Long-Term Outcomes Associated With β-Lactam Allergies

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Abstract

IMPORTANCE β-lactam (BL) allergies are the most common drug allergy worldwide, but most are reported in error. BL allergies are also well-established risk factors for adverse drug events and antibiotic-resistant infections during inpatient health care encounters, but the understanding of the long-term outcomes of patients with BL allergies remains limited.

OBJECTIVE To evaluate the long-term clinical outcomes of patients with BL allergies.

DESIGN, SETTING, AND PARTICIPANTS This longitudinal retrospective cohort study was conducted at a single regional health care system in western Pennsylvania. Electronic health records were analyzed for patients who had an index encounter with a diagnosis of sepsis, pneumonia, or urinary tract infection between 2007 and 2008. Patients were followed-up until death or the end of 2018. Data analysis was performed from January 2022 to January 2024.

EXPOSURE The presence of any BL class antibiotic in the allergy section of a patient’s electronic health record, evaluated at the earliest occurring observed health care encounter.

MAIN OUTCOMES AND MEASURES The primary outcome was all-cause mortality, derived from the Social Security Death Index. Secondary outcomes were defined using laboratory and microbiology results and included infection with methicillin-resistant Staphylococcus aureus (MRSA), Clostridium difficile, or vancomycin-resistant Enterococcus (VRE) and severity and occurrence of acute kidney injury (AKI). Generalized estimating equations with a patient-level panel variable and time exposure offset were used to evaluate the odds of occurrence of each outcome between allergy groups.

RESULTS A total of 20,092 patients (mean [SD] age, 62.9 [19.7] years; 12,231 female [60.9%]), of whom 4,211 (21.0%) had BL documented allergy and 15,881 (79.0%) did not, met the inclusion criteria. A total of 3,513 patients (17.5%) were Black, 15,358 (76.4%) were White, and 1,221 (6.0%) were another race. Using generalized estimating equations, documented BL allergies were not significantly associated with the odds of mortality (odds ratio [OR], 1.02; 95% CI, 0.96-1.09). BL allergies were associated with increased odds of MRSA infection (OR, 1.44; 95% CI, 1.36-1.53), VRE infection (OR, 1.18; 95% CI, 1.05-1.32), and the pooled rate of the 3 evaluated antibiotic-resistant infections (OR, 1.33; 95% CI, 1.30-1.36) but were not associated with C difficile infection (OR, 1.04; 95% CI, 0.94-1.16), stage 2 and 3 AKI (OR, 1.02; 95% CI, 0.96-1.10), or stage 3 AKI (OR, 1.06; 95% CI, 0.98-1.14).

CONCLUSIONS AND RELEVANCE Documented BL allergies were not associated with the long-term odds of mortality but were associated with antibiotic-resistant infections. Health systems should emphasize accurate allergy documentation and reduce unnecessary BL avoidance.


Key Points

Question What are the long-term clinical outcomes of patients with β-lactam allergies?

Findings In this cohort study following 20,092 adult patients for up to 12 years, a generalized estimating equation analysis model found that the presence of a documented β-lactam allergy was not associated with a statistically significant increase in the odds of all-cause mortality but was associated with an increase in antibiotic-resistant infections.

Meaning These findings suggest that documented β-lactam allergies are associated with substantial long-term clinical detriment, and health systems should prioritize initiatives to maximize the use of first-line antimicrobials and reduce unnecessary β-lactam avoidance.

Supplemental content

Author affiliations and article information are listed at the end of this article.
Introduction

Allergies to β-lactam (BL) class antibiotics are the most commonly reported drug allergy in the US, with 5% to 13% of the population reporting an allergy to at least 1 BL-class antibiotic.1-4 Patients with documented BL allergies incur increased rates of readmission, antibiotic-resistant infections, adverse events, and longer lengths of stay (LOSs) compared with patients without documented BL allergies.3,5-8 As a result of the harm associated with inpatient encounters for patients with documented BL allergies, there has been a large increase in initiatives that emphasize the delabeling of erroneous BL allergies, which are reported in error for more than 90% of the patients with documented BL allergies.9,11 However, the long-term clinical impact of BL allergies remain poorly understood.12

