergy
p<0.001
HCT n=743
Kidney n=560
Heart n=224
Liver n=378
Lung n=248
Transplant type
B
Penicillins
12%
13%
10%
8%
17%
p=0.02
C
Cephalosporins
7%
4%
4%
2%
6%
p<0.001
D
Sulfa
11%
8%
9%
5%
9%
p=0.04
E
Fluoroquinolones
8%
3%
3%
2%
6%
p<0.001
F
Vancomycin
7%
3%
1%
1%
4%
p=0.007*

Table 7. Prevalence of allergy labels by antibiotic class among SOT/HCT recipients[a,b]:

	Total n=2153	**Allogeneic n=743**	**Kidney n=560**	**Heart n=224**	**Liver n=378**	**Lung n=248**	**p-value**
Any Antibiotic	634 (29)	273 (37)	146 (26)	56 (25)	68 (18)	91 (37)	<0.001
Any Beta Lactam[c]	347 (16)	140 (19)	89 (16)	28 (12)	35 (9)	55 (22)	<0.001
Penicillins	256 (12)	87 (12)	71 (13)	23 (10)	32 (8)	43 (17)	0.02
Cephalosporins	105 (5)	55 (7)	22 (4)	8 (4)	6 (2)	14 (6)	<0.001
Carbapenems	16 (1)	11 (1)	1 (0.2)	0	0	4 (2)	0.003*
Sulfa	187 (9)	79 (11)	46 (8)	20 (9)	19 (5)	23 (9)	0.04
Fluoroquinolones	103 (5)	56 (8)	15 (3)	7 (3)	9 (2)	16 (6)	<0.001
Tetracyclines	37 (2)	14 (2)	4 (1)	4 (2)	5 (1)	10 (4)	0.03*
Aminoglycosides	10 (0.4)	0	2 (0.3)	0	1 (0.3)	7 (3)	0.03*
Macrolides	56 (3)	20 (3)	16 (3)	9 (4)	6 (2)	5 (2)	0.08*
Vancomycin	82 (4)	51 (7)	15 (3)	3 (1)	2 (1)	11 (4)	0.007*
Other[d]	61 (3)	28 (4)	11 (2)	2 (1)	4 (1)	16 (6)	0.36

* Computed using Fisher's exact test, remainder tested by chi-square test

[a]Numbers in table represent the number of patients (percentage) unless otherwise indicated.

[b]Patients with antibiotic allergy labels to more than one class are counted in both classes. There were 634/2153 (29%) patients who had at least one allergy label. Of those patients, 129/634 (20%) patients had antibiotic allergy labels to two different classes, 48/634 (8%) patients had labels to three classes, 14/634 (2%) patients had labels to four classes, 2/634 (0.3%) patients had labels to five classes, and 1/634 (0.1%) patient had labels to 7 classes of antibiotics.

[c]Patients who had multiple beta lactam drug allergies were counted only once. 26/347 (7%) had both a penicillin and cephalosporin allergy label, 1 (0.2%) had both a cephalosporin and carbapenem allergy label, 2 (0.6%) had penicillin and carbapenem labels, and 1 (0.3%) had labels to all three classes.

[d]Other includes: clindamycin (n=20), linezolid (n=2), metronidazole (n=8), nitrofurantoin (n=16), rifamycins (n=3), daptomycin (n=2), trimethoprim (n=1), aztreonam (n=5), polymyxins (n=5), telavancin (n=1).

Table 8. Frequency of reported reactions among SOT/HCT recipients with BLA labels[a,b,c]:

Reaction type	Patients with BLA labels n=347 (%)
Rash	146 (42)
Unknown/not recorded	61 (18)
Hives	61 (18)
Itching	36 (10)
GI symptom	30 (9)
Anaphylaxis	20 (6)
Swelling/edema, site unspecified	19 (5)
Dyspnea	11 (3)
Angioedema	10 (3)
Fever	7 (2)
Renal Dysfunction	3 (1)
Other[c]	31 (9)

[a]Numbers in table represent the number of patients (percentage) unless otherwise indicated.

