

# Impact of an antimicrobial stewardship initiative to evaluate $\beta$ -lactam allergy in patients ordered aztreonam

**Petra M. Estep, Pharm.D., BCPS,**  
Department of Pharmacy, UF Health  
Jacksonville, Jacksonville, FL.

**Jason A. Ferreira, Pharm.D., BCPS,**  
Department of Pharmacy, UF Health  
Jacksonville, Jacksonville, FL.

**Lori H. Dupree, Pharm.D., BCPS,**  
University of Florida College of Pharmacy,  
Jacksonville, FL.

**Petra J. Aldridge, M.S.,** Center for  
Health Equity and Quality Research, UF  
Health Jacksonville, Jacksonville, FL.

**Christopher A. Jankowski, Pharm.D.,  
BCPS,** Department of Pharmacy, UF  
Health Jacksonville, Jacksonville, FL.

**Purpose.** An evaluation of the clinical and economic impact of an antimicrobial stewardship quality initiative (ASQI) focusing on allergy assessment in patients with a documented  $\beta$ -lactam allergy prescribed aztreonam was conducted.

**Methods.** This retrospective study was executed at a hospital with an interdisciplinary antimicrobial stewardship program (ASP). A total of 186 patients with self-reported  $\beta$ -lactam allergies who were prescribed aztreonam while admitted during a 36-month time period surrounding the ASQI implementation were included. The primary study outcome was median time in hours to aztreonam discontinuation among nonanaphylactic patients.

**Results.** After implementation of the ASQI, the percentage of patients continued on aztreonam for the duration of therapy was nearly cut in half, and a greater percentage of patients were switched to  $\beta$ -lactam antibiotics. No adverse effects associated with  $\beta$ -lactam therapy were observed in any study patient. Antimicrobial cost savings was not associated with any difference in clinical outcomes. Overall, hospitalwide aztreonam prescribing and aztreonam use declined. Institutional aztreonam orders per 1000 patient-days decreased from 1.5 to 1 after implementation of the ASQI. Additionally, hospitalwide aztreonam days of therapy per 1000 patient-days was reduced from 3.6 in the pre-ASQI period to 1.8 in the post-ASQI period.

**Conclusion.** An ASQI that included critical evaluation of patient-reported  $\beta$ -lactam allergies led to decreased aztreonam use, reduced antimicrobial expenditure, and similar clinical outcomes to those observed before implementation.

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Address correspondence to Dr. Jankowski  
(christopher.jankowski@jax.ufl.edu).

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Antimicrobial stewardship programs (ASPs) aim to optimize patient outcomes by ensuring appropriate antimicrobial use while minimizing toxicity and adverse drug events.<sup>1-4</sup> Initially, programs focus on the most attainable targets, such as i.v.-to-oral conversions, therapeutic substitutions, optimization of dosing and therapy duration, and formulary restrictions.<sup>1</sup> In addition, ASPs are critical for identifying inappropriate therapy.<sup>2</sup> With upward of 30% of hospital pharmacy budgets allocated to antimicrobial agents, curtailing inap-

propriate use can result in significant cost savings.<sup>1</sup>

Inaccurate patient allergy identification can substantially impact antimicrobial prescribing, resulting in increased use of therapies incongruent with standards of care.<sup>3,5</sup> Approximately 10–15% of hospitalized patients report penicillin allergies, often exaggerating their severity.<sup>3,6,7</sup> Overestimation of cross-reactivity among  $\beta$ -lactams and unverified allergies can negatively affect patient outcomes by increasing treatment failures, intensive care unit admis-



Petra M. Estep, Pharm.D., BCPS, is a postgraduate year (PGY) 2 drug information pharmacy resident at UF Health Jacksonville. She received her Bachelor of Arts in Biological Sciences from the University of Chicago in 2007 and her Doctor of Pharmacy, summa cum laude, from the University of Florida College of Pharmacy in 2014. Dr. Estep also completed an ASHP-accredited PGY-1 Pharmacy Residency at UF Health Jacksonville. She is currently completing her Master in Health Administration at Louisiana State University Shreveport with hopes of pursuing a career in pharmacy administration. Her areas of interest include medication safety and formulary management.

sion rates, length of stay (LOS), and mortality while also increasing drug and treatment costs.<sup>3,5,6</sup>

