

Impact of Beta-Lactam Allergies on Selection of Antimicrobials in an Inpatient Setting Among Veteran Population

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ABSTRACT

Purpose:

Beta-lactam antibiotics are among the most common and widely used antibiotics. However, reported allergy to this class of antibiotics is also common, leading to the use of alternative broad-spectrum antibiotics by healthcare providers. This has led to the emergence of various negative health outcomes. The purpose of the study is to investigate the impact of using alternative antibiotics secondary to a beta-lactam allergy among U.S. veterans who have otherwise multiple comorbidities.

Methods:

This retrospective observational analysis was conducted over a 5-year period (January 1, 2011 to December 31, 2016) at the Memphis Veterans Affairs Medical Center (VAMC). Admitted patients with a documented beta-lactam allergy were categorized to preferred or non-preferred status based on initial antibiotic therapy antibiotic, allergy history, published guidelines, and local antibiogram. Preferred therapy was defined as the optimal antibiotic treatment for a given indication based on patient allergy history, published Infectious Disease Society of America guidelines, and local antibiogram of Memphis VAMC. The therapy was classified as “non-preferred” if it did not satisfy the preferred therapy criteria. Non-preferred treatments were further assessed for appropriateness based on indication and patient-specific factors. Chi-square and Fisher’s exact tests were conducted to find a difference in rates of negative sequelae among patients receiving preferred vs. non-preferred treatments and appropriate vs. inappropriate treatments.

Findings:

Of the 1806 admissions identified, data were collected on 95 unique patients with 147 different antibiotic regimens. There were 68 (52%) preferred treatment regimens and 64 (48%) non-preferred treatment regimens. Of the 64 non-preferred treatments, 43 (67%) were inappropriate. There was a statistically significant decrease in the number of adverse drug events and in the combined negative sequelae outcome among patients receiving preferred therapy vs. non-preferred therapy (2 vs. 12; $P < .01$ and 11 vs. 23; $P < .01$, respectively).

Implications:

The receipt of non-preferred antibiotic therapy among veterans with a recorded beta-lactam allergy may be associated with an increased risk of developing negative outcomes. Among military personnel, removing unnecessary beta-lactam allergies would improve readiness with optimal antibiotic choices and avoidance of unnecessary risks, expediting return to full duty.

INTRODUCTION

There are more than 21.3 million veterans in the USA per the 2015 U.S. Census and 9.3 million of them are more than 65 years old.¹ In general, veterans are often diagnosed with more health conditions (e.g., diabetes, lung disease, and hypertension) than the general population.¹ Beta-lactam antibiotic allergies are the most commonly reported medication allergies in the USA with ~10% of population reporting penicillin allergy.² In a study of 2.9 million veterans involving

10.9 million admissions, penicillin allergy was reported to be 13% followed by cephalosporins (0.4%), carbapenems, and aztreonams (<1%).³

In general, the presence of a beta-lactam allergy in a patient chart increases the chance that a more broad-spectrum antibiotic will be used than necessary for the indication.⁴ The beta-lactam allergy is either historically reported by the patient or verified by the healthcare provider. The use of alternative broad-spectrum antibiotic agents has been associated with an increased incidence of *Clostridium difficile*, development of multidrug-resistant (MDR) organisms, adverse drug events (ADEs), and treatment failure.^{5–10} These MDR pathogens include Enterobacteriaceae (e.g., *Escherichia coli* and *Klebsiella pneumoniae*) which produce enzymes called extended-spectrum beta-lactamases (ESBLs) that can degrade penicillin and cephalosporins, making them ineffective.¹¹

There is no prior published literature on the impact of beta-lactam allergies on hospitalized veterans who have multiple

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comorbidities. Our goal is to assess whether the use of alternative non-preferred antibiotics leads to adverse outcomes in this population cohort because of beta-lactam allergy.

METHODS

This single-center, retrospective, observational analysis included veterans aged 18 years or older that were admitted to the Memphis Veterans Affairs Medical Center (VAMC) with beta-lactam allergy and who received antibiotics during the hospitalization. Data were accumulated by Structured Query Language query and manual patient chart extraction from the Memphis VAMC database from January 1, 2011 to December 31, 2016. The study was approved by the Memphis VAMC institutional review board in Memphis, TN.