[b]Reactions are counted at the patient level. For example if one patient had fever and dyspnea, they would be counted in each category but the denominator was total number of patients. 57/347 (16%) patients had 2 listed reactions in the above category, 13/347 (4%) had 3 listed reactions or more.

[c]Other includes: Blisters (n=4), Tingling in mouth (n=2), Aseptic meningoencephalitis (n=1), Bruising (n=1), Burning tongue (n=1), Chest tightness (n=1), Drug induced lupus (n=1), Excessive urination (n=1), Facial swelling (n=1), Hypotension (n=1), Joint Swelling (n=1), “Mother said almost died as a child” (n=1), Mucositis (n=1), Penicillin test positive as a child (n=1), Pulmonary edema (n=1), Restlessness (n=1), Sweating (n=1), Ear swelling (n=1), Swelling of hands and feet (n=1), Tachycardia, palpitations (n=1), Throat swelling (n=1), Throat tightness (n=1), Tongue swelling (n=1), Tongue swelling and mouth sores (n=1), Seizure (n=1), Dizziness (n=1), Arrhythmia (n=1)

Table 9. Antibiotic use and clinical outcomes among HCT/SOT recipients with and without beta lactam allergy label at time of transplant.[a]

	Reported BLA n=347	No reported BLA n=1806
Any inpatient antibiotic use[b]:	328 (95)	1692 (94)
Number of inpatient antibiotics used per patient, median (IQR)	2 (1 – 3)	2 (1 – 3)
Antibiotic exposure days/1000 inpatient days, mean (range)	437.7 (0 – 1000)	407.4 (0 – 1000)
Antibiotic exposure days/1000 inpatient days, median (IQR)	400 (169 – 666.7)	347.8 (166.7 – 615.4)
Mean days of therapy (DOT)/1000 inpatient days (range)		
Clindamycin	4.6 (0 – 257.1)	1.1 (0 – 428.6)
Aztreonam[c]	27.7 (0 – 500)	3.1 (0 – 352.9)
Vancomycin	170.9 (0 – 1000)	166.7 (0 – 1000)
Fluoroquinolones[d]	134.4 (0 – 1000)	43.9 (0 – 1200)
Carbapenems	74.6 (0 – 1000)	43.2 (0 – 1000)
Ceftriaxone	34.1 (0 – 916.7)	44.8 (0 – 1000)
Ceftazidime	45.8 (0 – 937.5)	52.5 (0 – 1000)
Cefepime	60.2 (0 – 1000)	46.4 (0 – 1000)
Ampicillin-sulbactam/ Amoxicillin-clavulanate	1.1 (0 – 318.2)	9.5 (0 – 1117.6)
Piperacillin-tazobactam	15.5 (0 – 761.9)	30.1 (0 – 1000)
Healthcare utilization[a]:		
Inpatient days/1000 patient days alive, median (IQR)	188 (99 – 287)	168 (99 – 277)
Inpatient days/1000 patient days alive, mean (range)	254.6 (9.9 – 1000)	235.8 (9.9 – 1000)
Number of admissions in follow up period, median (IQR)	1 (1 – 2)	1 (1 – 2)
Clinical outcomes:		
C. difficile diagnosis	28 (8)	126 (7)
Death in first 100 days after transplant	25 (7)	79 (4)

[a]Numbers in table represent the number of patients (percentage) unless otherwise indicated. BLA, beta lactam allergy; IQR, inter-quartile range; HCT, hematopoietic cell transplant; SOT, solid organ transplant.
[b]measured in the 100 days following transplant, including perioperative antibiotics but excluding prophylactic antibiotics (such as sulfa in any patient or fluoroquinolones in the HCT patients).
[c]Aztreonam use only reported here in HCT recipients. Among SOT recipients, very few (n=29) used aztreonam (25/29 were lung transplant recipients) and all use was among patients with BLA, so aztreonam use was not analyzed in SOT recipients.
[d]Fluoroquinolone use only reported in SOT recipients.