In an attempt to verify allergies, penicillin skin testing (PST) may be used. Although studies have shown high negative predictive values for allergic reactions with PST, 80–90% of all patients reporting a penicillin allergy will have a negative test result.<sup>8</sup> Relatively low positive predictive values of PST (approximately 50%) have been reported and may limit the clinical utility of these tests, as the potential for unchallenged false-positive tests remains high.<sup>3,9,10</sup> Although some studies suggest that PST may marginally improve clinical outcomes and minimize adverse effects in serious infections with

penicillin-based first-line therapies, routinely performing PST on all patients reporting penicillin allergies may not be pragmatic in all settings because of the added acquisition cost of the test and the time commitment required to perform the test by trained personnel.<sup>11</sup> Critically evaluating allergies without using PST to determine probable risk of allergic reactions in patients self-reporting  $\beta$ -lactam allergies may improve patient care and offer a cost savings to the institution without adding undue hardship.

Aztreonam, an antipseudomonal monobactam, is an alternative for  $\beta$ -lactam allergic patients with serious infections because of the low risk of cross-reactivity.<sup>12</sup> Due to its suboptimal empiric susceptibilities in *Pseudomonas aeruginosa* isolates and high acquisition costs compared to therapeutic alternatives, aztreonam prescribing should be considered a trigger for antimicrobial stewardship intervention. The purpose of this study was to evaluate the clinical and economic impact of an antimicrobial stewardship quality initiative (ASQI) focusing on allergy assessment in patients with a documented  $\beta$ -lactam allergy prescribed aztreonam.

## Methods

This randomized, retrospective study compared adult patients with a self-reported  $\beta$ -lactam allergy of any severity who were admitted to an inpatient service during the two study periods (pre-ASQI: February 1, 2012, to July 31, 2013; post-ASQI: August 1, 2013, to January 31, 2015) and received an order for aztreonam. As part of the ASQI, patients ordered aztreonam were identified by pharmacists through real-time electronic medical record (EMR) reports or during the order verification process. The patient records were then reviewed to determine the accuracy of the documented allergy and previously tolerated  $\beta$ -lactams. If no previously tolerated  $\beta$ -lactams were documented in the EMR, a patient

or family member interview was performed, if feasible, to assess the accuracy of the documented allergies. If necessary, the patient's local pharmacy was contacted. Based on the information collected, the pharmacist completing the evaluation noted therapy recommendations and updated allergies within the EMR as appropriate. Patients were excluded if an anaphylactic reaction to a  $\beta$ -lactam antibiotic was witnessed by healthcare providers within this institution or if patients were pregnant, nursing, incarcerated, or currently enrolled in an ongoing clinical trial.

Although a structured evaluation of aztreonam use was only performed in the postintervention group, the ASP was active during both study periods. Therefore, a primary endpoint of time to discontinuation was expected to yield a more precise measurement of the ASQI impact than days of therapy. With an estimated hazard ratio of 1.5 for discontinuation of aztreonam, an a priori sample size calculation for the primary outcome determined the need for 68 patients reporting reactions other than anaphylaxis per group to achieve 80% power ( $\alpha = 0.05$ ). All patients with aztreonam orders during the periods were randomized using a random number generator and evaluated until the sample size was achieved in the nonanaphylaxis group. If patients had a documented anaphylaxis allergy (impairment to breathing due to tongue or throat swelling or that required immediate medical treatment for survival), they were evaluated for secondary endpoints, including time to aztreonam discontinuation. Secondary endpoints included the number of aztreonam orders per 1000 patient-days, days of aztreonam therapy per 1000 patient-days, percentage of orders placed during weekday per ASQI operating hours, incidence of antimicrobial allergy-related adverse effects, LOS, infection-related LOS (I-LOS), hospital costs during LOS and I-LOS, antimicrobial drug costs

during I-LOS, patient disposition, infection outcome, and alternative antimicrobial therapies used. Adverse-event data were collected from the EMR indicating the administration of diphenhydramine, corticosteroids, or epinephrine to treat a reaction to an antimicrobial. Infection outcome was classified as clinical cure or clinical failure (defined as escalation of antimicrobial therapy, addition of a second antipseudomonal agent within 48 hours

of initiating aztreonam, or patient death).