To our knowledge, there has been only one previous set of cohort studies13,14 that evaluated the long-term outcomes associated with the presence of a documented BL allergy, and those studies found that BL allergies were associated with a 14% increase in the hazards of mortality, a 69% increase in the hazards of infection with methicillin-resistant Staphylococcus aureus (MRSA), and a 26% increase in the risk of infection with Clostridium difficile. The poor documentation of BL allergies, which is often based on outdated and unreliable historical information, may be leading to the use of onetime stopgaps for immediate management, while allowing the allergy to remain present in the patient’s electronic health record (EHR) and lead to long-term harm through altered prescribing patterns.15-17 BL allergies, and drug allergies in general, should be considered a long-term risk factor because more than 80% of all documented drug allergies are never delabeled.18 Because BL antimicrobials are so frequently used, and drug allergies are rarely removed, more long-term evaluations of patients with BL allergies are required to understand the full scale of harm they may be causing on the population.

We sought to expand the understanding of the long-term clinical outcomes associated with patients who have a documented BL allergy. The current understanding of the long-term clinical outcomes of BL allergies is limited to one set of UK-based cohort studies,13,14 and given the scope and impact of BL allergies globally, further studies examining additional outcomes and using different populations are required. Our study aimed to expand upon these previous studies by using a cohort of regionally based health care encounters from the US and including secondary clinical outcomes of acute kidney injury (AKI) and additional antibiotic-resistant infections. Furthermore, our study identified patients for inclusion through a 2-year span of patients with targeted infectious diseases of pneumonia, urinary tract infection (UTI), and sepsis, which may increase the likelihood that included patients had their care affected by the presence of a BL allergy.

Methods

Study Design

We performed a retrospective cohort analysis using EHR data from 2007 to 2018. The University of Pittsburgh institutional review board reviewed the study protocol, and it was assigned exempt status. Informed consent was waived because the data were deidentified, in accordance with 45 CFR §46. This study was designed and conducted in accordance with the Reporting of Studies Conducted using Observational Routinely-Collected Data (RECORD) reporting guidelines for studies using health data,19 which is an extension of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.20

Data Cohort

Data were collected for a cohort of deidentified patient encounters occurring between 2007 and 2018 that was derived from the Medical Archival Retrieval System, an electronic medical data repository for patients from University of Pittsburgh Medical Center, a health system based in Western Pennsylvania.21,22 During the study, included hospitals were transitioning to a new EHR
system, and a total of 16 hospitals, which ranged in size from 40 to 900 beds, were included on an ongoing basis as their data became available. Patients were identified for inclusion through a hospital-based health care encounter between 2007 and 2008 with a diagnosis of sepsis, pneumonia, or UTI. Sepsis was defined using a previously established method requiring an International Classification of Diseases, Ninth Revision (ICD-9) code indicating infection and an ICD-9 code indicating organ damage (excluding mechanical ventilation codes). Pneumonia and UTI were similarly identified using previously published methods for identification of these diagnoses using ICD-9 codes. A full ICD-9 code list is shown in eTable 1 in Supplement 1. The cohort was limited to patients who were aged at least 18 years and had allergy information available for the index encounter. Included patients were followed-up until the earliest occurrence of 2 events: the end of 2018 or death.

Variables
BL allergy status was defined as the presence of any penicillin, cephalosporin, carbapenem, or aztreonam as an allergy in the patient’s allergy list. Allergy lists were derived from pharmacy discharge summaries and were recorded as free text. An online medication repository was used to assist in creating a full list of applicable products to search for allergies. Over the course of follow-up, 955 patients had their BL allergy status vary from the first observed encounter (eg, a BL-allergic patient had their documented allergy removed, or vice versa). In these situations, each patient’s initial allergy status was carried forward for the full follow-up period.

Independent variables included age, sex, race, baseline serum creatinine (Scr) level, Van Walraven comorbidity score and Elixhauser Comorbidity Index score, the number of health care encounters per patient, an indicator for intensive care unit (ICU) admission, dialysis utilization during each encounter, and an indicator for the individual hospital at which the health care encounter occurred. Hospital locations were referenced only as numeric indicators to protect patient identifiability. There were instances where some secondary outcomes were not observed at individual hospitals, meaning that encounters occurring at these hospitals could not be included for analysis when the outcome was not observed. Race was identified from the EHR and was condensed into 3 categories: Black, White, or other, which includes Aleutian-Indian, Asian, Chinese, Eskimo-Indian, Filipino, Hawaiian, Hispanic, Japanese, Middle Eastern, Oriental, Pacific Islander, multiracial, unknown, and other. Data on race are included in this study because race can be a risk factor for AKI. Baseline Scr was calculated by first determining whether a patient had a stable or unstable admission Scr, with an unstable Scr defined as a change in Scr greater than 0.3 mg/dL (to convert to micromoles per liter, multiply by 88.4) within 48 hours following the first recorded Scr. Those with stable admission Scr had their first admission Scr used as the baseline, and those with unstable Scr had a baseline Scr calculated using the Modification of Diet in Renal Disease equation.

