

Confronting the Challenge of Beta-Lactam Allergies: A Quasi-Experimental Study Assessing Impact of Pharmacy-Led Interventions

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Abstract

Objective: To improve allergy history documentation and increase the use of beta-lactams when appropriate in patients with a reported beta-lactam allergy. **Methods:** This pre-post study was conducted at a 167-bed tertiary care community hospital and evaluated multidisciplinary interventions on allergy documentation and antibiotic selection. Interventions included education, creation of local practice guidelines, and modified practices for pharmacists and pharmacy technicians. Inpatients with a reported beta-lactam allergy receiving at least 1 antibiotic for >24 hours were included; first admissions were assessed. Primary outcomes were documentation of reaction type and percentage of patients receiving non-beta-lactam therapy. Secondary outcomes included documentation of previously tolerated beta-lactams, modification of non-beta-lactam therapy, discharge antibiotics, and adverse reactions. **Results:** A total of 179 patients were included, 91 preintervention and 88 postintervention. No significant differences were observed between the before versus after groups in the percentage of patients with documentation of reaction type (90.1% vs 89.8%, $P = .940$) or the overall percentage of patients receiving non-beta-lactams (86.8% vs 84.1%, $P = .605$). However, significantly more patients in the after phase had documentation of previously tolerated beta-lactams (8.8% vs 28.4%, $P = .001$), and among patients receiving a non-beta-lactam, a greater percentage was subsequently switched to a beta-lactam (11.4% vs 25.7%, $P = .022$). One allergic reaction was documented during the study, which occurred in the before phase. **Conclusion:** Multidisciplinary education and local guideline implementation led by pharmacists may improve allergy documentation and antibiotic selection in patients with reported beta-lactam allergies.

Keywords

drug hypersensitivity, beta-lactam allergy, antimicrobial stewardship, quality improvement, pharmacy clinical service

Introduction

Pharmacists have been identified as key members in antimicrobial stewardship programs (ASPs) helping to optimize antibiotic therapy and improve patients outcomes.¹ One barrier to therapy selection is patient-reported beta-lactam allergies, with approximately 10% to 15% of hospitalized patients reporting penicillin as an allergy.² Having a penicillin allergy label has been associated with avoidance of other beta-lactam antibiotics and increased use of non-beta-lactams including vancomycin, fluoroquinolones, aminoglycosides, and clindamycin.²⁻⁴ These medications are associated with increased costs, adverse events, and reduced efficacy in certain clinical situations.⁵⁻⁷ For example, one recent study found beta-lactam allergic patients with methicillin-sensitive *Staphylococcus aureus* bacteremia who were treated with empiric vancomycin had lower cure rates and a higher reoccurrence relative to those receiving cefazolin following allergy workup.⁸ As a result, the Infectious Diseases Society of America recommends conducting allergy

assessments in order to increase use of first-line beta-lactams.¹ However, there are few studies detailing interventions to promote use of beta-lactams in this patient population. Many of the interventions described have focused on reducing aztreonam use.^{9,10} There are multiple issues that ultimately influence the decision to avoid beta-lactam therapy and each of these present opportunities for interventions in which pharmacy staff can play an important role.

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Beta-lactam allergy documentation is often inaccurate and many documented reactions represent common adverse drug reactions or intolerances including diarrhea, nausea, and headache as opposed to true allergic reactions.¹¹ Misclassified reactions can have a substantial impact on care, with patients reporting penicillin allergies being at greater risk of rehospitalization and increased likelihood to receive inappropriate antimicrobial therapy.^{12,13} Furthermore, among patients reporting penicillin allergy, 80% to 90% of patients will have a negative penicillin skin test and many of these patients have previously tolerated beta-lactam therapy.^{14,15} Pharmacy staff are in a unique position to help with allergy histories and documentation, given their interaction with patients and knowledge of adverse drug reactions. This may represent one strategy to help prescribers determine when patients with reported beta-lactam allergies remain appropriate candidates to receive beta-lactam therapy.

