

Impact of Reported Beta-Lactam Allergy on Inpatient Outcomes: A Multicenter Prospective Cohort Study

Derek R. MacFadden,¹ Anthony LaDelfa,² Jessica Leen,² Wayne L. Gold,¹ Nick Daneman,¹ Elizabeth Weber,⁴ Ibrahim Al-Busaidi,¹ Dan Petrescu,¹ Ilana Saltzman,¹ Megan Devlin,¹ Nisha Andany,¹ and Jerome A. Leis^{1,3}

¹Division of Infectious Diseases, Department of Medicine, ²Department of Medicine, and ³Centre for Quality Improvement and Patient Safety, University of Toronto, and ⁴Drug Safety Clinic, Sunnybrook Health Sciences Centre, Canada

(See the Editorial Commentary by Blumenthal and Shenoy on pages 911-3.)

Background. Reported allergy to beta-lactam antibiotics is common and often leads to unnecessary avoidance in patients who could tolerate these antibiotics. We prospectively evaluated the impact of these reported allergies on clinical outcomes.

Methods. We conducted a trainee-led prospective cohort study to determine the burden and clinical impact of reported beta-lactam allergy on patients seen by infectious diseases consultation services at 3 academic hospitals. The primary outcome was a composite measure of readmission for the same infection, acute kidney injury, *Clostridium difficile* infection, or drug-related adverse reactions requiring discontinuation. Predictors of interest were history of beta-lactam allergy and receipt of preferred beta-lactam therapy.

Results. Among 507 patients, 95 (19%) reported beta-lactam allergy; preferred therapy was a beta-lactam in 72 (76%). When beta-lactam therapy was preferred, 25 (35%) did not receive preferred therapy due to their report of allergy even though 13 (52%) reported non-severe prior reactions. After adjustment for confounders, patients who did not receive preferred beta-lactam therapy were at greater risk of adverse events (adjusted odds ratio [aOR], 3.1; 95% confidence interval [CI], 1.28–7.89) compared with those without reported allergy. In contrast, patients who received preferred beta-lactam therapy had a similar risk of adverse events compared with patients not reporting allergy (aOR, 1.33; 95% CI, .62–2.87).

Conclusions. Avoidance of preferred beta-lactam therapy in patients who report allergy is associated with an increased risk of adverse events. Development of inpatient programs aimed at accurately identifying beta-lactam allergies to safely promote beta-lactam administration among these patients is warranted.

Keywords. beta-lactam allergy; penicillin allergy; clinical outcome; quality improvement; antimicrobial stewardship.

Reported allergy to beta-lactam antibiotics is common and often leads to unnecessary avoidance in patients who could tolerate beta-lactam therapy. In fact, the majority of reported prior reactions are misclassified as allergies; moreover, many individuals with true prior immunoglobulin (Ig) E-mediated reactions have loss of hypersensitivity over time [1, 2].

Carrying a label of beta-lactam allergy is not inconsequential. Patients with reported allergies may be treated with alternative agents that can be clinically inferior [3] and pose increased risks of harm [4, 5]. Furthermore, alternative agents frequently have a broader spectrum of activity and may contribute to the emergence and spread of drug-resistant organisms [5].

Correctly confirming or refuting allergies to enable receipt of beta-lactam therapy, when indicated, is an important function of antibiotic stewardship [6–10]. Beta-lactam antibiotic agents are recommended first-line therapies for many infectious syndromes [6–

Clinical Infectious Diseases® 2016;63(7):904–10

9]. Currently, infectious diseases consultants make great efforts to verify details of reported prior allergies to beta-lactam agents in order to determine whether or not they can be safely prescribed. When history suggests a significant IgE-mediated allergy, patients often receive nonpreferred therapy because it is judged to be the safest option for the patient.