Outcomes
The primary outcome was all-cause mortality, defined using data from the Social Security Death Index. Secondary outcomes included the occurrence of AKI, grouped as stage 2 and 3 or stage 3 AKI defined by the Kidney Disease Improving Global Outcomes 2012 guidelines. Only follow-up encounters with at least one available Scr measurement were considered for analysis for AKI. Additional secondary outcomes included occurrence of infection with MRSA, C difficile, or vancomycin-resistant Enterococcus (VRE), that were defined using corresponding system-level microbiology codes, and the pooled occurrence of any of these 3 antibiotic-resistant infections.

Statistical Analysis
The analysis was performed between January 2022 and January 2024. Statistical analysis was conducted using Stata statistical software version 18.0 (StataCorp). Statistical significance was defined a priori as P < .05 using 2-sided statistical hypothesis testing. We evaluated baseline demographic and clinical characteristics at the earliest occurring encounter for each patient. These
were compared for significance using 2-sample t tests for continuous variables and χ² tests for binary variables. Missingness for age (<1%) and baseline SCr (22%) at baseline were imputed using multiple imputation by chained equation with predictive mean matching.33,34 We used multivariable generalized estimating equations to model the outcomes.35 A panel variable was included at the patient level, and all models used logit link functions and independent correlation structures. The time in days that each patient was exposed to each state was included as an offset variable. We analyzed patient data from the time of their index health care encounter to the first occurring instance of death or the end of the study period.

Outcomes were evaluated independently at each encounter, meaning that outcomes except death could recur within the same patient at different encounters. Bootstrapping (100 iterations) was used to calculate alternative 95% CIs. A sensitivity analysis was performed to compare the effect of analyzing BL allergy status as a dynamic variable, allowing patient allergy status to vary over time. For this sensitivity analysis, each patient’s BL allergy status was evaluated independently at each health care encounter, allowing it to vary over time, and the primary model was then repeated using this dynamic allergy variable. An additional sensitivity analysis was conducted in only the population for whom their allergy status changed over the follow-up period, as well as patients whose allergy status never changed. Because of the large amount of missingness in baseline SCr data that required imputation (22%), a sensitivity analysis was conducted to evaluate the results while not including baseline SCr as an independent variable. Finally, LOS was considered as a confounder and included as a covariate in a sensitivity analysis. We were unable to include LOS in the primary analysis owing to emergency department and same-day-surgery encounters not having a calculable LOS, and for this sensitivity analysis, we constrained LOS to have a value of 1 day if it was not able to be calculated.

Results

Cohort Characteristics
A total of 20,092 patients (mean [SD] age, 62.9 [19.7] years; 12,231 female [60.9%]) were identified who met the inclusion criteria, including 4,211 (21.0%) patients who had a documented BL allergy upon their first observed encounter and 15,881 (79.0%) who did not. A total of 3,513 patients (17.5%) were Black, 15,358 (76.4%) were White, and 1,221 (6.0%) were another race. Patients with a documented BL allergy were more likely to be female (2,911 patients [69.1%] vs 9,320 patients [58.7%]), older (mean [SD] age, 64.2 [19.9] years vs 62.6 [19.0] years), and White race (3,332 patients [79.1%] vs 12,026 patients [75.7%]) than those without a BL allergy. Baseline clinical characteristics, including baseline SCr level (median [IQR], 1.2 [0.9-1.7] vs 1.2 [1.0-1.7] mg/dL) and Elixhauser Comorbidity Index scores (mean [SD], 9.8 [9.6] vs 9.8 [9.9]) did not differ significantly between allergy groups. Patients with documented BL allergies incurred a higher average number of observed health care encounters (mean [SD], 12.5 [20.9] vs 10.6 [20.5] encounters) during the follow-up period, and a higher percentage of encounters with hemodialysis usage (mean [SD], 4.4% [20.6%] vs 4.2% [20.0%] encounters). The percentage of encounters that included an ICU admission (mean [SD], 10.6% [30.8%] vs 11.3% [31.6%]) was slightly higher in the non-BL-allergic group. The encounters occurred at 16 hospitals, with 3 hospitals (indicator numbers 13, 14, and 15), representing the largest number of encounters in both groups. The full demographics and characteristics can be seen in Table 1.