Figure 2. Mean percentage of total antibiotic exposure days that each antibiotic or class was given.
*Significant differences in antibiotic use per antibiotic exposure days by BLA group in the multivariable adjusted model. BLA, Beta lactam allergy; Amp-sul, ampicillin-sulbactam; Amox-clav, amoxicillin-clavulanic acid; pip-tazo, piperacillin-tazobactam.

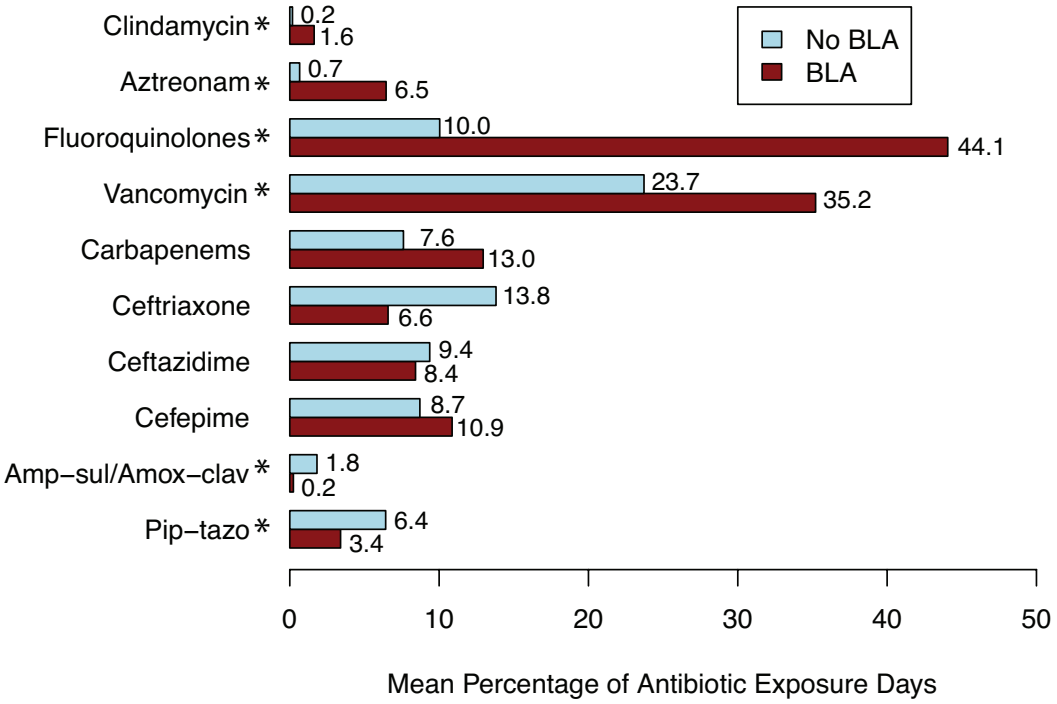

Figure 3: Mean percentage of antibiotic exposure days by transplant subgroups: A. Allogeneic hematopoietic cell transplant recipients; B. All solid organ transplant recipients; C. Kidney transplant recipients; D. Liver transplant recipients; E. Heart transplant recipients; F. Lung transplant recipients with cystic fibrosis; G. Lung transplant recipients without cystic fibrosis.

