

Impact of β -Lactam Allergies on Antimicrobial Selection in an Outpatient Setting

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Objective: The primary objective of this study was to determine whether patients prescribed nonpreferred antibiotics received appropriate alternative antibiotics.

Methods: This was a retrospective observational analysis of military veteran patients with a β -lactam allergy treated in an outpatient clinic or emergency department for an infection during a 5-year span. Antibiotic regimens were first stratified as preferred or nonpreferred based on infection-specific guidelines. The nonpreferred regimens were then evaluated for appropriateness based on allergy history and culture and sensitivity reports.

Results: Of 445 fills of antibiotics evaluated, 269 met inclusion criteria, comprising 253 unique infections in 80 patients. Patients received nonpreferred antibiotics for their infection type in 57% of cases. Of the nonpreferred antibiotics, 56% were inappropriate based on guideline-recommended alternatives, allergy history, and culture and sensitivity data. Of the 88 allergies, 97% were historical/self-reported and 48% were cutaneous. In addition, 39% of patients safely received β -lactam antibiotics after documentation of their allergy.

Conclusions: Patients with documented β -lactam allergies are at high risk of receiving nonpreferred and inappropriate antibiotics, and many reactions likely do not reflect true allergies. These data emphasize the negative impact of the " β -lactam allergy" label and the importance of reassessing allergies.

Key Words: adverse drug reaction, allergy, antibiotics, bacterial infection, primary care

Penicillin allergies are among the most commonly documented drug allergies, with as many as 10% of patients reporting an allergy to one or more β -lactam antibiotics.¹ Studies have shown, however, that nearly 90% of these patients do not demonstrate a true immunoglobulin E (IgE)-mediated reaction, suggesting

that β -lactams could be used safely in many of these patients.² This prompted the 2016 guidelines from the Infectious Diseases Society of America on the implementation of antimicrobial stewardship programs to recommend that patients with β -lactam allergy undergo allergy assessment and β -lactam allergy skin testing (BLAST) or oral challenge.³ This is not yet routinely available at many institutions, and most patients receive broader spectrum, nonpreferred antibiotics because of the concern for adverse drug reactions.⁴⁻⁶ Use of nonpreferred antibiotics in patients with β -lactam allergies has been shown to increase treatment failure,⁷ in-hospital mortality,⁸ length of stay,^{8,9} and risk of *Clostridium difficile* infection.⁹ In addition, the increased use of broader spectrum antibiotics has been theorized to place these patients at a higher risk of multidrug-resistant (MDR) pathogens.⁹ Until recently, researchers have examined the impact of β -lactam allergies on patients who were admitted to the hospital. In the abstract of a presentation, however, Blumenthal and colleagues described the first study on the impact of β -lactam allergies in outpatients. They reported that patients with reported penicillin allergies had a 62% and 27% increased risk of methicillin-resistant *Staphylococcus aureus* (MRSA) and *C. difficile* infection, respectively. They concluded that the use of alternative antibiotics accounted for 53% and 25% of the increased risk, respectively.¹⁰ The present study sought to investigate the impact of β -lactam allergies on antimicrobial selection and the possible sequelae of prescribing

Key Points

- Patients with β -lactam allergies often receive nonpreferred antibiotics for the treatment of their infections.
- Many patients do not have true immunoglobulin E-mediated reactions and could safely receive the preferred treatment agents.
- The impact of β -lactam allergies on antimicrobial prescribing is less studied in the outpatient setting.
- This study emphasizes that the receipt of nonpreferred and inappropriate antibiotics remains a major issue within this setting.
- This study emphasizes the need for further evaluation of a patient's β -lactam allergy before prescribing antimicrobials.