Primary Outcome
The full unadjusted outcome counts can be seen in Table 2. The unadjusted mortality rate between allergy groups was higher in the BL-allergic group than in the group without BL allergy (9,602 patients [60.5%] vs 26,353 patients [62.6%]). There was not a significant difference in the time of death during follow-up, with a roughly equal proportion of deaths occurring within the first 2 years of follow-up (4,648 patients [48.4%] without BL allergy vs 1,261 patients [47.9%] with BL allergy) compared with the remaining 8 years (4,954 patients [51.7%] without BL allergy vs 1,374 patients [52.2%] with BL...
allergy). When the rate of mortality was compared using multivariable generalized estimating equations, patients with documented BL allergies did not experience a statistically significant difference in the odds of all-cause mortality compared with patients who did not have a documented BL allergy (OR, 1.02; 95% CI, 0.96-1.09). The full multivariable model results including secondary outcomes are shown in Table 3. When evaluating the full model, age, other race, increased Elixhauser Comorbidity Index score, and ICU encounters were significantly associated with an increase in all-cause mortality. The full model with all covariate effects is shown in eTable 2 in the Supplement.

**Secondary Outcomes**

Patients with documented BL allergies experienced higher rates of all antibiotic-resistant infection outcomes compared with the group without BL allergy, including MRSA (3870 patients [24.4%] vs 1208 patients [28.7%]), *C. difficile* (1393 patients [8.8%] vs 388 patients [9.2%]), and VRE (1189 patients [7.5%] vs 385 patients [9.1%]). In addition, the unadjusted rate of any antibiotic-resistant infection was increased in the group with documented BL allergy vs the group without BL allergy.

<table>
<thead>
<tr>
<th>Table 1. Cohort Demographic and Clinical Characteristics</th>
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<tbody>
<tr>
<td>Characteristic</td>
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<tr>
<td>----------------</td>
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<tr>
<td>Age, mean (SD), y</td>
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<tr>
<td>Sex</td>
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<td>Race</td>
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<tr>
<td>Baseline serum creatinine, median (IQR), mg/dL</td>
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<td>Baseline estimated glomerular filtration rate, median (IQR), mL/min/1.73 m²</td>
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<td>Elixhauser Comorbidity Index weighted summary score, mean (SD)</td>
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<tr>
<td>Total No. of encounters&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td>Health care encounters per patient over follow-up period, mean (SD), No.&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td>Encounters with intensive care unit admissions, mean (SD), %&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Encounters with hemodialysis usage, mean (SD), %&lt;sup&gt;c&lt;/sup&gt;</td>
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</table>

<sup>a</sup> Baseline characteristics were evaluated at first observed admission for each patient.

<sup>b</sup> Other race refers to Aleutian-Indian, Asian, Chinese, Eskimo-Indian, Filipino, Hawaiian, Hispanic, Japanese, Middle Eastern, Oriental, Pacific Islander, multiracial, unknown, and other or declined.

<sup>c</sup> Encounter-related data were calculated using information for the full follow-up period.