Another important pharmacy opportunity is helping with the understanding of both the determinants and likelihood of beta-lactam cross-reactivity. Traditional teaching and earlier studies suggested cross-reactivity rates between penicillin and cephalosporins to be as high as 10%.^{16,17} As a result, beta-lactam antibiotics are still commonly avoided in patients with an allergy to an antibiotic of the same or different beta-lactam class. However, more recent studies have reported cross-reactivity between penicillins and first-generation cephalosporins to be approximately 2% and cross-reactivity between penicillins and either later generation cephalosporins or carbapenems to be less than or equal to 1%.¹⁸⁻²¹ The current prevailing theory is that side chains are the most important predictor of cross-reactivity as compared to a common beta-lactam ring.^{15,22} In light of this new evidence, patients with a history of nonimmunoglobulin E (IgE)-mediated, nonsevere beta-lactam allergies are often able to safely receive beta-lactams that are structurally dissimilar. Pharmacists may be key resources in helping compare beta-lactam structures and identifying suitable treatment options. In addition, patients with IgE-mediated reactions may still be appropriate candidates for beta-lactam therapy following the use of penicillin skin testing, graded challenge, or desensitization.¹⁴

Improved allergy histories and documentation may impact antibiotic selection and is an important focus for ASPs with the potential to improve outcomes in patients with reported beta-lactam allergies.¹ Pharmacy staff are positioned to help with both allergy assessment and antibiotic selection in this patient population. The objectives of this study were to (1) improve allergy histories and documentation and (2) increase the use of beta-lactams, when appropriate, among patients with a reported beta-lactam allergy.

Methods

Study Design

This was a quasi-experimental, pre-post study assessing the impact of multidisciplinary education, creation of local

practice guidelines, and modified practices for pharmacists and pharmacy technicians. Educational efforts were initiated in December 2015 and all education and interventions were implemented as of January 4, 2016. The before phase consisted of eligible hospitalized patients admitted between September 1, 2015, and November 30, 2015, and the after phase between January 5, 2016, and April 30, 2016.

Site and Patient Population

This study was performed at Aurora BayCare Medical Center, a 167-bed tertiary care community hospital located in Green Bay, Wisconsin. This project was reviewed by the institutional review board (IRB) of the Aurora Health Care, and was deemed to not constitute human subject research. As such, it did not require Aurora IRB oversight. Inpatients with reported beta-lactam allergies were included in this study if they received an antibiotic for greater than 24 hours. Patients receiving antibiotics for surgical prophylaxis and/or who were readmitted to the hospital during the study period were excluded.

Interventions

Allergy history and documentation. Prior to interventions, registered nurses were responsible for all allergy histories and documentation. During educational efforts, nurses were reeducated on the importance of allergy assessment and documentation, impact of incomplete allergy documentation, and where and how to document information in the electronic health record. After implementation, nurses continued to perform allergy assessments with an emphasis on complete documentation of reaction type.

At our institution, there is a pharmacy technician role dedicated to completing medication histories during the first and second shifts. Prior to interventions, medication history technicians did not assess allergies; as a part of this effort, medication history technicians were trained to ask about reactions to reported beta-lactam allergies as well as inquire about previously tolerated beta-lactams including penicillin, amoxicillin, and cephalexin. A documentation tool with scripted questions was created to help facilitate standardization and collection of beta-lactam allergy information. Common beta-lactams were listed on top of the tool to help technicians independently identify patients needing further allergy assessment. Pharmacists were responsible for directing technician follow-up for more uncommon beta-lactam allergies. Once allergy assessment was complete, information was presented to pharmacists who then completed any necessary documentation in the allergy section of the electronic health record.

Pharmacist workflow was modified in 2 ways when verifying orders and monitoring patients with reported beta-lactam allergies. First, pharmacists were expected to screen for patients lacking documentation of a reaction type. These patients were flagged for follow-up in the electronic health record for the responsible medication history technician or decentralized pharmacist to ensure allergy history assessment.

