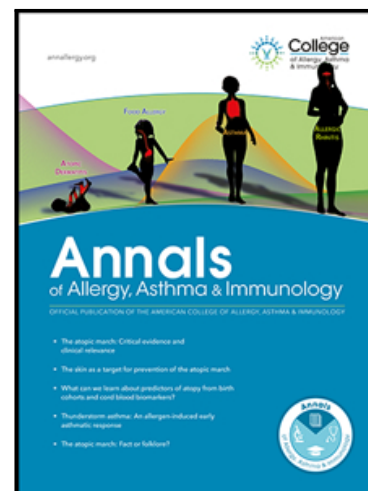


Association of Beta-Lactam Allergy Documentation and Antibiotic Use in Patients with Febrile Neutropenia

Caitlin Naureckas Li MD , Xiaoqing Fu MS ,
Christian M. Mancini BS , Yuqing Zhang DSc ,
Kimberly G. Blumenthal MD, MSc

PII: S1081-1206(21)00355-0
DOI: <https://doi.org/10.1016/j.anai.2021.05.009>
Reference: ANAI 3602



To appear in: *Annals of Allergy, Asthma Immunology*

Received date: 11 February 2021
Revised date: 29 March 2021
Accepted date: 9 May 2021

Please cite this article as: Caitlin Naureckas Li MD , Xiaoqing Fu MS , Christian M. Mancini BS , Yuqing Zhang DSc , Kimberly G. Blumenthal MD, MSc , Association of Beta-Lactam Allergy Documentation and Antibiotic Use in Patients with Febrile Neutropenia, *Annals of Allergy, Asthma Immunology* (2021), doi: <https://doi.org/10.1016/j.anai.2021.05.009>

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Association of Beta-Lactam Allergy Documentation and Antibiotic Use in Patients with Febrile Neutropenia

Caitlin Naureckas Li, MD^{1,2,3}

Xiaoqing Fu, MS^{4,5}

Christian M. Mancini, BS^{4,5}

Yuqing Zhang, DSc^{3,4,5}

Kimberly G. Blumenthal, MD, MSc^{2,3,4,5}

¹Division of Infectious Diseases, Boston Children's Hospital, Boston, MA, USA

²Lawrence Center for Quality and Safety, Massachusetts General Hospital, Boston, MA, USA

³Harvard Medical School, Boston, MA, USA

⁴Division of Rheumatology, Allergy, and Immunology, Department of Medicine, Massachusetts General Hospital, Boston, MA, USA

⁵The Mongan Institute, Massachusetts General Hospital, Boston, MA, USA

Corresponding Author:

Kimberly G. Blumenthal, MD, MSc

Division of Rheumatology, Allergy and Immunology, The Medical Practice Evaluation Center,

The Mongan Institute, Massachusetts General Hospital

100 Cambridge Street, 16th Floor, Boston, MA 02114

p-(617) 726-3850, f-(617) 724-7441

email: kblumenthal@mgh.harvard.edu; twitter: @KimberlyBlumen1

Conflicts of Interest: Dr. Blumenthal reports a beta-lactam allergy clinical decision support tool licensed to Persistent Systems. Caitlin Naureckas Li, Xiaoqing Fu, MS, Christian Mancini, and Yuqing Zhang, DSc report no conflicts of interest.

Funding Source: Dr. Naureckas Li is supported by the Harvard Medical School Fellowship in Safety and Quality through CRICO and the Risk Management Foundation. Dr. Blumenthal receives career development support from the National Institutes of Health (NIH) K01AI125631, the American Academy of Allergy Asthma and Immunology (AAAAI) Foundation, and the Massachusetts General Hospital (MGH) Claflin Distinguished Scholar Award. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH, AAAAI Foundation, nor the MGH. Funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; nor preparation, review, or approval of the manuscript. No funding for this study was received from Vizient, Inc.