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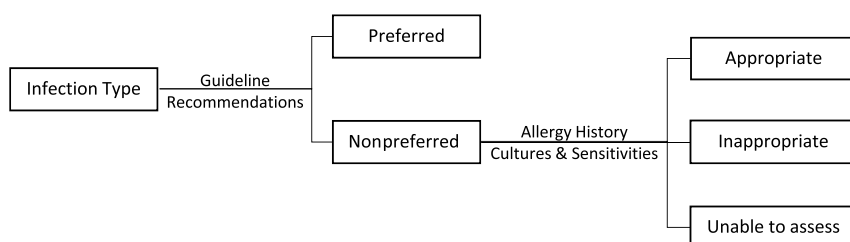


Fig. 1. Process used to determine the appropriateness of antibiotics used. To assess the appropriateness of antibiotic selection, the type of infection being treated was first determined and guideline recommendations^{11–38} were reviewed to assess whether the patient received a preferred or nonpreferred antibiotic. The patients who received nonpreferred antibiotics were further assessed based on allergy history and culture and sensitivity reports to determine whether the nonpreferred antibiotics were an appropriate alternative. Guideline recommendations for alternative antibiotics were also used to assess appropriateness.

nonpreferred antibiotic therapy among a military veteran population in an outpatient setting.

Methods

This was a retrospective chart review of military veteran patients with a documented β -lactam allergy who filled a prescription for an antibiotic from an outpatient clinic or the emergency department between January 1, 2011 and December 31, 2016. The study was submitted to and approved by the Memphis Veterans Affairs Medical Center Institutional Review Board. A Structured Query Language (SQL) query was performed to identify patients with a β -lactam allergy who filled an outpatient antibiotic prescription during the defined time frame. Patients then were sorted by their Social Security number for randomization. Chart review was completed sequentially until 80 patients were included. Patients could have multiple antibiotic fills for different infections. Patients were included if they had a β -lactam allergy and received an outpatient prescription for an antibiotic resultant from an outpatient clinic or emergency department visit. Patients were excluded if they were admitted to the hospital, guidelines with treatment recommendations for the type of infection were unavailable, antibiotics were not indicated for the type of infection, the antibiotics were a continuation of a

previous antibiotic course, the antibiotics were for a nonacute infection (eg, acne), the type of infection was unable to be determined, or there was documented noncompliance with the antibiotic course in the medical record. Baseline demographic data were collected, along with allergy history, history of antibiotic use, type of infection, culture and sensitivity reports, antibiotic treatment regimen, and adverse events to antibiotic regimen. Demographic data were analyzed only once for each patient; however, patients could have allergies to multiple β -lactams or received treatment for multiple infections, each of which were counted as separate entities.

The primary objective of this study was to determine whether patients who were prescribed nonpreferred antibiotics received appropriate or inappropriate alternative antibiotics. To accomplish this, the type of infection being treated was assessed and guideline recommendations^{11–38} were reviewed. Patients who received guideline-recommended first-line therapies were determined to have received a preferred antibiotic, whereas those who did not were determined to have received a nonpreferred antibiotic. The patients who received nonpreferred antibiotics were further assessed based on allergy history and culture and sensitivity reports to determine whether the nonpreferred antibiotics were an appropriate alternative. Guideline recommendations

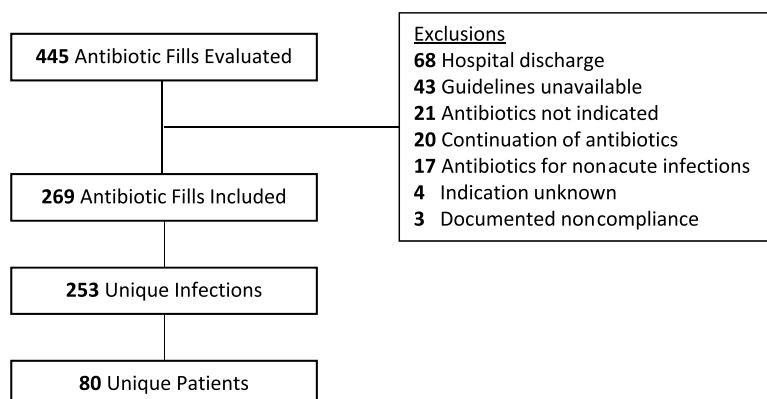


Fig. 2. Flowchart describing included and excluded antibiotic prescriptions. The initial Structured Query Language query resulted in >10,000 antibiotics filled by veterans with β -lactam allergies in the 5-year span. Of these fills, a random selection of 445 antibiotic fills were evaluated. After evaluation, 176 fills met the exclusion criteria, as outlined here. This resulted in 269 antibiotic fills included in the final analysis. This was made up of 253 unique infections in 80 unique patients.