Whether or not the risk of allergy from beta-lactam use in some patients reporting allergy is outweighed by the toxicity or potentially inferior efficacy associated with alternate therapies has not been systematically evaluated. We hypothesized that receipt of alternative therapy when a beta-lactam agent is the preferred therapy would lead to worse clinical outcomes. To test this hypothesis, we conducted a trainee-led prospective cohort study to determine the burden and clinical impact of reported beta-lactam allergy on patients seen by infectious diseases consultation services at 3 academic hospitals.

METHODS

Infectious diseases residents developed and initiated the study as the initial phase of a division-wide, trainee-led quality improvement initiative [11] and took place at the following academic hospitals: Toronto General Hospital (417 beds), Mount Sinai Hospital (442 beds), and Sunnybrook Health Sciences Centre (824 beds).

Received 17 January 2016; accepted 15 June 2016; published online 11 July 2016. Correspondence: D. R. MacFadden, 200 Elizabeth Street 13EN-213, University Health Network, Toronto, Ontario, Canada M5G 2C4 (derek.macfadden@mail.utoronto.ca).

[©] The Author 2016. Published by Oxford University Press for the Infectious Diseases Society of America. All rights reserved. For permissions, e-mail journals.permissions@oup.com. DOI: 10.1093/cid/ciw462

Toronto General Hospital and Mount Sinai Hospital share the same teaching service and were considered jointly (TGH/MSH); Sunnybrook Health Sciences Centre represented a separate teaching service (SHSC). Participating trainees used a point-of-care electronic data entry system for prospective data collection. Research ethics boards at the 3 participating hospitals approved the study. The need for individual patient consent was waived.

Eligibility

The study population was comprised of all inpatients seen in consultation by infectious disease services at the participating hospitals between April 2014 and January 2015 on days that the subspecialty infectious diseases residents were present for the review of cases. The days infectious diseases residents were present included both weekdays and weekends; they were routinely absent for 1 half-day per week of scheduled teaching, without other systematically excluded days. Only initial patient assessments were considered; repeat consultations were not included in the analysis.

Prospective Assessment of Beta-Lactam Allergy

Participating infectious diseases residents recorded study data using encrypted database software on password-protected tablets. This was done during consultation review rounds on the days they were present for service. Variables were collected at the time of patient consultation and included historical: history of beta-lactam allergy, characterization of previous allergic reaction (IgE-mediated with urticaria, bronchospasm, angioedema, or anaphylaxis; rash; Stevens Johnson syndrome [SJS], toxic epidermal necrolysis [TEN], and drug rash eosinophilia and systemic symptoms [DRESS]; serum sickness; other, with option to specify); date of consultation, teaching service, referring service; demographic (age, gender, immunocompromise, pregnancy); and therapeutic (preferred antibiotic therapy and initial chosen antibiotic therapy). Immunocompromise was defined as presence of chronic human immunodeficiency virus infection, solid organ transplantation, stem cell transplantation, primary immunodeficiency, or any patient receiving chemotherapy or immunomodulators. Preferred and chosen antibiotic therapies were determined by the consultant infectious diseases service based on the initial patient presentation and assessment. IgE-mediated reactions or other serious reactions, including SJS, TEN, or DRESS, were classified as "severe" reactions. For simplicity of analysis, only 1 antibiotic was recorded that represented the most important component of the regimen (eg, piperacillin/tazobactam for treatment of febrile neutropenia, vancomycin for empiric treatment of gram-positive cocci in the blood, or ceftriaxone for community acquired pneumonia requiring admission). De-identified data were stored on the encrypted devices and transferred at regular intervals to a secure common server.