Data collected from the initial antibiotic regimen included name of antibiotic(s), therapeutic indication, and negative outcomes associated with antibiotic treatment. Negative outcomes assessed included antibiotic treatment failure, ADEs, incidence of *C. difficile*, and incidence of MDR bacteria. The nature of the beta-lactam allergy and the precipitating allergic reactant were also recorded for each patient.

The first antibiotic treatment regimen received by the hospitalized patient was assessed and classified into either preferred or non-preferred antibiotic therapy (Fig. 1). Preferred therapy was defined as the optimal antibiotic treatment for a given indication based on patient allergy history, published Infectious Disease Society of America guidelines, and local antibiogram of Memphis VAMC.¹² Non-preferred therapy was further assessed into appropriate or inappropriate categories. Appropriate therapy was defined as the proper treatment alternative based on antibiotic indication, published Infectious Disease Society of America guidelines, and patient-specific factors.

The primary outcome was the number of patients receiving non-preferred antibiotic therapy and the number of patients receiving inappropriate antibiotic therapy. Secondary outcomes included rates of treatment failure; ADEs; development of *C. difficile*; and development of MDR pathogens including ESBL-producing bacteria, methicillin-resistant *Staphylococcus aureus* (MRSA), and vancomycin-resistant *Enterococcus* (VRE) among patients receiving non-preferred vs. preferred and inappropriate vs. appropriate antibiotic regimens. The difference in rates of antibiotic regimens associated with at least one negative outcome (composite outcome) in the non-preferred vs. preferred and inappropriate vs. appropriate antibiotic regimens was examined as a secondary outcome. Antibiotic regimens were associated with the development of MDR bacteria or *C. difficile* if they were observed within 6 months of receipt of the antibiotic regimen.

The primary and secondary outcomes were assessed using chi-square and Fisher's exact tests among patients receiving preferred vs. non-preferred therapy and patients receiving appropriate vs. inappropriate therapy for each potential negative outcome.

RESULTS

Of the 1,806 admissions identified, data were collected on 8%, representing 95 unique patients with 147 different antibiotic regimens. Of the 147 antibiotic regimens reviewed, 15 regimens were excluded because the continuation of antibiotics started on an outpatient basis once the patient was admitted. The remaining 132 regimens represented 95 unique patients included in the study. Patients were primarily Caucasian (56%) and males (70%) with an average age of 70 years.

There were a total of 98 beta-lactam allergies documented for the 95 patients. A total of 91 penicillin allergies were observed in comparison to seven cephalosporin allergies.

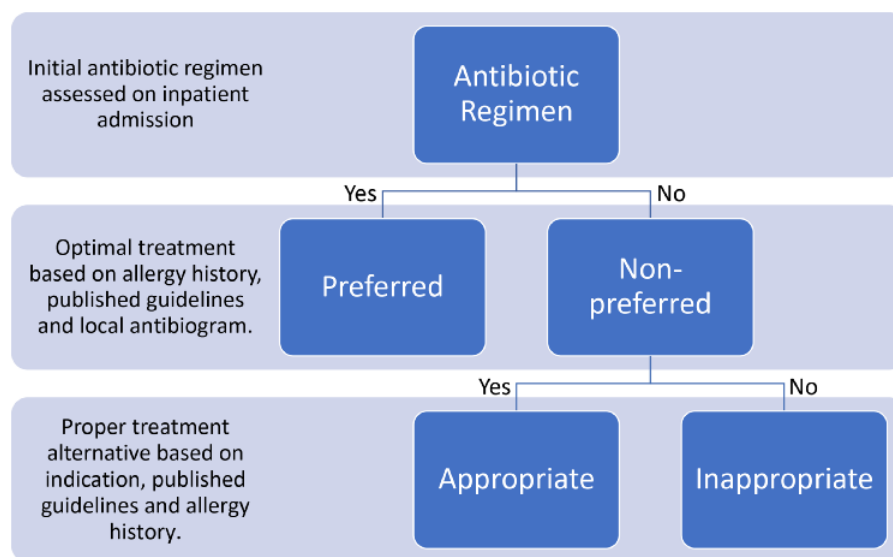


FIGURE 1. Classification of antibiotic regimens.