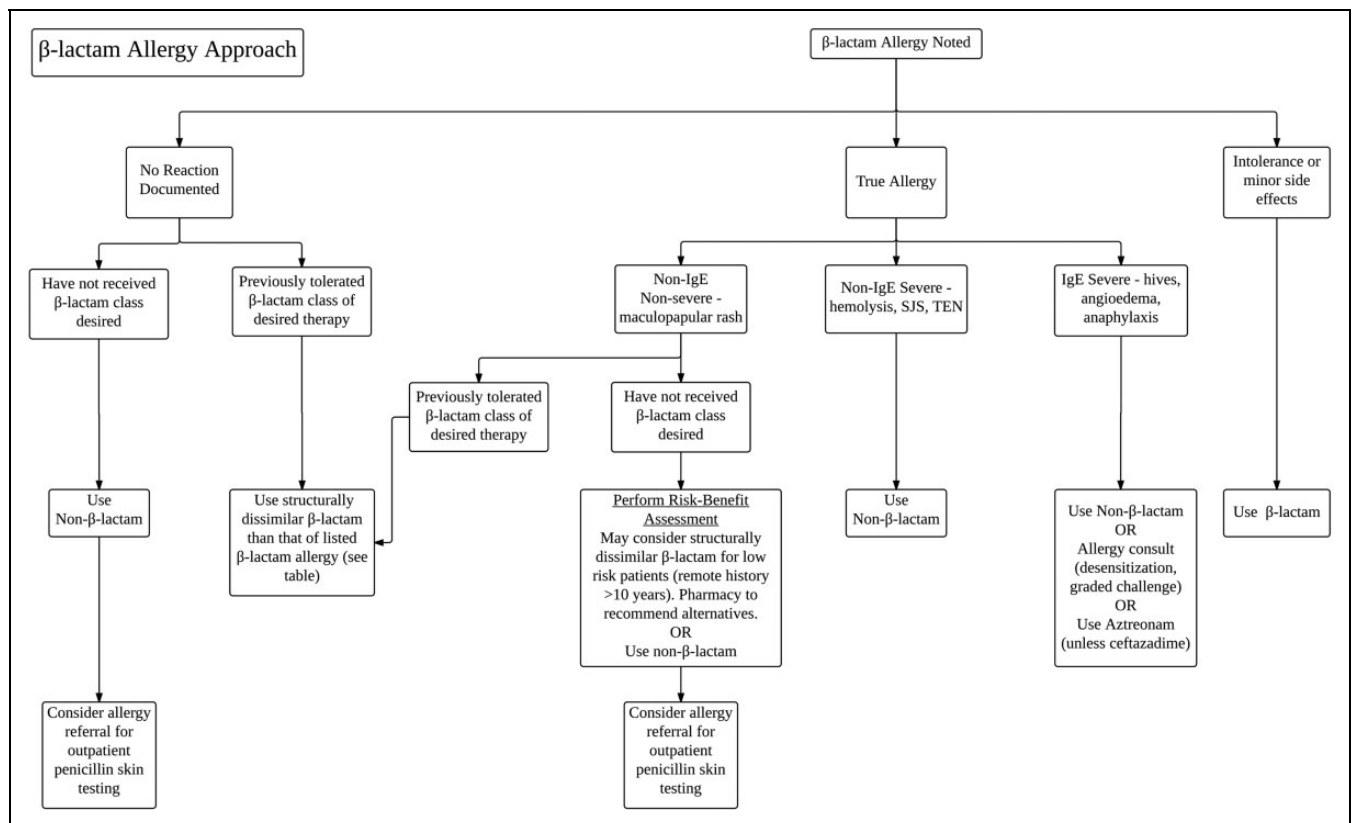


Figure 1. Beta-lactam allergy approach flowchart. SJS indicates Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

They then reviewed allergy history information obtained by medication history technicians or performed the allergy history and input this information into the allergy section of the electronic health record. Second, pharmacists were trained to perform historical antibiotic profile reviews using the electronic health record. All previously administered antibiotics within our health-care system were screened. Patients were considered tolerant to a beta-lactam if they had received more than 1 dose of the same antibiotic without incident. Pharmacists then input this information into the allergy section of the electronic health record.