SI conversion factor: To convert serum creatinine to micromoles per liter, multiply by 88.4.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Patients, No. (%)</th>
<th>Non–β-lactam allergic (n = 15881)</th>
<th>β-lactam allergic (n = 4211)</th>
<th>P value</th>
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<td>2635 (62.6)</td>
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<td>966 (36.7)</td>
<td>.72</td>
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<td>1 to &lt;2</td>
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<td>295 (11.2)</td>
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<td>687 (26.1)</td>
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<td>5 to 10</td>
<td>2501 (26.1)</td>
<td>687 (26.1)</td>
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<td>MRSA infection</td>
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<td>3870 (24.4)</td>
<td>1208 (28.7)</td>
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<td>375 (9.7)</td>
<td>128 (10.6)</td>
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<td>192 (15.9)</td>
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<td>471 (12.2)</td>
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<td>No. of encounters with MRSA, mean (maximum)</td>
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<td>0.57 (20)</td>
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<td>C difficile infection</td>
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<td>1393 (8.8)</td>
<td>388 (9.2)</td>
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<td>0 to &lt;1</td>
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<td>38 (9.8)</td>
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<td>2 to &lt;5</td>
<td>231 (16.6)</td>
<td>72 (18.6)</td>
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<td>5 to 10</td>
<td>211 (15.2)</td>
<td>71 (18.3)</td>
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<td>No. of encounters with C difficile, mean (maximum)</td>
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<td>0.13 (8)</td>
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<td>VRE infection</td>
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<td>1189 (7.5)</td>
<td>385 (9.1)</td>
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<td>34 (8.8)</td>
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<td>5 to 10</td>
<td>113 (9.5)</td>
<td>48 (12.5)</td>
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<td>No. of encounters with VRE, mean (maximum)</td>
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<td>Any antibiotic-resistant infection</td>
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<td>5215 (12.8)</td>
<td>1549 (36.8)</td>
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<td>Time to first antibiotic-resistant infection, y</td>
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<td>1023 (66.0)</td>
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<td>1 to &lt;2</td>
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<td>586 (11.2)</td>
<td>159 (10.3)</td>
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<td>0.61 (41)</td>
<td>0.77 (22)</td>
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<td>Stage 2 and 3 AKI</td>
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<td>0 to &lt;1</td>
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<td>1 to &lt;2</td>
<td>254 (5.8)</td>
<td>87 (7.5)</td>
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<td>143 (12.3)</td>
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<td>5 to 10</td>
<td>459 (10.5)</td>
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<tr>
<td>No. of encounters with stage 2 and 3 AKI, mean (maximum)</td>
<td>0.79 (232)</td>
<td>0.96 (160)</td>
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<tr>
<td>Stage 3 AKI</td>
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<td>3164 (25.6)</td>
<td>843 (25.5)</td>
<td>.93</td>
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<tr>
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<td>0 to &lt;1</td>
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<td>5 to 10</td>
<td>340 (10.8)</td>
<td>95 (11.3)</td>
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<td>No. of encounters with stage 3 AKI, mean (maximum)</td>
<td>0.69 (232)</td>
<td>0.87 (160)</td>
<td>.02</td>
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</tr>
</tbody>
</table>

Abbreviations: AKI, acute kidney injury; C difficile, Clostridium difficile; MRSA, methicillin-resistant Staphylococcus aureus; VRE, vancomycin-resistant Enterococcus.

* Outcomes are expressed as an indicator variable of occurrence vs not.
However, the unadjusted rate of stage 2 and 3 AKI (4375 patients [27.6%] vs 1161 patients [27.6%]) and stage 3 AKI (3164 patients [25.6%] vs 843 patients [25.5%]) did not differ between allergy groups.

Because secondary outcomes could occur more than once, we also evaluated the mean number of encounters per patient where each secondary outcome occurred, as well as the maximum number of each outcome experienced by a single patient in each allergy group. Similar to the overall percentage, the mean number of encounters with antibiotic-resistant infections was higher in the group with documented BL allergy, with MRSA (mean, 0.43 vs 0.57 encounters; maximum, 39 vs 20 encounters), C difficile (mean, 0.12 vs 0.13 encounters; maximum, 17 vs 8 encounters), VRE (mean, 0.10 vs 0.12 encounters; maximum, 17 vs 8 encounters), and pooled antibiotic-resistant infections (mean, 0.61 vs 0.77 encounters; maximum 41 vs 22 encounters) all being higher in the group of patients with documented BL allergies. In contrast to the overall binary occurrence, the mean number of encounters with AKI stage 2 and 3 AKI (mean, 0.96 vs 0.79 encounters; maximum, 232 vs 160 encounters) or stage 3 AKI (mean, 0.87 vs 0.69 encounters; maximum, 232 vs 160 encounters) per patient was higher in the BL-allergic group. In all instances, the maximum number of outcomes was higher in the group without documented BL allergies.

In the multivariable generalized estimating equations, the odds of MRSA (OR, 1.44; 95% CI, 1.36-1.53), VRE (OR, 1.18; 95% CI, 1.05-1.32), and pooled antibiotic-resistant infections (OR, 1.33; 95% CI, 1.30-1.36) were significantly associated with the presence of a documented BL allergy. There was no statistically significant difference in the rate of C difficile (OR, 1.04; 95% CI, 0.94-1.16), stage 2 and 3 AKI (OR, 1.02; 95% CI, 0.96-1.10), or stage 3 AKI (OR, 1.06; 95% CI, 0.98-1.14).