Table 1. Patient characteristics (N = 80)

Age, y, mean $\pm$ SD	65 $\pm$ 15
Male sex, no. (%)	54 (68)
Ethnicity, no. (%)	
White	55 (69)
African American	22 (28)
Other	3 (4)
β -Lactam allergies per patient, median (range)	1 (1–3)

SD, standard deviation.

for alternative antibiotics were also used to assess appropriateness. A flowchart of this decision process is outlined in Figure 1. Secondary outcomes included the number of patients who received a β -lactam after allergy documentation and incidence of treatment failure, *C. difficile*, and MDR pathogens. Allergy documentation was defined as the first time the patient's allergy was recorded in the medical record. Treatment failure was defined as the receipt of another antibiotic for the same infection within 30 days of the initial antibiotic prescription. The following bacteria were considered MDR pathogens: MRSA, vancomycin-resistant *Enterococcus*, carbapenem-resistant *Enterobacteriaceae*, and extended-spectrum β -lactamase producers.

Data for the primary and secondary outcomes were analyzed using descriptive statistics. The relations of the secondary outcomes to the primary outcome were analyzed by correlation coefficients.

Results

The initial SQL query resulted in >10,000 antibiotics filled by veterans with β -lactam allergies in the 5-year span. Of these fills, a random selection of 445 antibiotic fills were evaluated. After evaluation, 176 fills met the exclusion criteria, resulting in 269 antibiotic fills included in the final analysis. This

consisted of 253 unique infections in 80 unique patients (Fig. 2). Demographic data for the patients are shown in Table 1. Although this is an average of approximately 3 infections per patient during the 5-year span, patients most commonly had 1 (26 patients, 33%), 2 (18 patients, 23%), or 3 (12 patients, 15%) infections. The average number of infections per patient was increased by the remaining 24 patients, who had >3 infections, with 2 patients having 10 infections each in the time frame of the study.

Among the 80 patients evaluated, there were 86 documented penicillin allergies and 2 cephalosporin allergies. Of these 88 allergies, only 3 (3.4%) were documented in the medical record as observed by a medical professional (Fig. 3A). The remaining 86 allergies were self-reported, historical reactions. The types of allergic reactions documented are detailed in Figure 3B. Cutaneous reactions were the most common, occurring in 48% of patients, followed by unknown/undocumented in 20%, and anaphylaxis in 15%.

The infection types treated are shown in Figure 4 and the antibiotics received are detailed in Figure 5B. Skin and soft tissue infections (19%), urinary tract infections (17%), and sinusitis (15%) were the most commonly observed infections. Fluoroquinolones (27%), macrolides (19%), and clindamycin (19%) made up the majority of the antibiotics prescribed. It is interesting to note that 4% and 1% of the antibiotics prescribed were cephalosporins and penicillins, respectively. There were 5 adverse reactions documented with the antibiotic prescribed: tendonitis to ciprofloxacin (1), rash to minocycline (1), rash to doxycycline (1), nausea and vomiting to moxifloxacin (1), and diarrhea with ciprofloxacin (1).

When antibiotics were assessed based on guideline recommendations, 57% of antibiotics prescribed were nonpreferred agents (Fig. 5B). Upon further evaluation 38% of the nonpreferred agents were appropriate based on allergy history and/or culture and sensitivity data. Of the remaining nonpreferred antibiotics, 56% were inappropriate, and insufficient information was documented to assess appropriateness in 6% (Fig. 5C).