This study was approved by the hospital's institutional review board. Ten percent of the collected data were validated by a coinvestigator for interrater reliability, resulting in 100% agreement. Continuous variables were described using medians and interquartile ranges (IQRs) and analyzed with Wilcoxon's rank sum test. Categorical variables were described using counts and percent-

ages and analyzed with Fisher's exact tests. All analyses were performed using SAS version 9.3 for Windows (SAS Institute, Cary, NC).

## Results

A total of 68 nonanaphylactic patients were included per group with 11 and 39 anaphylactic patients included in the pre-ASQI group and post-ASQI group, respectively. Eleven patients were excluded because of the absence of a documented

**Table 1.** Baseline Characteristics of Patients Before and After Implementation of ASQI<sup>a</sup>

| Variable                                                   | Before Implementation<br>(n = 79) | After Implementation<br>(n = 107) | p      |
|------------------------------------------------------------|-----------------------------------|-----------------------------------|--------|
| Median age (IQR) <sup>a</sup> , yr                         | 61 (48–76)                        | 61 (50–72)                        | 0.534  |
| Male, no. (%)                                              | 27 (34.2)                         | 42 (39.3)                         | 0.540  |
| Race, no. (%)                                              |                                   |                                   | 0.139  |
| African American                                           | 42 (53.2)                         | 46 (43.0)                         |        |
| Caucasian                                                  | 32 (40.5)                         | 58 (54.2)                         |        |
| Hispanic                                                   | 1 (1.3)                           | 0                                 |        |
| Other, refused                                             | 4 (5.1)                           | 3 (2.8)                           |        |
| Median height (IQR), cm                                    | 165 (160–175)                     | 168 (160–175)                     | 0.502  |
| Median weight (IQR), kg                                    | 77.6 (59.2–93.6)                  | 82.9 (61.3–97.3)                  | 0.437  |
| Median age-adjusted Charlson Comorbidity Index score (IQR) | 5 (1–7)                           | 4 (3–6)                           | 0.471  |
| Treatment indication, no. (%)                              |                                   |                                   | 0.158  |
| Pneumonia                                                  | 26 (32.9)                         | 29 (27.1)                         |        |
| Empiric therapy                                            | 11 (13.9)                         | 31 (29.0)                         |        |
| Urinary tract infection/pyelonephritis                     | 16 (20.2)                         | 13 (12.1)                         |        |
| Sepsis                                                     | 10 (12.7)                         | 10 (9.3)                          |        |
| Skin and skin structure infection                          | 14 (17.7)                         | 15 (14.0)                         |        |
| Intraabdominal infection                                   | 2 (2.5)                           | 7 (6.5)                           |        |
| Endocarditis                                               | 0                                 | 1 (0.9)                           |        |
| Ventriculitis                                              | 0                                 | 1 (0.9)                           |        |
| Documented reaction, no. (%) <sup>b</sup>                  |                                   |                                   |        |
| Dermal reaction                                            | 35 (44.3)                         | 41 (38.3)                         | 0.452  |
| Angioedema                                                 | 1 (1.3)                           | 9 (8.4)                           | 0.046  |
| Mouth/lip/throat swelling                                  | 5 (6.3)                           | 23 (21.5)                         | 0.006  |
| Nausea/vomiting                                            | 5 (6.3)                           | 4 (3.7)                           | 0.498  |
| Miscellaneous                                              | 10 (12.7)                         | 63 (58.9)                         | <0.001 |
| Unspecified                                                | 27 (34.1)                         | 32 (30.0)                         | 0.633  |

<sup>a</sup>ASQI = antimicrobial stewardship quality initiative, IQR = interquartile range.

<sup>b</sup>Patients may report more than one reaction.

$\beta$ -lactam allergy, and 1 excluded patient had a witnessed anaphylactic reaction. All baseline characteristics were similar between groups, with the most common indications for aztreonam therapy being pneumonia (55 of 186, 29.6%) and empiric treatment in nonseptic patients (42 of 186, 22.6%) (Table 1). The most frequent nonanaphylactic reactions reported by patients were dermal reactions (76 of 186, 40.8%) and miscellaneous reactions (73 of 186, 39.2%).