Review of Patient Outcomes

Additional patient variables and outcome data were collected and abstracted in a second data collection step by 2 trainees. This occurred after the initial assessment by the clinical service provider using comprehensive electronic medical records (including scanned medical documents). Variables/outcomes of interest included: Historical (date of admission, date of discharge, length of stay, Charlson Comorbidity Index [12]), and Therapeutic/Outcome (indication for antibiotic therapy, survival to discharge, readmission for the same infection, duration of antibiotic therapy, microbiologically confirmed Clostridium difficile infection (CDI) within 3 months of antibiotic initiation, acute kidney injury defined by Risk, Injury, Failure, Loss, and End-stage kidney disease criteria as >50% reduction in glomerular filtration rate or doubling of baseline creatinine [13], and antibiotic-related adverse reactions requiring discontinuation). The index admission was considered as the time frame up until discharge or in-hospital death. We did not capture specific data on readmission diagnoses apart from whether or not they were associated with the index infection. Point-of-care data were also confirmed during the clinical review process where possible. In order to confirm reproducibility of data abstraction, 7 key covariates among 10% of cases were randomly chosen and double-abstracted by independent chart reviewers, and a kappa statistic of interuser variability was calculated, which was determined to be 94%. Two infectious diseases physicians reviewed the final data for completeness and clinical accuracy and to resolve any discrepancies.

Data Analyses

The primary predetermined outcome was treatment-related adverse event. This was comprised of any of the following outcomes: acute kidney injury while on treatment, CDI (within 3 months of treatment), suspected drug-related adverse reaction while on treatment and requiring discontinuation, or readmission with the same infection. The individual outcomes, along with mortality, were also evaluated as secondary endpoints. In order to evaluate the impact of reported beta-lactam allergy on these outcomes, we categorized the main predictor variable as follows: patients with no reported beta-lactam allergy; patients with reported beta-lactam allergy for whom preferred therapy was not a beta-lactam agent; patients with reported beta-lactam allergy for whom preferred therapy was a beta-lactam agent and the preferred beta-lactam agent was administered; and patients with a history of reported beta-lactam allergy for whom the preferred treatment was a beta-lactam agent, but an alternative antibiotic agent was administered. While uncommon, if an individual with a reported beta-lactam allergy received a beta-lactam agent, but it was not the preferred beta-lactam agent, they were classified as patients with reported beta-lactam allergy for whom preferred therapy was a beta-lactam agent and the preferred beta-lactam agent was administered. Univariate analysis of the primary and secondary outcomes was performed using χ^2 or Fisher exact testing. Multivariable logistic regression analysis, with the primary outcome of adverse events, the main predictor variable, and remaining covariates, was performed. Covariates were selected for the model based on clinical judgment and prior evidence, with the goal of identifying potential confounders between the predictor and outcome. Selected

Table 1. Characteristics of Patients Seen by the Infectious Diseases Consultation Services Stratified by Reported Beta-Lactam Allergy and Preferred and Administered Treatments

		Reported History of	Reported History of Beta-Lactam Allergy Where Preferred Therapy is a Beta-Lactam Agent	
Characteristic	No Reported History of Beta-Lactam Allergy (%)	Beta-Lactam Allergy Where Preferred Therapy is Not a Beta-Lactam Agent (%)	Preferred Therapy Received (%)	Preferred Therapy Not Received (%)
No. of patients	412	23	47	25
Age, y				
Median	65	69	59	64
IQR	24	34	30	20
Sex				
Male	254 (62)	9 (39)	30 (64)	3 (12)
Female	158 (38)	14 (61)	17 (36)	22 (88)
Hospital				
Toronto General Hospital/Mount Sinai Hospital	213 (52)	16 (70)	28 (60)	4 (16)
Sunnybrook Health Sciences Centre	199 (48)	7 (30)	19 (40)	21 (84)
Referring service				
Medical	207 (50)	13 (57)	25 (53)	11 (44)
Surgical	140 (34)	10 (43)	11 (23)	10 (40)
Critical (emergency room, intensive care unit, critical care unit)	65 (16)	0	11 (23)	4 (16)
Length of stay (days)				
Median	14	10	12	15
IQR	25	31	19	18
Duration of treatment (days)				
Median	15	18	14	19
IQR	33	32	18	33
Pregnant	5 (1)	1 (4)	1 (2)	1 (4)
Immunocompromised	72 (17)	5 (22)	9 (19)	3 (12)
Charlson comorbidity index				
Median	4	5	4	4
IQR	5	4	5	4
Antibiotic administered				
Penicillin	45 (11)	0	7 (15)	0
Cephalosporin	124 (30)	0	22 (47)	1 (4)
Beta-lactam/beta-lactamase inhibitor	101 (25)	0	8 (17)	1 (4)
Carbapenem	34 (8)	1 (4)	10 (21)	3 (12)
Fluoroquinolone	22 (5)	5 (22)	0	8 (32)
Clindamycin	1 (0.2)	1 (4)	0	5 (20)
Glycopeptide	50 (12)	12 (52)	0	5 (20)
Aminoglycoside	3 (1)	1 (4)	0	1 (4)
Other	32 (8)	3 (13)	0	1 (4)
Reported allergy description				
IgE-mediated reaction ^a		7 (30)	7 (15)	11 (44)
Drug rash, eosinophilia, systemic symptoms/Stevens Johnson syndrome/toxic epidermal necrolysis		0	0	1 (4)
Rash		9 (40)	15 (32)	9 (36)
Other or Unknown		7 (30)	25 (53)	4 (16)