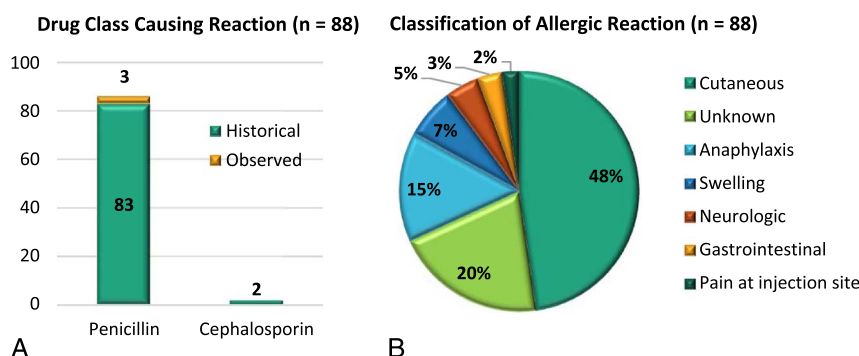


Fig. 3. Characterization of reported allergic reactions. (A) Drug classes causing reaction. The bar graph depicts which drug class the patient had a reported allergy to, either penicillin or cephalosporin, and whether reactions were historical (self-reported) or observed by a medical professional. Of the allergies assessed, 98% were secondary to penicillin antibiotics and only 3% were observed by a medical professional. **(B) Classification of allergic reaction.** The pie chart classifies the nature of the allergic reactions documented in the medical record based on the primary organ system affected. If the reaction was considered anaphylactic in nature, this was classified separately. In addition, if no documentation was available regarding the details for the reaction, this was classified as unknown. Nearly half of the reactions were cutaneous in nature and an additional 20% of reactions were unknown.

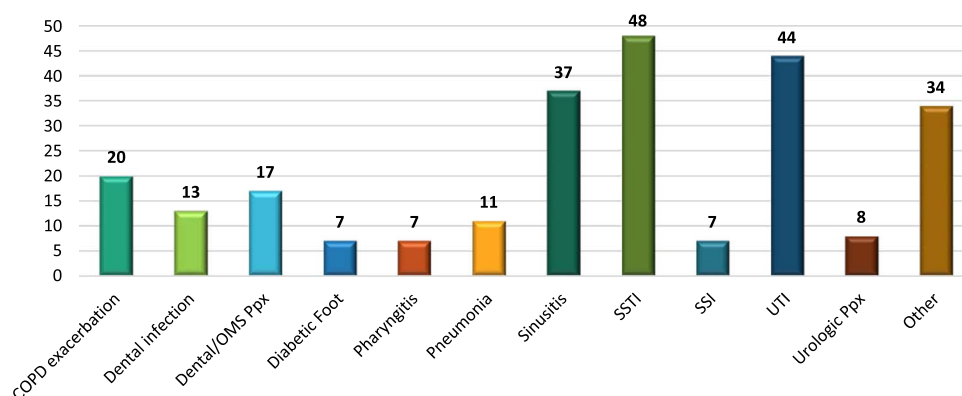


Fig. 4. The bar graph details the number and types of infections that were included in this study. The most common infection types were SSTI, UTI, and sinusitis. COPD, chronic obstructive pulmonary disease; OMS, oral maxillofacial surgery; PPx, prophylaxis; SSI, surgical site infection; SSTI, skin and soft tissue infection; UTI, urinary tract infection.

Review of the medical record revealed that 31 patients received ≥ 1 β -lactam antibiotics following the initial entry of their allergy into the electronic medical record. Of the antibiotics received, 6 were penicillins, 44 were cephalosporins, and 8 were carbapenems. There was no record found of any patients experiencing an adverse or allergic reaction to these β -lactam agents.

The rates of secondary outcomes were relatively low. There were 8 MDR pathogens occurring at any time point among the 80 patients, 0 *C. difficile* infections occurring within 30 days of receipt of antibiotics, and 7 *C. difficile* infections occurring within the year before receiving antibiotics. On further analysis there was no correlation between the incidence of MDR pathogens (Table 2) or *C. difficile* infection (Table 3) and the receipt of nonpreferred or inappropriate antibiotics. Of the 253 infections, there was a treatment failure rate of 12%; this also was not correlated with the receipt of nonpreferred or inappropriate antibiotics (Table 3). When all of the secondary outcomes were looked at as a combined outcome, there remained no correlation between the combined outcome and the receipt of nonpreferred or inappropriate antibiotics (Table 3).