TABLE I. Number of Treatment Regimens per Antibiotic Indication

Antibiotic indication	Number of treatment regimens
Aspiration pneumonia	3
Bacteremia	1
Bronchitis	3
Community-acquired pneumonia	10
Cellulitis	7
Combination of indications	4
COPD exacerbation	5
Febrile neutropenia	2
Healthcare-associated pneumonia	15
Intra-abdominal infection	6
Meningitis	2
Nausea	1
Osteomyelitis	2
Perioperative	27
Pyelonephritis	1
SBP prophylaxis	3
Sepsis	20
Skin and soft tissue infection	4
Urinary tract infection	16

Abbreviations: COPD, Chronic Obstructive Pulmonary Disease; SBP, Spontaneous Bacterial Peritonitis.

The most common allergy classification was a cutaneous reaction accounting for 37% of all allergies, although anaphylactic reactions were observed in 15% of patients (Fig. S1).

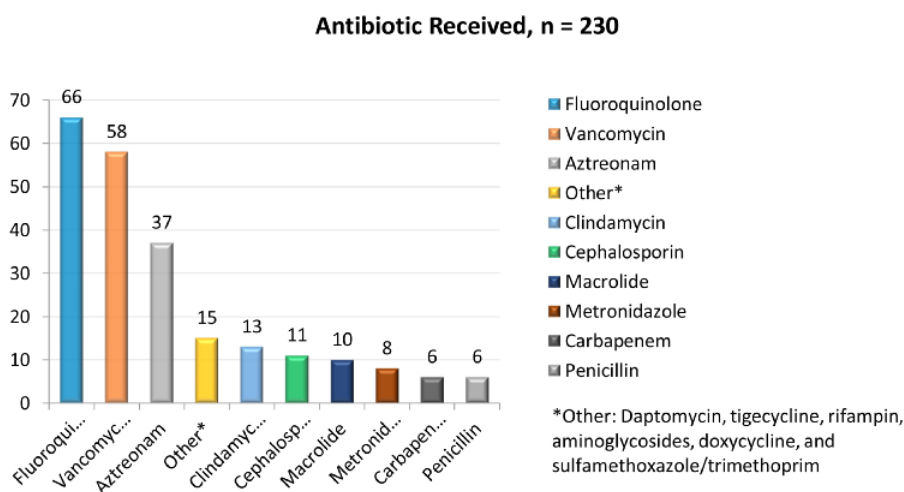
Of the 132 treatment regimens, the most commonly encountered antibiotic indications were pneumonia (21%), perioperative indication (20%), sepsis (15%), and urinary tract infection (12%) (Table I). Fluoroquinolones encompassed 29% of the administered antibiotics, while 10% were beta-lactams (Fig. 2). Out of the 132 antibiotic regimens, 52% ($n=68$) were classified as preferred therapy and 48% ($n=64$) were classified as non-preferred therapy. Of the non-preferred regimens, 67% ($n=43$) were classified as inappropriate (Fig. S2). The composite outcome for the number

TABLE II. Differences of Negative Sequelae Based on Antibiotic Selection Preference

	Antibiotic selection		
	Preferred	Non-preferred	<i>P</i> -value
Number of antibiotic regimens, $n = 132$	68	64	–
Adverse consequences	–	–	–
Treatment failure	6	9	0.34
<i>Clostridium difficile</i>	3	7	0.2
ADEs	2	12	<0.005
MDR pathogens	–	–	–
ESBL	1	6	0.06
MRSA	3	3	1
VRE	0	2	–
Combined outcome, $n = 132$	11	23	0.009

Abbreviations: ADEs, adverse drug events; ESBL, extended-spectrum beta-lactamase; MDR, multidrug-resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant *Enterococcus*.

of non-preferred antibiotic treatment regimens displaying at least one negative outcome was statistically significant when compared to preferred therapy (23 vs. 11; $P < .01$) (Table II). There was no statistically significant difference in the number of antibiotic treatment regimens associated with at least one negative outcome among patients receiving inappropriate and appropriate antibiotic therapy (15 vs. 8; $P = .8$) (Table S1). Additionally, the number of ADEs in the non-preferred group exhibited a statistically significant increase from those in the preferred group (12 vs. 2; $P < .01$).