Antibiotic selection. Once beta-lactam allergy information was complete, pharmacists were responsible for making recommendations to prescribers regarding antibiotic selection and use of beta-lactams, as appropriate. To help facilitate selection of appropriate therapy, a local antibiotic selection guideline for patients with reported beta-lactam allergies was utilized. This guideline was developed in collaboration with allergy and infectious diseases physicians and was based on current literature and guidelines (Figure 1).¹⁴ In determining the appropriateness of a beta-lactam as a treatment option, several factors were considered including allergy reaction type, beta-lactam history, and beta-lactam structure. In helping assess beta-lactam structural similarity, a chart with 31 common beta-lactams comparing side chain structures was provided. Beta-lactams were listed both on the top row and first column

so that an allergen could be easily cross-referenced with various beta-lactams to quickly assess side chain similarity. Additionally, a quick reference table of potential beta-lactam treatment options for patients with non-IgE nonsevere reaction types (eg rash) was developed (Figure 2). All reference tools were distributed to pharmacists and prescribers prior to implementation of interventions.

Following development of reference tools, brief discipline-specific presentations were delivered to pharmacists and prescribers on antibiotic selection in patients with reported beta-lactam allergies. Pharmacists were educated via both formal group presentations and individually on allergy mechanisms, beta-lactam cross-reactivity rates and use of the developed reference tools. Regarding prescriber education, hospitalists and intensivists were the focus of education on the efficacy, safety, and economic implications of consistent avoidance of beta-lactams in patients with reported beta-lactam allergies. In addition, current estimates of cross-reactivity rates between beta-lactam classes were presented. Finally, explanation of the local antibiotic selection guideline and reference tools was provided to facilitate ease of use prior to the implementation date.

Data Collection, Definitions, and Outcomes

A retrospective query was performed using the electronic health record to identify patients with a beta-lactam allergy and receipt of an antibiotic during their inpatient stay. Patients may

Allergy	Treatment Options
If Penicillin allergy	• 3rd/4th generation cephalosporins - ceftriaxone, cefdinir, cefpodoxime, ceftazidime, cefepime • Others - cefuroxime, ertapenem, meropenem
If Aminopenicillin allergy (amoxicillin, ampicillin, Augmentin)	• 3rd/4th generation cephalosporins - ceftriaxone, cefdinir, cefpodoxime, ceftazidime, cefepime • Others - cefuroxime, ertapenem, meropenem
If Cephalosporin allergy	
1 st generation (cephalexin, cefazolin)	• 3rd/4th generation cephalosporins - ceftriaxone, cefdinir, cefpodoxime, ceftazidime, cefepime • Others - cefuroxime, meropenem
2 nd generation (cefuroxime, cefotetan, cefaclor)	• 3rd/4th generation cephalosporins - ceftriaxone, cefdinir, cefpodoxime, ceftazidime, cefepime • Others - meropenem
3 rd /4 th generation (ceftriaxone, cefpodoxime, cefepime)	• Penicillins - piperacillin/tazobactam, nafcillin, amoxicillin • 1st/2nd generation cephalosporins - cephalexin, cefazolin, cefuroxime • Carbapenems - ertapenem, meropenem

Figure 2. Non-IgE (nonsevere) reaction type reference.

have received a non-beta-lactam only, beta-lactam only, or a combination of both. Following the query, a manual chart review was performed for each patient identified to collect pertinent data.

Patients with multiple beta-lactam allergies were counted as having documentation of reaction type if a reaction was documented for at least one of their listed allergies. Length of stay was defined as 1 day if the patient was hospitalized for any part of the day. When assessing days of therapy for beta-lactams and non-beta-lactams, receipt of at least a single dose constituted 1 day. Only patients receiving the antibiotic category in question were included when determining treatment days. Transitioning from a non-beta-lactam to a beta-lactam was defined as a cessation of at least 1 non-beta-lactam in order to initiate a beta-lactam for continuation or completion of therapy. Patients may have been receiving monotherapy with a non-beta-lactam or combination therapy with non-beta-lactams during the time of therapy transition.