Discussion

In this study we found that patients with β -lactam allergies have a high likelihood of receiving nonpreferred antibiotics based on guideline recommendations. More concerning, 56% of the nonpreferred antibiotics were inappropriate alternatives based on guideline recommendations, the patient's allergy history, and culture and sensitivity data. The receipt of nonpreferred or inappropriate antibiotics was not associated in our study with an increased risk of treatment failure, MDR infections, or *C. difficile* infection. Our data did indicate, however, that many patients had historical, likely non-IgE-mediated reactions, and could safely receive β -lactam antibiotics. In fact, 39% of the patients in our study did safely receive a β -lactam even after documentation of their allergy.

To our knowledge, data from only one other study have been presented detailing the effects of β -lactam allergies on antimicrobial prescribing patterns and the negative sequelae of the

prescribing patterns in an outpatient setting. This study was a much larger multicenter study looking at >60,000 patients with penicillin allergies. Similar to our study, Blumenthal and colleagues found that many patients with β -lactam allergies were receiving alternative agents. They found that these alternative agents could account for 25% to 50% of the risk of developing a new MRSA or *C. difficile* infection.¹⁰ This is in contrast to our study, in which no correlation was found between our secondary outcomes and the receipt of nonpreferred antibiotics. Based on the small number of secondary outcomes, it is likely that our study was underpowered to detect a difference in the risk of MRSA or *C. difficile* infection. Our study also was unique from the Blumenthal et al study because it is the first to look at the effects of β -lactam allergies in a veteran population.

β -Lactam allergies, in particular penicillin allergies, are the most commonly reported drug allergies.¹ It cannot be emphasized enough, however, that many patients do not have true IgE-mediated allergies that would prevent the use of β -lactam agents. It is not uncommon for patients to have resolution of their allergic response to penicillins 5 to 10 years after their reaction occurred, even if their reaction at the time could be considered anaphylaxis. This was demonstrated in a study by Blanca et al, in which serial BLAST was completed on patients at 1, 3, and 5 years after their reaction.³⁹ Of the 55 patients who were

Table 2. Incidence of MDR pathogens (N = 80)

Pathogens	No. (%)	Correlation	
		Nonpreferred	Inappropriate
	6 patients (8)	0.088	0.149
MRSA	5 (6)		
VRE	1 (1)		
CRE	1 (1)		
ESBL	1 (1)		

CRE, carbapenem-resistant Enterobacteriaceae; ESBL, extended spectrum β -lactamase; MDR, multidrug resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant *S. aureus*.

Table 3. Incidence of *Clostridium difficile* infection and treatment failure

	Nonpreferred (n = 253)		Inappropriate (n = 144)	
	No. (%)	Correlation	No. (%)	Correlation
Treatment failure	31 (12)	0.064	15 (10)	−0.086
<i>C. difficile</i> within 30 d	0 (0)	—	0 (0)	—
<i>C. difficile</i> 1 y prior	7 (3)	1.28×10^{-17}	4 (3)	0.071
Combined outcome	55 (22)	−0.006	31 (22)	0.158

Table 4. Possible outcomes of β -lactam allergy assessment protocol

Assessment	Outcome
Adverse reaction (eg, nausea, vomiting)	Remove allergy
Received and tolerated allergen	Remove allergy
Received and tolerated other β -lactam antibiotics	Recommend alternative β -lactams
IgE-mediated reaction >5 y ago	Recommend β -lactam skin testing
IgE-mediated reaction <5 y ago	Recommend avoiding β -lactam antibiotics
Severe non-IgE-mediated reaction (eg, SJS, TEN, hemolytic anemia)	Recommend avoiding β -lactam antibiotics

IgE, immunoglobulin E; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

studied, 38 (70%) tested negative at year 5 and an additional 5 patients (9%) were lost to follow-up.³⁹ A second study by Sullivan and colleagues found that only 22% of patients tested positive on BLAST when rechallenged ≥ 10 years after their reaction.⁴⁰ In addition, what many patients refer to as an allergy could be characterized as an adverse drug event, the most common of these being nausea and vomiting. Our data highlight the

importance of investigating a β -lactam allergy, with the majority of the reactions being either cutaneous or unknown and 97% of reactions being historical. Although 15% of reactions could be classified as anaphylaxis, based on the historical nature of our data and the understanding of the chronicity of penicillin allergies,^{39,40} it is possible that many of those patients are no longer allergic, warranting further testing to confirm.