**FIGURE 2.** Antibiotics received.

DISCUSSION

This is the first study examining the impact of beta-lactam allergy among veterans who were hospitalized for various reasons and required inpatient antibiotics. Our study showed that 48% of patients received non-preferred antibiotics and the majority of these antibiotic regimens were inappropriate. This may be attributable to a common misconception among providers to avoid beta-lactam antibiotics for patients reporting a beta-lactam allergy.¹³ Our results are like other studies showing a higher percentage of patients receiving inappropriate therapy. In a study from an Australian tertiary center, 29% of patients received inappropriate antibiotics with an antibiotic allergy (mostly to a beta-lactam) compared with those without the allergy (29% vs. 23%).¹⁴ In another study, 35% of patients with a beta-lactam allergy did not receive preferred therapy for their indication, even though a majority of them reported a non-severe reaction.¹⁵ There are differences between studies because of site-specific variability in assessing the preferred status or appropriateness based on differing antibiograms and national guidelines. In our study, fluoroquinolones were the most prescribed alternative agents (29%) followed by vancomycin (25%), aztreonam (16%), and clindamycin (6%) by healthcare providers when encountering a beta-lactam allergy. This prescribing pattern is similar to other studies of beta-lactam allergy in hospitalized patients in which fluoroquinolones, vancomycin macrolides, and clindamycin were used more frequently.^{16–20} Prior fluoroquinolone use has been associated with increased incidence of fluoroquinolone resistance.²¹ More specifically, fluoroquinolone resistance was indicated as a risk factor for the development of ESBLs in *E. coli* isolates.²¹ To help prevent the alarming rates of fluoroquinolone resistance and ESBL development, judicious use of fluoroquinolones is necessary and one way in which every institution can more appropriately use fluoroquinolones is to regularly conduct beta-lactam allergy assessments on patients presenting to the hospital with a reported beta-lactam allergy.

In our population, non-preferred therapy was associated with a statistically significant increased incidence of the composite outcome and number of ADEs associated with antibiotic therapy. This result was largely due 12 instances of ADEs in the non-preferred group vs. 2 instances occurring in the preferred group. There was a trend toward association between non-preferred antibiotic regimens and ESBL development (6 vs. 1; $P = .06$), but there was no statistically significant difference in the amount of MDR organisms among patients receiving non-preferred vs. preferred antibiotics. The increased incidence of adverse events was secondary to the use of broad-spectrum alternative antibiotics, which is similar to the findings of other investigators.^{15,18,19} Macy and colleagues showed increased incidence of MRSA (14.1%), *C. difficile* (23.4%), and vancomycin-resistant enterococci infections (30.1%) compared with control subjects.¹⁸ Blumenthal and colleagues showed increased use of vancomycin in methicillin-sensitive *S. aureus* (MSSA) is associated with increased recurrence rate of infections and adverse

reactions.¹⁹ Empirical anti-MRSA therapy (e.g., vancomycin and linezolid) was associated with increased 30-day mortality among a large cohort of hospitalized veterans because of various reasons (e.g., renal toxic effects, allergy, and superinfection).²² Beta-lactams are considered the drug of choice for MSSA infections. Compared to the aforementioned retrospective studies, Van Dijk and colleagues in a prospective matched cohort study found patients with a penicillin allergy were more likely to receive reserve antibiotics (RR, 1.38; 95% CI, 1.22–1.56) and more likely to be readmitted within 12 weeks (RR, 1.28; 95% CI, 1.10–1.49).²³ Other consequences of inappropriate antibiotics prescription use in beta-lactam allergy patients include increased cost, multiple antibiotics prescription, increased length of stay, increased ICU admissions, and treatment failure.^{16,24,25}

In our study there were no differences in other secondary outcomes among patients receiving inappropriate therapy when compared to patients receiving appropriate therapy. One possible reason for the lack of difference was sample size, as only 64 antibiotic regimens were assessed for appropriateness.