Key Words: Beta-lactam, allergy, penicillin, cephalosporin, febrile neutropenia

Abbreviations:

Adjusted Odds Ratios (aOR)

Confidence Interval (CI)

Febrile Neutropenia (FN)

Infectious Diseases Society of America (IDSA)

Intensive Care Unit (ICU)

Interquartile Range (IQR)

Methicillin-Resistant *Staphylococcus aureus* (MRSA)

Standard Deviation (SD)

Vancomycin Resistant *Enterococcus* (VRE)

Approximately 10% of patients report an allergy to penicillin antibiotics, although over 90% can safely receive penicillin and other beta-lactams.¹ Patients with beta-lactam allergies documented in their chart may receive antibiotics that are not first-line, which can lead to healthcare-associated infections, antimicrobial resistance, and increased costs.²

Neutropenia is a common side effect of cytotoxic chemotherapy requiring over 100,000 hospitalizations per year,³ and fever can be the only sign of serious infection. To guide clinicians in selecting antimicrobials in febrile neutropenia (FN), an Infectious Diseases Society of America (IDSA) clinical practice guideline emphasizes the need for an anti-Pseudomonal beta-lactam antibiotic other than ceftazidime (i.e. cefepime, imipenem-cilastatin, meropenem, or piperacillin-tazobactam) due to increased mortality associated with gram-negative rod bacteremia, particularly *Pseudomonas aeruginosa*.⁴ Ceftazidime monotherapy is not

recommended given limited activity against gram-positive organisms and decreasing susceptibility in gram-negative bacteria.⁴

We hypothesized that patients with documented beta-lactam allergy would be less likely to receive first-line antibiotic management of FN.

This was a secondary analysis of a cross-sectional nationwide study of hospitalized patients. Members of Vizient Inc.'s Acute Care Hospital Groups were invited to participate via listserv. Participating sites completed intake questionnaires (09/18/2018-10/12/2018), and additional hospital demographics were extracted from the Definitive Healthcare database.⁵

Participating sites entered de-identified clinical data from a single day (10/16/2018-01/13/2019) for all admitted patients receiving any antibiotic. If the site was not able to enter data for all patients receiving antibiotics, a random subset was identified. The targeted infection was identified by manual electronic health record (EHR) review and selected from a list of 19 specific infections, "other," and "unknown;" more than one selection could be made. For this study, we included any patient treated for "neutropenic fever."

Subjects were grouped by beta-lactam allergy status (penicillin and/or cephalosporin allergy in the EHR). The primary outcome was treatment with first-line FN therapy, an anti-Pseudomonal beta-lactam agent other than ceftazidime.⁴ Secondary outcomes were receipt of alternative antibiotics (ceftazidime and non-beta lactam antibiotics with activity against *Pseudomonas aeruginosa*) and receipt of adjunctive antibiotics (all others).

For categorical variables, we reported numbers with frequencies; for continuous variables we calculated means and standard deviations or medians and interquartile ranges. Chi-squared and T-tests were used for univariate comparisons. We used two-sided p-values and considered $p < 0.05$ considered to be statistically significant. We designated age, sex, race/ethnicity, ICU

admission status, MRSA colonization, VRE colonization, and hospital day *a priori* as potential confounding variables for multivariable models. We used Generalized Estimating Equations models with logit link used to account for correlation within a hospital.

We report adjusted odds ratios (aOR) with 95% confidence intervals (CIs) as our measure of effect. SAS version 9.4 (Cary, NC, US) was used for statistical analyses.

The MassGeneral Brigham Institutional Review Board determined that this study was not human subjects research.

Of 147 eligible hospital sites, 106 fully participated with complete data for 10,992 inpatients. There were 290 (2.6%) unique patients with FN from 64 U.S. hospitals.

Fifty-five patients (19%) had documented beta-lactam allergies: 36 (65%) with documented penicillin allergy, 12 (22%) with documented cephalosporin allergy, and 7 (13%) with both. The most commonly documented reactions were rash (56%), unknown (16%), and urticaria (13%).