The primary outcomes assessed were the percentage of beta-lactam allergic patients with documentation of reaction type and the percentage of patients receiving non-beta-lactams as either monotherapy or in combination with beta-lactam therapy. Secondary outcomes included the percentage of beta-lactam allergic patients with documentation of previously

tolerated beta-lactam antibiotics, the percentage of patients receiving a non-beta-lactam who were transitioned to a beta-lactam, discharge antibiotic therapy, and adverse events related to interventions.

Statistical Analysis

Categorical data are displayed as percentages and were compared via the χ^2 test or Fisher's exact test. Continuous data were assessed for distribution; nonnormally distributed data are displayed as median with interquartile ranges and were compared using the Mann-Whitney *U* test. All *P* values were 2 tailed and considered statistically significant at $\alpha \leq .05$. All statistical analyses were conducted with SPSS, version 23.0 (IBM Corp, Armonk, New York).

Results

A total of 179 patients were included in this study, with 91 and 88 patients in the preintervention and postintervention groups, respectively. Patients in both groups were similar in their described baseline characteristics (Table 1). Penicillin was the most commonly reported beta-lactam allergy in both the

Table 1. Baseline Characteristics.^a

Variables	Preintervention (n = 91)	Postintervention (n = 88)
Age, median (IQR), years	68 (57-80)	67 (57-77)
Women (%)	57.1	56.8
Ordering department (%)		
Hospitalist	62.6	61.5
Intensivist	19.8	24.6
Infectious disease	2.2	1.7
Other	15.4	12.3
Total antibiotic treatment days, median (SD)	5 (3-7)	5 (3-6)
Length of stay, median (IQR), days	5 (4-8)	5 (3-7)
ID consult (%)	19.8	27.3
Reported beta-lactam allergy (%)		
Penicillin	81.3	86.4
Cephalosporin first generation	2.2	2.3
Cephalosporin second generation	4.4	2.3
Cephalosporin third generation	2.2	1.1
Cephalosporin unspecified	0.0	2.3
More than one beta-lactam allergy (%)	9.9	5.7
Previously received beta-lactam as inpatient (%)	33.0	29.5

Abbreviations: IQR, interquartile range; SD, standard deviation; ID, infectious disease.

^aP >.05 for all comparisons.

preintervention and postintervention groups (81.3% and 86.4%, respectively).

The percentage of patients with documentation of reaction type was high in both groups and not significantly different (90.1% vs 89.8%, $P = .940$). Rash was the most common reaction type noted and anaphylaxis was documented in 3.7% and 8.9% of the preintervention and postintervention allergens, respectively. Breakdown of other reaction types is displayed in Table 2. There was a 3-fold increase in the percentage of patients with documentation of previously tolerated beta-lactams in the postintervention group relative to the preintervention group (28.4% vs 8.8%, $P = .001$). However, prior receipt of inpatient beta-lactam therapy was similar between groups, as reported in Table 1.

There was no significant difference in the overall percentage of patients receiving non-beta-lactams between the preintervention and postintervention groups (86.8% vs 84.1%, $P = .605$). However, among patients initially receiving non-beta-lactams, the percentage of those transitioned to a beta-lactam was significantly greater in the postintervention group relative to the preintervention group (25.7% vs 11.4%, $P = .022$). The most commonly used non-beta-lactams were vancomycin and fluoroquinolones; additional therapy details for the 2 groups are displayed in Table 3. Beta-lactam use between the groups was similar, with approximately 60% of patients receiving a beta-lactam as monotherapy or a part of combination therapy. No significant difference was noted between groups in the duration of non-beta-lactam or beta-

Table 2. Allergy History Documentation Outcomes.

Variables	Preintervention (n = 91)	Postintervention (n = 88)	P Value
Reaction type documented (%)	90.1	89.8	.940
Documented reactions (%) ^a			
Rash	40.2	41.8	
Hives	24.4	16.5	
Angioedema/swelling	7.3	5.1	
Anaphylaxis	3.7	8.9	
Bronchospasm/SOB	1.2	1.3	
GI upset (N/V/D)	11.0	12.7	
Itching	0.0	1.3	
Flushing	1.2	0.0	
Other	7.3	8.9	
Unknown	3.7	3.8	
Previously tolerated beta-lactams documented (%)	8.8	28.4	.001

Abbreviations: GI, gastrointestinal; N/V/D, nausea, vomiting, diarrhea; SOB, shortness of breath.