The results of this study add to the growing evidence of negative consequences from alternative broad-spectrum use of antibiotics secondary to beta-lactam allergies. Most subjects labeled with a beta-lactam allergy are not evaluated for the accuracy or persistence of the allergy.^{18,26} Majority of patients (>95%) tolerate penicillin who are labeled as being allergic to penicillin.²⁷ Completing a more thorough beta-lactam allergy assessment and documentation could potentially reduce the incidence of the negative outcomes associated with a beta-lactam allergy. This would involve collecting a more detailed patient history regarding a beta-lactam allergy and documenting the nature of reaction and potentially penicillin testing and drug challenge if required. Besides the allergists, this can be performed by other healthcare providers (e.g., hospitalists, infectious disease specialists, and clinical pharmacists) through focused education and training. In fact, in our medical center, many clinical pharmacists are trained to do beta-lactam allergy assessment, testing, and drug challenge.

Finally, beta-lactam allergy has real implication in military medicine. In a recent study involving 402 healthy marines with penicillin allergy, only 1.5% had positive reaction to penicillin testing and penicillin challenge. The rest of them (98.5%) were able to receive penicillin prophylaxis.²⁸ Military recruits are routinely treated with penicillin G against streptococcal prophylaxis.²⁹ Military personnel operate in remote locations and are at increased risk of infection, given the highly mobile nature of their deployment and living in crowded conditions.²⁹ The ability to use beta-lactam antibiotics including penicillin is important for military readiness.²⁹

Weaknesses of this study include the retrospective nature of its design that limited us to prospectively assess the nature of beta-lactam allergies. Although 98 beta-lactam allergies were assessed overall, 15 of these allergies were classified as anaphylactic, leaving a potential 83 allergies that may have been further assessed and possibly removed from the

patient chart. Other limitation includes site-specific variability in assessing the preferred status or appropriateness based on differing antibiograms and national guidelines. Finally, the small sample size of our study limited to one VAMC is another weakness of our study. However, our results align with multiple other non-VA studies and it can be generalizable to other medical centers.

CONCLUSION

We showed the negative health outcomes secondary to beta-lactam allergies in a high-risk population (e.g., veterans) who are already burdened with multiple comorbidities. Adding additional and potentially unnecessary adverse effects to this high-risk group can be further avoided by system-wide application of proper allergy documentation and assessment by healthcare providers in the VA healthcare system providing care to millions of veterans.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *Military Medicine* online.

FUNDING

There are no sources of funding to disclose.

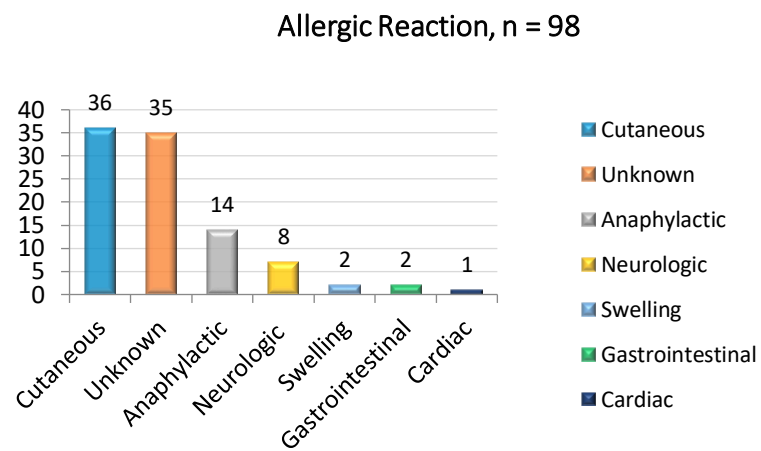
CONFLICT OF INTEREST

The authors have no financial disclosures to declare and no conflicts of interest to report.