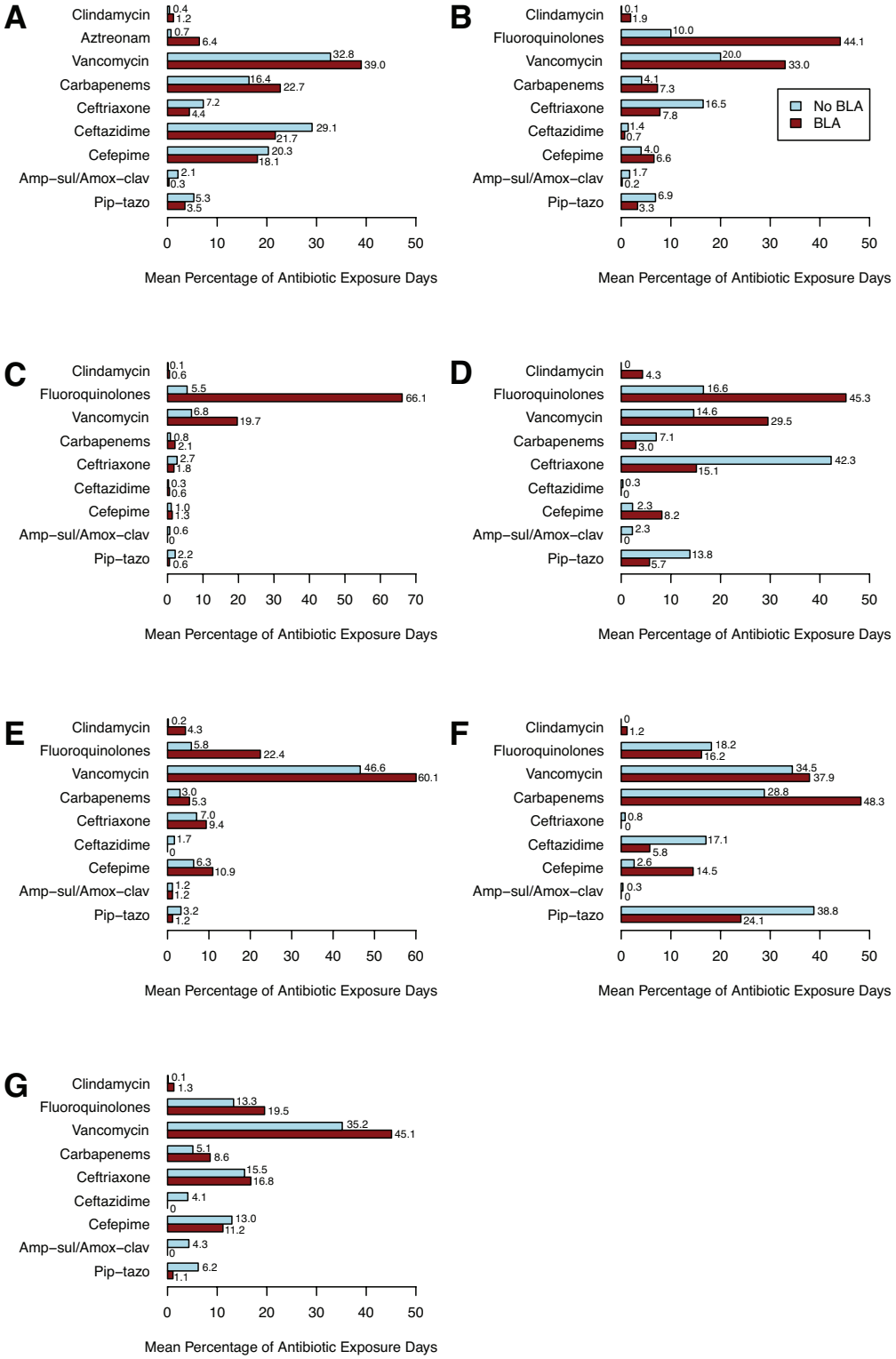

Figure 4. Results from univariate and multivariable negative binomial models[a] examining days of therapy/1000 inpatient days (A, figures shown on the left) and percentage of antibiotic exposure days (B, figures shown on the right) for each antibiotic. Estimates shown in blue are adjusted for age, transplant type, and diagnosis of cystic fibrosis, as appropriate; estimates shown in green are unadjusted. Points represent incidence rate ratio estimates and horizontal bars represent 95% confidence intervals. Clindamycin and aztreonam are shown separately to allow viewing of high incidence rate ratio estimates; upper limit of confidence interval may extend beyond the plot (represented by arrow). [a]Aztreonam use only measured in HCT recipients, fluoroquinolone use only measured in SOT recipients. IRR, Incidence Rate Ratio; CI, confidence interval; SOT, Solid organ transplant; HCT, hematopoietic cell transplant; Amp-sul, Ampicillin-sulbactam; Amox-clav, Amoxicillin-clavulanic acid; Pip-tazo, Piperacillin-tazobactam.