This was a retrospective, observational analysis among a military veteran patient population, limiting its applicability to other patient populations. In addition, compared with the available dataset of >10,000 antibiotic fills, only a random limited sample was analyzed. It could be postulated that a correlation between primary and secondary data could have been discovered with a larger patient population. This study also was limited by variations in chart documentation, potentially affecting our ability to appropriately assess antimicrobial treatment regimens. The ability to understand the impact of a patient's penicillin allergy on appropriateness of treatment regimen in this dataset is further limited by the lack of a control, nonpenicillin allergic group.

Conclusions

This study found that among patients who had previously reported β -lactam allergies, the majority received nonpreferred

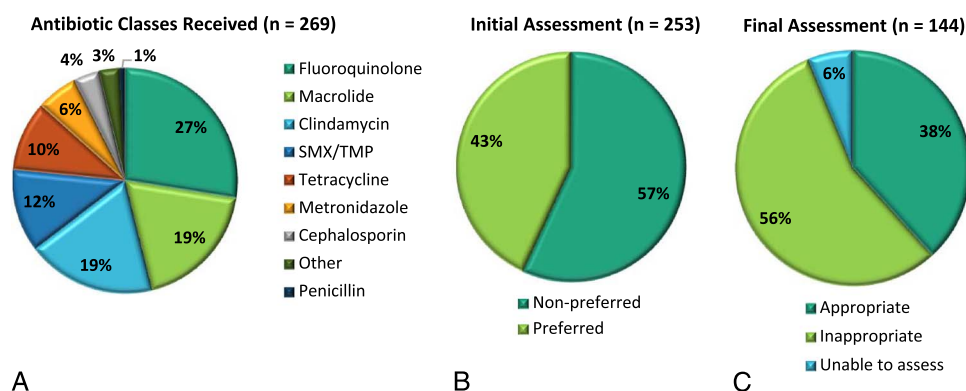


Fig. 5. Antibiotic classes received and characterization of appropriateness of antibiotics selected. (A) The pie chart details antibiotic classes that were prescribed and filled. The most commonly filled antibiotics were fluoroquinolones, followed by macrolides and clindamycin. The group of “other” antibiotics consisted of neomycin, nitrofurantoin, and vancomycin. **(B)** The pie chart shows the outcome of the initial assessment of an antibiotic's appropriateness, demonstrating that >50% were nonpreferred based on guideline recommendations^{11–38} for the infection type being treated. **(C)** The antibiotics determined to be nonpreferred in **B** were then further assessed for appropriateness based on guideline recommendations for alternative antibiotics, allergy history, and culture and sensitivity data. If insufficient information was documented, then the antibiotic was classified as unable to be assessed. Based on these evaluation parameters, >50% of the nonpreferred antibiotics also were considered to be inappropriate.

and inappropriate antibiotics for their infection type based on guideline recommendations, allergy history, and culture and sensitivity data. Nearly half of the previously reported allergies were cutaneous in nature, and one-fifth had no documentation of the type of allergy. Overall, these data emphasize the negative impact of patients having documented but unverified β -lactam allergies on antimicrobial prescribing patterns and the importance of reassessing allergies, because most patients likely do not have a true IgE-mediated allergy. Because of these data, our institution has implemented a β -lactam assessment protocol that can be used to further investigate a patient's allergy history. This protocol is being used by pharmacists at our institution to classify patients into one of six categories:

1. The allergy was an adverse reaction (eg, nausea/vomiting) and can be removed from the allergy list
2. The patient has received and tolerated his or her original allergen and the allergy can be removed
3. The patient has received and tolerated other β -lactam antibiotics, such as cephalosporins, and can safely receive those agents
4. The patient had a suspected true IgE-mediated reaction >5 years ago and should undergo BLAST
5. The patient had a recent (<5 years ago) documented IgE-mediated reaction and β -lactam antibiotics should be avoided
6. The patient had a severe non-IgE medication (eg, Stevens-Johnson syndrome, toxic epidermal necrolysis, hemolytic anemia) and β -lactam antibiotics should be avoided (Table 4)

We are also in the process of involving pharmacists in the allergy and immunology clinic to help with BLAST. Further research into the impact of this β -lactam assessment protocol and expansion of BLAST is under way.

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