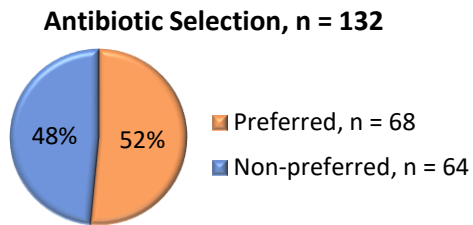
REFERENCES

- Richardson LM, Hill JN, Smith BM, et al: Patient prioritization of comorbid chronic conditions in the Veteran population: implications for patient-centered care. *SAGE Open Med* 2016; 4(Nov): 2050312116680945.
- Shenoy ES, Macy E, Rowe T, Blumenthal KG: Evaluation and management of penicillin allergy: a review. *JAMA* 2019; 321(2): 188-99.
- Mcconeghy K, Morrill H, Caffrey A, et al: Prevalence of documented beta-lactam allergies in the veterans affairs health system from 2000-2014. *Open Forum Infect Dis* 2016; 3(Suppl 1): 1799.
- Solensky R, Earl HS, Gruchalla RS: Clinical approach to penicillin-allergic patients: a survey. *Ann Allergy Asthma Immunol* 2000; 84(3): 329-33.
- Muto CA, Pokrywka M, Shutt K, et al: A large outbreak of *Clostridium difficile*-associated disease with an unexpected proportion of deaths and colectomies at a teaching hospital following increased fluoroquinolone use. *Infect Control Hosp Epidemiol* 2005; 26(3): 273-80.
- Pepin J, Saheb N, Coulombe MA, et al: Emergence of fluoroquinolones as the predominant risk factor for *Clostridium difficile*-associated diarrhea: a cohort study during an epidemic in Quebec. *Clin Infect Dis* 2005; 41(9): 1254-60.
- US Food and Drug Administration: FDA drug safety communication: FDA requires label changes to warn of risk for possibly permanent nerve damage from antibacterial fluoroquinolone drugs taken by mouth or by injection. Available at <https://www.fda.gov/media/86575/download>; accessed November 26, 2020.
- Briasoulis A, Agarwal V, Pierce WJ: QT prolongation and torsade de pointes induced by fluoroquinolones: infrequent side effects from commonly used medications. *Cardiology* 2001; 120(2): 103-10.
- Fuller JD, Low DE: A review of *Streptococcus pneumoniae* infection treatment failures associated with fluoroquinolone resistance. *Clin Infect Dis* 2005; 41(1): 118-21.
- Lautenbach E, Metlay JP, Mao X, et al: The prevalence of fluoroquinolone resistance mechanisms in colonizing *Escherichia coli* isolates recovered from hospitalized patients. *Clin Infect Dis* 2010; 51(3): 280-5.
- Malande OO, Nuttall J, Pillay V, Bamford C, Eley B: A ten-year review of ESBL and non-ESBL *Escherichia coli* bloodstream infections among children at a tertiary referral hospital in South Africa. *PLoS One* 2019; 14(9): e0222675.
- IDSA practice Guidelines: [Practice Guidelines \(idsociety.org\)](https://www.idsociety.org/practice-guideline); accessed January 14, 2021.
- Albin S, Agarwal S: Prevalence and characteristics of reported penicillin allergy in an urban outpatient adult population. *Allergy Asthma Proc* 2014; 35(6): 489-94.
- Trubiano JA, Cairns KA, Evans JA, et al: The prevalence and impact of antimicrobial allergies and adverse drug reactions at an Australian tertiary center. *BMC Infect Dis* 2015; 15(Dec): 572.
- MacFadden DR, LaDelfa A, Leen J, et al: Impact of reported beta-lactam allergy on inpatient outcomes: a multicenter prospective cohort study. *Clin Infect Dis* 2016; 63(7): 904-10.
- Sade K, Holtzer I, Levo Y, Kivity S: The economic burden of antibiotic treatment of penicillin-allergic patients in internal medicine wards of a general tertiary care hospital. *Clin Exp Allergy* 2003; 33(4): 501-6.
- Picard M, Bégin 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 Pract* 2013; 1(3): 252-7.
- 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): 790-6.
- Blumenthal KG, 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(5): 741-9.
- Blumenthal KG, Oreskovic NM, Fu X, et al: High-cost, high-need patients: the impact of reported penicillin allergy. *Am J Manag Care* 2020; 26(4): 154-61.
- Talan DA, Takhar SS, Krishnadasan A, et al: Fluoroquinolone-resistant and extended-spectrum β -lactamase-producing *Escherichia coli* infections in patients with pyelonephritis, United States. *Emerg Infect Dis* 2016; 22(9): 1594-603.
- Jones BE, Ying J, Stevens V, et al: Empirical anti-MRSA vs standard antibiotic therapy and risk of 30-day mortality in patients hospitalized for pneumonia. *JAMA Intern Med* 2020; 180(4): 552-60.
- Van Dijk SM, Gardarsdottir H, Wassenberg MW, et al: The high impact of penicillin allergy registration in hospitalized patients. *J Allergy Clin Immunol Pract* 2016; 4(5): 926-31.
- Du Plessis T, Holland D, Jordan A, et al: Beta-lactam allergy assessment and management service: a pharmacist-led approach. *Open Forum Infect Dis* 2016; 3(Suppl 1): 1853.
- Jeffres MN, Narayanan PP, Shuster JE, et al: Consequences of avoiding beta-lactams in patients with beta-lactam allergies. *J Allergy Clin Immunol* 2016; 137(4): 1148-53.
- Blumenthal KG, Shenoy ES, Huang M, et al: The impact of reporting a prior penicillin allergy on the treatment of methicillin-sensitive *Staphylococcus aureus* bacteremia. *PLoS One* 2016; 11(7): e0159406.
- Sacco KA, Bates A, Brigham TJ, Imam JS, Burton MC: Clinical outcomes following inpatient penicillin allergy testing: a systematic review and meta-analysis. *Allergy* 2017; 72(9): 1288-96.
- Tucker MH, Lomas CM, Ramchandar N, Waldram JD: Amoxicillin challenge without penicillin skin testing in evaluation of penicillin allergy in a cohort of Marine recruits. *J Allergy Clin Immunol Pract* 2017; 5(3): 813-5.
- Lee RU: Penicillin allergy delabeling can decrease antibiotic resistance, reduce costs, and optimize patient outcomes. *Fed Pract* 2020; 37(10): 460-5.