Abbreviations: IgE, immunoglobulin E; IQR, interquartile range.

^a Immunoglobulin E was classified as urticaria, bronchospasm, angioedema, or anaphylaxis.

model covariates included age, sex, hospital, referring service, length of stay, duration of antibiotic therapy, Charlson comorbidity index, and immunocompromise. All models demonstrated Hosmer-Lemeshow goodness-of-fit test P values >.05. All analyses were performed using SAS, version 9.4 (Cary, North Carolina).

RESULTS

Of 542 patients receiving antibiotic therapy, 21 (4%) were excluded due to incorrect linkage data, 5 (1%) were excluded due to incomplete data, and 9 (2%) were excluded due to duplication. Baseline characteristics of the 507 patients who received

Table 2. Additional Characteristics of Patients Seen on the Infectious Diseases Consultation Services Stratified by Reported Beta-Lactam Allergy and Preferred and Administered Treatments

Characteristic	No Reported History of Beta-Lactam Allergy (%)	Reported History of Beta-Lactam Allergy Where Preferred Therapy is Not a Beta-Lactam Agent (%)	Reported History of Beta-Lactam Allergy Where Preferred Therapy is a Beta-Lactam Agent	
			Preferred Therapy Received (%)	Preferred Therapy Not Received (%)
Site of infection				
Bacteremia without Primary source	59 (14)	4 (17)	14 (30)	4 (16)
Skin/soft tissue	54 (13)	3 (13)	7 (15)	5 (20)
Bone/joint	53 (13)	5 (22)	5 (11)	2 (8)
Gastrointestinal	60 (15)	5 (22)	5 (11)	4 (16)
Genitourinary	52 (13)	2 (9)	5 (11)	5 (20)
Neurologic	19 (5)	1 (4)	0	0
Cardiac	23 (6)	1 (4)	2 (4)	0
Pulmonary	56 (14)	2 (9)	8 (17)	4 (16)
Vascular	6 (1)	0	0	0
Multisystem	5 (1)	0	0	0
Other	25 (6)	0	1 (2)	1 (4)
Baseline creatinine (µmol/L)				
Median	83	83	89	90
Interquartile range	59	85	66	117
Comorbidities				
Diabetes mellitus	101 (25)	6 (26)	11 (23)	11 (44)
Congestive heart failure	37 (9)	4 (17)	4 (9)	25 (5)
Chronic lung disease	31 (8)	5 (22)	8 (17)	1 (4)
Prior myocardial infarction	66 (16)	5 (22)	11 (23)	12 (12)
Stroke/transient ischemic attack	43 (10)	5 (22)	7 (15)	2 (8)
Dementia	21 (5)	2 (9)	2 (4)	2 (4)
Cancer	150 (37)	8 (35)	10 (21)	8 (32)