Sensitivity Analysis

We performed 4 sensitivity analyses to further explore our results. First, when modeling documented BL allergy status as a dynamic variable (eTable 3 in the Supplement), documented BL allergy status contrasted with the effect seen using a static allergy status and was significantly associated with an increase in the odds of all-cause mortality (OR, 1.10; 95% CI, 1.07-1.17). The outcomes observed in the primary model with regard to the odds of infection with MRSA (OR, 1.56; 95% CI, 1.48-1.65), VRE (OR, 1.27; 95% CI, 1.14-1.42), and pooled antibiotic-resistant infections (OR, 1.36; 95% CI, 1.33-1.39) remained concordant with the primary model. However, when examining BL allergies as a dynamic variable evaluated at each encounter, documented BL allergies were significantly associated with
VRE (OR, 1.27; 95% CI, 1.14-1.42), stage 2 and 3 AKI (OR, 1.07; 95% CI, 1.01-1.15), and stage 3 AKI (OR, 1.14; 95% CI, 1.06-1.23).

We then repeated the analysis while stratifying the cohort by whether a patient’s documented BL allergy status changed over follow-up, using both static and dynamic BL-allergy variables (eTables 4, 5, and 6 in Supplement 1). Documented BL allergies were more highly associated with all-cause mortality when examining only patients whose allergy status changed during follow-up; however, this represents a much smaller population than the full cohort, with only 955 patients having their allergy status change during follow-up. Analyzing only the patients whose allergy status did not change over follow-up did not appreciably change the results from the primary analysis. Next, we explored the potential bias introduced by imputing a relatively large (22%) percentage of baseline SCr values by repeating the analysis and not including baseline SCr as a covariate (eTable 7 in Supplement 1). All effect directions remained consistent when excluding baseline SCr as a covariate. We repeated the analysis while including LOS as a potential confounder. After including LOS as a covariate, the results did not appreciably change from those seen in the primary model (eTable 8 in Supplement 1).

**Discussion**

This cohort study included 20,092 patients, of whom 4,211 had documented BL allergy at the beginning of follow-up. Higher proportions of patients with documented BL allergies were older, female, and White race, which is consistent with demographics of previous allergy evaluations. Patients with documented BL allergies incurred higher rates of unadjusted all-cause mortality. When using generalized estimating equations to model clinical outcomes, the annual long-term adjusted odds of all-cause mortality was not significantly different in patients who had documented BL allergies compared with those who did not. We found that the risk for antibiotic-resistant infections was significantly increased in patients who had documented BL allergies, including increases of 44% and 18% in the odds for MRSA and VRE, respectively. However, we did not find statistically significant differences in the odds of stage 2 and 3 AKI or stage 3 AKI, or the odds of *C. difficile* across BL allergy groups.

There has been only 1 previous set of long-term (>5 years follow-up) studies on the clinical outcomes of BL allergies, and they found a 14% increase in all-cause mortality and significant increases in the hazards of both MRSA and *C. difficile*. Our results are similar to the previous results in terms of finding significant associations between documented BL allergies and an increase in MRSA infection, but our results also found a significant association of VRE infection with documented BL allergies, as well as the risk of the pooled rate of infection with MRSA, *C. difficile*, and VRE. In contrast, our primary results did not find a significant difference in all-cause mortality associated with documented BL allergies. However, we did find a significant association of all-cause mortality with documented BL allergy status when using a time-varying allergy status, so the long-term association of documented BL allergy status with all-cause mortality remains unclear. Compared with the previous studies by Blumenthal et al., our study provides a unique perspective using data from a different region and the consideration of documented BL allergy status to act as a dynamic variable. Although a relatively small amount of our population experienced a change in their documented BL allergy status during follow-up, the association of documented BL allergies with mortality was greater when modeling allergy status in a dynamic manner, and future studies should further evaluate whether changes in a patient’s documented BL allergy status over time affect the care they receive.