^aPatients may report more than one reaction.

Table 3. Antibiotic-Related Outcomes.

Variables	Preintervention (n = 91)	Postintervention (n = 88)	P Value
Non-beta-lactam use (%)	86.8	84.1	.605
Fluoroquinolone	46.2	47.7	
Vancomycin	39.6	48.9	
Aminoglycosides	0.0	3.4	
Non-beta-lactam treatment days, median (IQR)	4 (3-6)	4 (3-5)	.091
Non-beta-lactams changed to beta-lactams (%)	11.4	25.7	.022
Beta-lactam use (%)	64.8	65.9	.880
Penicillin	17.6	14.8	
Cephalosporin first generation	7.7	10.2	
Cephalosporin second generation	0.0	0.0	
Cephalosporin third generation	40.7	29.5	
Cephalosporin fourth generation	19.9	17.0	
Cephalosporin advanced generation	0.0	1.1	
Carbapenem	8.8	9.1	
Beta-lactam treatment days, median (IQR)	4 (3-6)	3 (2-5)	.078
Received antibiotics at discharge (%)	36.3	56.8	.006
Non-beta-lactam	72.7	56.0	
Beta-lactam	18.2	42.0	.031
Non-beta-lactam + beta-lactam	9.1	2.0	

Abbreviation: IQR, interquartile range.

lactam therapy. More patients received antibiotics at discharge in the postintervention group relative to preintervention (56.8% vs 36.3%, $P = .006$). Among patients receiving antibiotic prescriptions at discharge, significantly more patients received beta-lactams in the postintervention versus preintervention group (42% vs 18% respectively, $P = .031$). There were no reported adverse events associated with transitioning to beta-lactam therapy.

Discussion

In this pre–post study, multidisciplinary education and pharmacy-led efforts to target allergy history documentation and antibiotic selection among patients with reported beta-lactam allergies were not associated with a difference in the documentation of reaction types for patients with reported beta-lactam allergies. Although prior receipt of beta-lactam therapy was similar between groups, there was a significant increase in the percentage of patients with documentation of previously tolerated beta-lactams in the postintervention group, suggesting interventions had a significant impact. One explanation for the former is that baseline documentation of reaction types for patients was much greater than anticipated based on the reviewed literature and it was therefore difficult to improve on this outcome further.²³ Documentation of previously tolerated beta-lactam therapy was not emphasized prior to interventions. Furthermore, medication history technicians played a novel role in allergy history collection and may have facilitated the collection and documentation of important allergy history details including previously tolerated beta-lactam therapy. Our findings demonstrate that targeted education and modified pharmacy workflow can positively impact documentation of allergy history details and this may have contributed to the impact on subsequent antibiotic selection.

This study did not find an overall reduction in the use of non-beta-lactams. However, we observed a substantial increase in the percentage of patients being transitioned from non-beta-lactams to beta-lactams as well as greater use of beta-lactams in patients receiving antibiotics at discharge. These findings may reflect the reality that it often takes time to ascertain sufficient allergy history details to allow for a corresponding intervention (when appropriate) and that interventions distinct from those implemented at our site may be required to impact choice of empiric therapy. Prescriber and pharmacist education emphasized the importance of avoiding delay in antibacterial therapy in favor of a comprehensive allergy follow-up. This is something that must be considered when designing interventions and may explain the lack of difference between groups in the overall use of non-beta-lactams. Interestingly, there was a significant difference observed between treatment groups in the number of patients receiving antibiotics at discharge. One potential explanation for this is that data were collected from patients admitted during different seasons during the year. Nonetheless, these data suggest that the interventions made had an impact on antibiotic selection during the inpatient stay and at the time of hospital discharge.

The incidence of adverse reactions among beta-lactam allergic patients receiving a beta-lactam was low in this study. The lone incident occurred in the preintervention group when a patient with a cefazolin allergy (hives) received cefepime and developed shortness of breath and rash. The cefepime was immediately stopped and the patient was treated with an antihistamine and corticosteroid with resolution of symptoms. The low frequency of events supports the notion that multidisciplinary interventions and education may optimize antibiotic selection in these patients without compromising patient safety; however, further safety data are needed to substantiate our observation.