antibiotic therapy, stratified by report of beta-lactam allergy and preferred/chosen therapy, are listed in Table 1. Additional characteristics are listed in Table 2. Of 95 (19%) patients with reported beta-lactam allergy, preferred therapy was a beta-lactam agent in 72 (76%) cases and non-beta-lactam agents in 23 (24%) cases. In the group of patients with reported beta-lactam allergy, where beta-lactam was considered preferred therapy, 47 (65%) received a beta-lactam agent, while 25 (35%) received non-beta-lactam therapy. Less than half (48%) of patients who reported beta-lactam allergy and did not receive preferred beta-lactam therapy reported a history of a severe reaction, which was significantly higher than in the group reporting beta-lactam allergy who received preferred beta-lactam therapy (15%), P = .004.

Univariate and multivariable analyses are presented in Table 3 and Supplementary Table 1. Patients with reported beta-lactam allergy who did not receive preferred betalactam therapy were more likely to have an adverse event compared with those who did not report beta-lactam allergy (unadjusted odds ratio [uOR], 3.43; 95% confidence interval [CI], 1.48–7.96). This primary endpoint was driven largely by increased rates of readmission and adverse reactions (requiring discontinuation of therapy), which were both significantly more frequent than in the group of patients not reporting beta-lactam allergy. There were no significant differences in mortality when compared with patients not reporting allergy.

After adjusting for potential confounders, multivariable logistic regression analysis confirmed that patients reporting beta-lactam allergy who did not receive preferred beta-lactam therapy were more likely to have an adverse outcome than those patients not reporting beta-lactam allergy (aOR, 3.18; 95% CI, 1.28-7.89). There was no significant difference in adverse outcomes detected between patients with reported betalactam allergy who nonetheless received preferred beta-lactam therapy and patients who did not report beta-lactam allergy (aOR, 1.33; 95% CI, .62-2.87). In order to adjust for possible confounding by a diagnosis of bacteremia without an identified primary source, an unbalanced diagnosis across the groups (Table 2), we performed an additional regression analysis by adding this diagnosis to the existing logistic regression model, which yielded no significant change in the results (Supplementary Table 1). Moreover, when restricting the study population to either only those surviving to discharge or only those surviving to discharge or event, both analyses resulted in no significant changes to the findings (Supplementary Table 1).

Table 3. Comparison of Outcomes Including Readmission, *Clostridium difficile* Infection, Adverse Drug Reaction, Acute Kidney Injury, and Mortality According to Reported Beta-Lactam Allergy and Treatment Administered

Outcome	No Reported History of Beta-Lactam Allergy (%)	Reported History of Beta-Lactam Allergy Where Preferred Therapy is Not a Beta-Lactam Agent (%)	Reported History of Beta-Lactam Allergy Where Preferred Therapy is a Beta-Lactam Agent	
			Preferred Therapy Received (%)	Preferred Therapy Not Received (%)
Primary Outcome				
(readmission, CDI, drug reaction, or AKI)	67 (16)	5 (22)	10 (21)	10 (40) ^a
Secondary Outcome				
Readmission	24 (6)	1 (4)	2 (4)	6 (24) ^a
CDI	18 (4)	1 (4)	0	0
Drug reaction	2 (0.5)	0	4 (9) °	2 (8) ª
AKI	29 (7)	3 (13)	5 (11)	4 (16)
Mortality	55 (13)	1 (4)	10 (21)	2 (8)
Univariate analysis				
Primary Outcome				
(readmission, CDI, drug reaction, or AKI)		1.43 (0.51–3.99)	1.39 (0.66–2.93)	3.43 (1.48–7.96) ^a
Multivariable analysis ^b				
Primary Outcome				
(readmission, CDI, drug reaction, or AKI)		1.40 (0.49-4.01)	1.33 (0.62–2.87)	3.18 (1.28–7.89) [◎]

No reported history of beta-lactam allergy is reference for univariate/multivariable odds ratios (ORs). Univariate/multivariable results expressed as ORs and 95% confidence intervals in parentheses. Abbreviations: AKI, acute kidney injury (RIFLE criteria) [13]; CDI, *Clostridium difficile* infection.