Our study also extends upon these previously completed cohort studies by analyzing an additional resistant infection of VRE, as well as evaluating the long-term association of documented BL allergies with AKI, which to the best of our knowledge, has not been previously described. Previous shorter-term studies have examined the association of documented BL allergies with AKI, with inconsistent results that have often not met statistical significance. Our results also did not find a statistically significant association of documented BL allergies with either stage 2 and 3 AKI or
stage 3 AKI, but did find a significant association when modeling documented BL allergy status as a
dynamic variable. Our analysis was limited by only using SCr level to evaluate AKI, and we were only
able to evaluate health care encounters where at least 1 SCr measurement was present. Future
studies should aim to improve upon the understanding of the long-term association of BL allergies
with AKI by including additional laboratory values and attempting to more directly link changes in
prescribing practices to AKI.

The long-term clinical outcomes of BL allergies are understudied, and our study addressed this
gap in the literature by being uniquely designed to evaluate the long-term clinical outcomes
associated with BL allergies in a novel population.12 Shorter-term studies41,42 have not consistently
found an association between BL allergies and mortality. However, longitudinal evaluations such as
the results of our study using a time-varying allergy status and the previous cohort studies conducted
by Blumenthal et al13,14 have more consistently identified potential positive associations of BL
allergies with increased mortality, and this may indicate that the mortality-related effects associated
with BL allergies become more apparent over an extended time.14 Future studies should further
explore the long-term effect of documented BL allergy status and mortality, as well as expand the
understanding of the long-term effects of BL allergy delabeling by comparing the outcomes for
patients who had BL allergies delabeled.

Limitations
Although our study had an overall large sample size of more than 20 000 patients, it is smaller than
previous cohort studies examining similar outcomes.14 Overall, our study used data from a single
regionally based health care system in western Pennsylvania and may not apply broadly outside this
region. The definition used to define AKI was limited to changes in SCr alone, which is further
complicated by the lack of evidence-supported consensus methods for the establishment of baseline
SCr, but is the first attempt to relate long-term effects of BL allergies to kidney-related outcomes.31
Our analysis was not able to evaluate whether the cause of death was related to infectious causes,
which would be valuable to understanding whether documented BL allergies have a differential
effect on these causes of death. Our population was also limited to patients with a diagnosis of
sepsis, pneumonia, and UTI between a 2-year span, and although limiting our cohort to these
diagnoses reduced the risk for immortal time bias and indication bias, it reduces the external
generalizability and sample size of our results. In addition, we were unable to account for the severity
of particular BL allergies, which would be of great interest to examining whether more severe
reactions are underlying the observed higher rates of mortality and resistant infections due to
necessitating a higher level of change in clinical practice than less severe allergies.

Conclusions
In this 12-year longitudinal analysis, we used generalized estimating equations to evaluate the long-
term clinical consequences of patients having a BL allergy documented in their EHR. The presence of
a documented BL allergy was not associated with a statistically significant difference in the odds of
all-cause mortality compared with patients without a documented BL allergy. Documented BL
allergies were associated with increased odds of antibiotic-resistant infections, including MRSA, VRE,
and the pooled odds of infection with MRSA, VRE, and C difficile. Health systems should support
accurate allergy labeling and reduce the risk of unnecessary BL avoidance to improve patient
outcomes.
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Author Contributions: Dr Gray had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition, analysis, or interpretation of data: Gray, Kirisci, Boyce, Kane-Gill.

Drafting of the manuscript: Gray, Kane-Gill.

Critical review of the manuscript for important intellectual content: All authors.

Statistical analysis: Gray, Kirisci.

Administrative, technical, or material support: Gray.

Supervision: Kirisci, Boyce, Kane-Gill.

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REFERENCES


**SUPPLEMENT 1.**

*eTable 1.* Definition of Pneumonia, UTI and Sepsis Using ICD-9 Codes

*eTable 2.* Full Model Summary of Generalized Estimating Equation Predicting All-Cause Mortality

*eTable 3.* Results of Generalized Estimating Equations Using Dynamic Allergy Status

*eTable 4.* Results Among Patients Whose β-Lactam Allergy Status Changed During Follow-up (Initial Allergy Status Held Constant)

*eTable 5.* Results Among Patients Whose β-Lactam Allergy Status Changed During Follow-up (Time-Varying Allergy Status)

*eTable 6.* Results Among Patients Whose β-Lactam Allergy Status Did Not Change During Follow-up

*eTable 7.* Results of Generalized Estimating Equations Sensitivity Analysis Excluding Baseline Serum Creatinine as a Covariate

*eTable 8.* Results of Generalized Estimating Equations Sensitivity Analysis Including Length of Stay

**SUPPLEMENT 2.**

Data Sharing Statement