Supplementary Figure 1. Classification of Reported Allergic Reactions

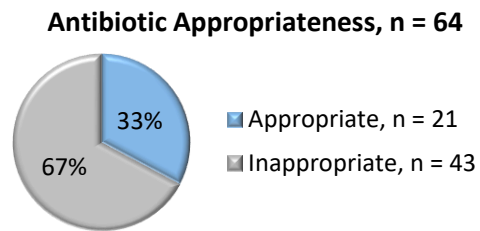


Supplementary Figure 2: Preference and Appropriateness of Antibiotic Selection



Preferred therapy: Optimal antibiotics treatment for a given indication based on patient allergy history, published IDSA guide line and local antibiogram.

IDSA: Infectious Disease Society of America



Appropriate therapy: Proper treatment alternative based on antibiotic indication, published IDSA guidelines and patient specific factor

Supplementary Table 1: Differences in Negative Sequalae Based on Antibiotic	Antibiotic Appropriateness		
	Appropriate	Inappropriate	<i>p-value</i>
Number of Antibiotic Regimens, n = 64	21	43	----
Adverse Consequences	----	----	----
Treatment failure	2	7	0.71
<i>C. diff</i>	4	3	0.2
Adverse Drug Events	3	9	0.74
MDR Pathogens	----	----	----
ESBL	2	4	1
MRSA	1	2	1
VRE	0	2	----
Combined Outcome, n = 64	8	15	0.8