^a Significant (P < .05) (in bold) compared with no history of reported beta-lactam allergy.

^b Multivariable model adjusted for age, sex, teaching service, referring service, length of stay, duration of antibiotic therapy, Charlson comorbidity index [12], and immunocompromise (Supplementary Table 1).

DISCUSSION

In this multicenter prospective cohort study of inpatients seen by infectious diseases consultation services, reported beta-lactam allergy was common and led to a significant proportion of patients receiving alternative antimicrobial therapy. This avoidance of preferred beta-lactam therapy was associated with increased adverse outcomes, including readmission to the hospital and adverse reactions that required discontinuation of therapy.

The impact of carrying a label of beta-lactam allergy has been documented in prior retrospective studies. One single-center study suggested increased mortality rates and intensive care admissions among patients labelled as having a penicillin allergy [4]. Another retrospective cohort study of 51 582 patients found that carrying a label of penicillin allergy was associated with prolonged length of stay, an increased rate of CDI, as well as acquisition of antibiotic-resistant organisms, such as vancomycin-resistant *enterococci* and methicillin-resistant *Staphylococcus aureus* [5].

In contrast, the prospective nature of our study allowed us to determine the patient's preferred therapy and best available allergy history and to determine the impact of reported allergy on clinical care decisions and outcomes. This analysis suggests that increased adverse events among patients labelled with a beta-lactam allergy may be a consequence of use of alternative antibiotic therapy. In fact, those who received preferred betalactam therapy despite reporting allergy had a similar risk of adverse outcomes compared with patients not reporting allergy. Interestingly, one prior study found no increase in the rates of readmission among those reporting beta-lactam allergy [4], possibly due to the inability to separate out the patients who received preferred beta-lactam therapy despite their allergy label. Of note, a previous study in a tertiary care center in Quebec, Canada, noted that 61% of patients with a history of beta-lactam allergy received beta-lactam therapy, similar to our findings; however, it was not specified in the study whether they received the specific preferred beta-lactam [14].

The increased readmissions noted among the patients reporting beta-lactam allergy who did not receive preferred beta-lactam therapy has at least 2 plausible explanations. First, alternate therapies often represent inferior treatment to beta-lactams. For example, vancomycin treatment for methicil-lin-susceptible *S. aureus* bacteremia is associated with recrudescence of disease [3]. Second, adverse reactions to certain non-beta-lactam drugs occur with higher frequency than reactions to beta-lactam agents, which may also contribute to readmission during the course of treatment [15].

It is worth highlighting that the risk of antibiotic-related reactions that required discontinuation of therapy was higher among all patients carrying a label of beta-lactam allergy, regardless of whether or not they received preferred beta-lactam therapy. This finding may be related to the underlying propensity for multiple drug allergies in some patients [16]. It is possible that the preponderance of women who did not receive preferred therapy could have been due to a higher prevalence of multiple drug allergy syndrome in females [13]; however, sex-based adjustment was performed in the analysis. Although there were differences in the classes of antibiotics received by patients reporting beta-lactam allergy, including agents known to increase the development of CDI (fluoroquinolones and clindamycin) [17], there was no difference in the incidence of CDI, which may be related to sample size and to the significant use of antibiotic therapy associated with CDI (third-generation cephalosporins) in patients not reporting beta-lactam allergy.

Recently, the Association of Medical Microbiology and Infectious Diseases-Canada released its Choosing Wisely statements, which included the declarative statement: "Don't prescribe alternate second-line antibiotics to patients reporting non-severe reactions to penicillin when beta-lactams are the recommended first-line therapy" [18]. In our study, the avoidance of betalactam therapy in patients for whom beta-lactam therapy was preferred occurred more frequently among patients with more serious allergy histories, in keeping with an increased degree of physician caution. Despite this, more than one-third of patients who had a clinical indication for beta-lactam did not get preferred treatment even though over half of these had a history of non-severe reactions. This finding suggests that there is marked room for improvement in the prescribing of preferred beta-lactam therapy in these patients. In this context, the Center for Disease Control and Prevention recently published an educational fact sheet to raise awareness regarding the unnecessarily broad-spectrum antibiotics prescribed for patients with penicillin allergy [19].