Numerous studies have been performed focusing on the consequences of unnecessary avoidance of beta-lactams in patients with reported allergies including increased costs, bacterial resistance, and decreased safety and efficacy.^{5–7} Despite these findings, there are relatively few studies detailing interventions to improve allergy history assessment as well as antibiotic selection in this patient population. The most pertinent studies to date have focused on curtailing aztreonam use. One such study conducted by Staicu et al utilized a combination of a penicillin allergy screening tool, education, order sets, and prospective aztreonam order review.⁹ Following implementation, aztreonam usage was significantly reduced, while the use of beta-lactams was increased. Another study conducted by Estep et al focused on improving allergy histories and documentation through patient interviews and electronic health record review and evaluated the impact on aztreonam use.¹⁰ Interventions resulted in a decreased duration of aztreonam therapy and a greater percentage of patients being switched to beta-lactam antibiotics. Although our interventions were not specific for aztreonam, we also observed an increase in the number of patients who were transitioned to beta-lactam therapy following implementation of interventions. We targeted the problem more broadly focusing on the use of all non-beta-lactams as opposed to aztreonam, which may have been targeted by other investigators due to its cost and reduced antibiotic spectrum of activity.

Through multidisciplinary education and pharmacy-led efforts, we realized a significant impact on both beta-lactam allergy documentation and antibiotic selection. As a result, our interventions are being targeted for system-wide implementation at all 16 hospitals in our health system over the coming year. Given the prevalence of inaccurate and incomplete beta-lactam allergy documentation and resultant consequences on antibiotic selection, it is critical that there are continued efforts to optimize allergy documentation and antibiotic selection in these patients. We believe this represents the “low-hanging fruit” in many centers and is an important area for antimicrobial stewardship process improvement efforts. Additional strategies to consider include use of penicillin skin testing, graded challenges, and desensitization in appropriate scenarios. Recent studies have shown that incorporation of these interventions into clinical practice, when appropriate, can also increase the use of beta-lactams in this population and may have a greater impact on empiric selection.^{24,25} We did not include these as part of our initial strategy, but plan to consider in the future.

This study had several limitations. First, we excluded patients with beta-lactam allergies not receiving antibiotics and those receiving antibiotics for surgical prophylaxis. As a result, we did not collect data on allergy documentation in these populations, nor did we collect antibiotic selection data in the surgical population, which may have impacted our results for these particular outcomes and limits applicability to certain populations. However, as logistics differ significantly in the surgical population, we felt it was appropriate to exclude these patients and have made this population a focus for subsequent quality improvement. Second, defining documentation of reaction type for patients with multiple beta-lactam allergies as documentation of at least a single reaction type may have impacted this outcome. However, given the small number of patients with multiple beta-lactam allergies, this appeared to have minimal impact. Third, our primary outcome of non-beta-lactam use did not differentiate between those receiving non-beta-lactam monotherapy versus in combination with beta-lactams. There may have been a greater effect of interventions noted in the monotherapy group. However, we were looking to assess the net impact of interventions on overall antibiotic selection. Fourth, preintervention data were collected for patients admitted during the fall as opposed to the spring for the postintervention group. There may have been significant differences in the incidence of disease states between groups not taken into account. Furthermore, indications for therapy were not assessed. However, use of various non-beta-lactams appeared similar between groups and non-beta-lactam therapy may have been appropriate given suspected infection or organism. Finally, no formal calculation was used to estimate the needed sample size.

Conclusion

Multidisciplinary education combined with pharmacy-led efforts to confront the challenge of beta-lactam allergies among hospitalized patients was not associated with an overall reduction in non-beta-lactam use, but did increase the number of patients transitioned from non-beta-lactam to beta-lactam therapy. These findings suggest this may be a meaningful strategy for process improvement with a positive contribution toward antimicrobial stewardship efforts. Further investigation of interventions to improve allergy histories and antibiotic selection in this population is warranted.

Declaration of Conflicting Interests

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