Patients with documented beta-lactam allergy were older and more frequently female and white compared to patients without. Patients with documented beta-lactam allergy were less likely to receive first-line FN antibiotic agents (36% vs 63%, Table 1). In patients with documented allergy, cefepime (36%) and meropenem (35%) were more commonly used than piperacillin-tazobactam (9%). Compared to patients without documented beta-lactam allergy, patients with allergy had lower cefepime use (36% vs 63%) and higher meropenem use (35% vs 11%). Patients with allergy were more likely to receive an alternative antibiotic (22% vs 11%). There was no difference in adjunctive antibiotic use by allergy status (55% vs 49%).

After adjustment, patients with FN and documented beta-lactam allergy were less likely to receive first-line antibiotic agents for FN (aOR 0.35, [95% CI 0.20, 0.63]). Patients with

allergy were also more likely to receive alternative antibiotics (unadjusted OR 2.24 [1.05, 4.81]) and comparably likely to receive adjunctive antibiotics (aOR 1.24 [0.67, 2.32]).

In this national cross-sectional sample of inpatients with FN, documented beta-lactam allergy was associated with a significant 65% decrease in use of first-line antibiotics after adjustment for potential confounders. Previous research demonstrated that patients with malignancy reporting beta-lactam allergies had increased mortality attributed to differences in antibiotic administration.⁶ However, large studies, including in patients with cancer, demonstrate that the vast majority of inpatients with documented penicillin allergy would have their allergy disproved with formal testing.^{1,7,8}

We noted no significant difference in use of adjunctive antibiotics by documented beta-lactam allergy status. While IDSA guidelines do not recommend MRSA-directed therapy for all patients with FN, they discuss MRSA coverage when catheter-related infection is suspected.⁴ As many patients receiving marrow-suppressive chemotherapy require a central line for treatment administration, we hypothesize this concern may have been a significant driver of vancomycin use. Similarly, both the IDSA and the American Society of Clinical Oncology recommend that patients at risk for *Pneumocystis jirovecii* pneumonia (PJP) receive prophylaxis and trimethoprim-sulfamethoxazole is considered first-line.⁹

Although first-line therapy use was overall decreased in patients with beta-lactam allergy labels, we found a higher frequency of meropenem use in this group. This finding suggests increased comfort prescribing carbapenems over cephalosporins in patients with documented beta-lactam allergies.

Because this study recruited through an antibiotic stewardship listserv within Vizient, data may not be generalizable. We had to assume all inpatients with FN were high-risk, although

some may have been low-risk and thus eligible for oral therapy. However, any low-risk inpatients would be expected to be distributed evenly by documented beta-lactam allergy status. Finally, although we were able to measure first-line, guideline-concordant antibiotic use for FN, we could not evaluate key patient outcomes such as sepsis or death. Additional work is needed to further characterize the impact of documented beta-lactam allergy on FN outcomes, but these data suggest systematic strategies to remove inaccurate beta-lactam allergy labels may benefit this high-risk patient population.

Acknowledgements:

The authors are grateful to Michael Postelnick, RPh, BCPS AQ-ID; Lucas T. Schulz, PharmD, BCIDP; Tanaya Bhowmick, MD; Francesca Lee, MD; and Vizient, Inc. for supporting this study through use of their hospital network.

References:

1. Blumenthal KG, Shenoy ES, Varughese CA, Hurwitz S, Hooper DC, Banerji A. Impact of a Clinical Guideline for Prescribing Antibiotics to Inpatients Reporting Penicillin or Cephalosporin Allergy. *Ann Allergy Asthma Immunol*. 2015;115(4):294-300.e2.
2. Macy E, Contreras R. Health Care Use and Serious Infection Prevalence Associated with Penicillin “Allergy” in Hospitalized Patients: A Cohort Study. *J Allergy Clin Immunol*. 2014;133(3):790-796.
3. Tai E, Guy GP, Dunbar A, Richardson LC. Cost of Cancer-Related Neutropenia or Fever Hospitalizations, United States, 2012. *J Oncol Pract*. 2017;13(6):e552-e561.
4. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer: 2010 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2011;52(4):e56-e93.
5. Medicare Provider Cost Report Public Use Files, Centers for Medicare & Medicaid Services. Accessed August 24, 2020. <https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Medicare-Provider-Cost-Report>
6. Huang K-HG, Cluzet V, Hamilton K, Fadugba O. The Impact of Reported Beta-Lactam Allergy in Hospitalized Patients with Hematologic Malignancies Requiring Antibiotics. *Clin Infect Dis*. 2018;67(1):27-33.
7. Taremi M, Artau A, Foolad F, et al. Safety, Efficacy, and Clinical Impact of Penicillin Skin Testing in Immunocompromised Cancer Patients. *J Allergy Clin Immunol Pract*. 2019;7(7):2185-2191.e1.
8. Trubiano JA, Grayson ML, Phillips EJ, Stewardson AJ, Thursky KA, Slavin MA. Antibiotic Allergy Testing Improves Antibiotic Appropriateness in Patients with Cancer. *J Antimicrob Chemother*. 2018;73(11):3209-3211.
9. Taplitz RA, Kennedy EB, Bow EJ, et al. Antimicrobial Prophylaxis for Adult Patients with Cancer-Related Immunosuppression: ASCO and IDSA Clinical Practice Guideline Update. *J Clin Oncol*. 2018; 36(30):3043-3054.

Table 1. Antibiotic Use Among Patients Treated for Febrile Neutropenia by Documented Beta-Lactam Allergy Status

		Documented Beta-Lactam Allergy (n = 55)	No Documented Beta-Lactam Allergy (n = 235)	P-value	Odds Ratio Unadjusted (95% CI) ^d	Odds Ratio Adjusted (95% CI) ^e
First-line agents	Cefepime	20 (36)	149 (63)	< 0.001		
	Meropenem	19 (35)	26 (11)	< 0.001		
	Piperacillin/ Tazobactam	5 (9)	35 (15)	0.26		
	All first-line	20 (36)	149 (63)	< 0.001	0.33 (0.20, 0.53)	0.35 (0.20, 0.63)
Alternative Antibiotics	Fluoroquinolones ^a	8 (15)	21 (9)	0.21		
	Aztreonam	3 (5)	1 (<1)	0.023		
	Aminoglycosides ^b	0 (0)	4 (2)	1.00		
	Ceftazidime	1 (2)	1 (<1)	0.34		
	All Alternative	12 (22)	26 (11)	0.033	2.24 (1.05, 4.81)	--
Adjunctive Antibiotics	Vancomycin	18 (33)	89 (38)	0.48		
	Sulfamethoxazole/ Trimethoprim	8 (15)	22 (9)	0.26		
	Metronidazole	2 (4)	16 (9)	0.38		
	Other ^c	9 (16)	20 (9)	0.081		
	All Adjunctive	30 (55)	115 (49)	0.45	1.25 (0.71, 2.20)	1.24 (0.67, 2.32)

^a Fluoroquinolones included levofloxacin (n=17) and ciprofloxacin (n=12)^b Aminoglycosides included tobramycin (n=2), gentamicin (n=1), and amikacin (n=1)^c Other included: doxycycline (n=8), azithromycin (n=6), daptomycin (n=4), minocycline (n=3), ceftazidime (n=2), clindamycin (n=2), ertapenem (n=2), ampicillin (n=1) and linezolid (n=1)^d Odds ratios compare febrile neutropenia inpatients with a documented beta-lactam allergy compared to no documented beta-lactam allergy^e Odds ratios are adjusted for age, sex, race/ethnicity, whether patient was admitted to ICU, MRSA colonization, VRE colonization, and hospital day. There were insufficient alternative antibiotics to perform multivariable adjustment.