Our study highlights the significant need to develop formal models of care within infectious diseases practices in order to objectively assess reported beta-lactam allergies and optimize beta-lactam use among patients without IgE-mediated allergy or other serious reactions. A recent quasi-experimental study at a single hospital using a detailed allergy history suggested that patients with reported allergies consisting of rashes (without features of SJS/TEN or IgE-mediated events) could be safely trialed on the preferred beta-lactam therapy if simple test dosing was used [20]. Recently, beta-lactam skin testing has also been proposed as an antibiotic stewardship activity to exclude IgE-mediated allergies and promote the use of first-line betalactam therapy in patients with reported allergy who test negative [21, 22]. While penicillin skin testing has been shown to have a negative predictive value of 97%-99% when used in the outpatient setting, further research is needed to evaluate the performance characteristics and feasibility of inpatient skin testing [1].

This study was designed and implemented by infectious diseases trainees during the initial descriptive phase of a continuous quality improvement course that was incorporated into their training curriculum, which builds on a need to introduce self-audit skills and practice improvement and resource stewardship at the trainee level [23]. The participating residents used a custom point-of-care data entry approach with mobile and secure data entry. The advantage of this method is that it allowed collection of the most accurate available allergy histories and evaluation of the impact of these allergies at the point of clinical decision-making. This work builds on the movement of introducing continuous quality improvement into trainee programs [23].

This study has several limitations. One limitation is the use of a composite outcome, which was required to generate sufficient power over the anticipated study period but which limited the ability to analyze all of the outcomes individually. However, the composite outcome is comprised of clinically relevant individual outcomes and reflects treatment-related adverse outcomes as a whole. A second limitation is that the impact of reported beta-lactam allergy among patients encountered by the infectious diseases consultation services may be more significant compared with other hospitalized patients. However, the prevalence of beta-lactam allergy as a whole in our sample is not largely different than population estimates [24, 25] and suggests this sample was not heavily biased to referral by allergy history alone. Moreover, infectious diseases consultants are often consulted for complex cases, illustrated by the prolonged length of stay (10-15 days) compared with average ranges for the participating hospitals (5-7 days), underscoring the importance of optimizing antibiotic treatment in these patients. Lastly, due to the nature of the outcome data abstraction, it was not possible to blind abstractors to the exposure at the time of consultation and initial data entry. However, during the double-abstraction evaluation, the abstractors were blinded, and a high kappa was still achieved, arguing against the presence of differential misclassification.

Our multicenter prospective cohort study suggests that avoidance of preferred beta-lactam therapy in patients who report allergy is associated with an increased risk of adverse events. Since more than half of patients who received alternate therapy had nonsevere allergy histories, increasing beta-lactam use in these patients may improve patient outcomes. Development of inpatient programs aimed at accurately identifying beta-lactam allergies in order to safely promote beta-lactam administration among those with reported allergy is warranted.

Supplementary Data

Supplementary materials are available at http://cid.oxfordjournals.org. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Note

Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

- Blanca M, Torres MJ, Garcia JJ, et al. Natural evolution of skin test sensitivity in patients allergic to beta-lactam antibiotics. J Allergy Clin Immunol 1999; 103:918–24.
- Solensky R, Khan D. Drug allergy: an updated practice parameter. Ann Allergy Asthma Immunol 2010; 105:259–73.
- McDanel J, Perencevich E, Diekema D, et al. Comparative effectiveness of betalactams versus vancomycin for treatment of methicillin-susceptible *Staphylococcus aureus* bloodstream infections among 122 hospitals. Clin Infect Dis 2015; 61: 361–7.
- Charneski L, Deshpande G, Smith S, et al. Impact of an antibiotic allergy label in the medical record on clinical outcomes in hospitalized patients. Pharmacotherapy 2011; 31:742–7.
- Macy E, Contreras R. Healthcare use and serious infection prevalence associated with penicillin "allergy" in hospitalized patients: a cohort study. J Allergy Clin Immunol 2014; 133:790–6.
- Mandell L, Wunderink R, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007; 44:S27–72.
- Tunkel A, Hartman B, Kaplan S, et al. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis 2004; 39:1267–84.
- Solomkin J, Mazuski J, Bradley J, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Clin Infect Dis 2010; 50:133–64.
- Stevens D, Bisno A, Chambers H, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis 2014; 1:1–43.
- Dellit T, Owens R, McGowan J, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antibiotic stewardship. Clin Infect Dis 2007; 44:159–77.
- Wong BM, Goguen J, Shojania KG. Building capacity for quality: a pilot colearning curriculum in quality improvement for faculty and resident learners. J Grad Med Educ 2013; 5:689–93.
- Charlson M, Pompei P, Ales K, MacKenzie C. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987; 40:373–83.

- Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute renal failure: definition, outcome measures, animal models, fluid therapy and information technology needs—The Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004; 8:R204–12.
- Picard M, Begin P, Bouchard H, et al. Treatment of patients with a history of penicillin allergy in a large tertiary-care academic hospital. J Allergy Clin Immunol 2013; 1:252–7.
- Shehab N, Patel PR, Srinivasan A, Budnitz DS. Emergency department visits for antibiotic-associated adverse events. Clin Infect Dis 2008; 47:735–43.
- Gex-collet C, Helbling A, Pichler W. Multiple drug hypersensitivity—proof of multiple drug hypersensitivity by patch and lymphocyte transformation tests. J Invest Allergol Clin Immunol 2005; 15:293–6.
- Owens R, Curtis D, Gaynes R, et al. Antimicrobial-associated risk factors for *Clos-tridium difficile* infection. Clin Infect Dis 2008; 46:S19–31.
- Choosing Wisely Canada: AMMI Canada Recommendations. Association of Medical Microbiology and Infectious Disease Canada. Available at: http://www. choosingwiselycanada.org/wp-content/uploads/2015/09/Medical-microbiologyand-Infectious-Disease.pdf. Accessed 29 April 2016.
- Is It Really a Penicillin Allergy? Centers for Disease Control. Available at: http:// www.cdc.gov/getsmart/week/downloads/getsmart-penicillin-factsheet.pdf. Accessed 29 April 2016.
- Blumenthal K, Shenoy E, Varughese C, et al. Impact of a clinical guidelines for prescribing antibiotics to inpatients reporting penicillin or cephalosporin allergy. Ann Allergy Asthma Immunol 2015; 115:294–300.
- Unger N, Gauthier T, Cheung L. Penicillin skin testing: potential implications for antibiotic stewardship. Pharmacotherapy 2013; 33:856–67.
- Blumenthal K, Parker RA, Shenoy ES, Walensky RP. Improving clinical outcomes in patients with methicillin-sensitive *Staphylococcus aureus* bacteremia and reported penicillin allergy. Clin Infect Dis 2015; 61:741–9.
- Jeffrey J. Quality improvement in resident education: a pilot project to mitigate metabolic side effects from atypical antipsychotic medications in youth. BMJ Qual Improv Report 2015; doi:10.1136/bmjquality.u208804.w3544.
- 24. NICE. Drug allergy: diagnosis and management of drug allergy in adults children and young people. Clinical Guideline 183. NICE, **2014**. Available at: www.nice.org. uk/guidance/CG183.
- Trubiano J, Cairns K, Evans J, et al. The prevalence and impact of antimicrobial allergies and adverse drug reactions at an Australian tertiary centre. BMC Infect Dis 2015; 15:572.