The median time to discontinuation of aztreonam among nonanaphylactic patients was shorter in the post-ASQI group compared with the pre-ASQI group (pre-ASQI: 30.7 hours with an interquartile range [IQR] 1 of 10.1–72.3 hours; post-ASQI: 12.7 hours with an IQR of 0–20.3 hours;  $p = 0.02$ ). This decrease in time to discontinuation was greater among anaphylactic patients as the median time to discontinuation declined from 138.1 hours (IQR, 67.2–164.2 hours) in the pre-ASQI group to 43.1 hours (IQR, 6.2–111.4 hours) in the post-ASQI group ( $p = 0.02$ ). A larger percentage of aztreonam orders were placed during weekday hours in the pre-ASQI group (40.5% versus 27.1%).

After implementation of the ASQI, the percentage of patients

continued on aztreonam for the duration of therapy was nearly cut in half (7.6% versus 3.7%) and a greater percentage of patients were switched to  $\beta$ -lactam antibiotics (22.8% versus 34.6%). Even among patients with anaphylactic-type reactions documented in the EMR, more patients in the post-ASQI group were deemed eligible to be switched to  $\beta$ -lactam antibiotics (9.1% versus 20.5%). No adverse effects associated with  $\beta$ -lactam therapy were observed in any study patient.

Antimicrobial cost savings was not associated with any difference in clinical outcomes (Table 2). Among patients with presumed or culture-proven bacterial infections, the rate of clinical cure was comparable between groups (70 of 75, 93.3% versus 87 of 95, 91.6%). Upon discharge, utilization rates of i.v. antimicrobials (20.5% versus 13.1%), oral antimicrobials (29.5% versus 26.2%), and no antimicrobials (50.0% versus 60.7%) were similar between pre-ASQI and post-ASQI groups, respectively.

Overall, hospitalwide aztreonam prescribing and aztreonam use declined. Institutional aztreonam orders per 1000 patient-days decreased from 1.5 to 1 after implementation of the ASQI. Additionally, hospitalwide aztreonam days of therapy per 1000 patient-days was reduced from 3.6

in the pre-ASQI period to 1.8 in the post-ASQI period.

## Discussion

Self-reported  $\beta$ -lactam allergies can severely limit the options for antibiotic treatment of many infectious diseases. ASPs can utilize prospective audit interventions to educate prescribers on the use of appropriate antimicrobials to optimize clinical outcomes without superfluous antimicrobial exposure or cost to the institution. This study demonstrates the positive impact of ASP intervention, with a low additional resource requirement that employs both education and patient interview techniques to determine the appropriateness of aztreonam prescribing in an academic medical center.

The implementation of the ASQI allowed for increased awareness of the many inaccuracies of self-reported  $\beta$ -lactam allergies within this institution. After implementation, a greater percentage of patients were switched to  $\beta$ -lactam antibiotics, which consequently resulted in a statistically significant decrease in time to aztreonam discontinuation among both anaphylactic and nonanaphylactic patients. This decrease was greater among anaphylactic patients because there is a greater hesitancy to recommend  $\beta$ -lactam thera-

**Table 2.** Secondary Outcomes Before and After Implementation of the ASQI<sup>a</sup>

| Variable                              | Before Implementation<br>( <i>n</i> = 79) | After Implementation<br>( <i>n</i> = 107) | <i>p</i> |
|---------------------------------------|-------------------------------------------|-------------------------------------------|----------|
| Median aztreonam cost (IQR), \$       |                                           |                                           |          |
| Anaphylaxis group                     | 1,285 (603–1,567)                         | 402 (80–803)                              | 0.011    |
| Nonanaphylaxis group                  | 241 (80–643)                              | 161 (0–643)                               | 0.095    |
| Median antimicrobial cost (IQR), \$   | 1,052 (352–1,536)                         | 465 (86–813)                              | <0.001   |
| Median LOS (IQR), days                | 9 (5–15)                                  | 9 (6–17)                                  | 0.200    |
| Median LOS hospital costs (IQR), \$   | 58,590 (32,981–119,892)                   | 76,895 (39,182–160,962)                   | 0.090    |
| Median I-LOS (IQR), days              | 7 (5–11)                                  | 7 (4–12)                                  | 0.780    |
| Median I-LOS hospital costs (IQR), \$ | 44,994 (26,041–94,742)                    | 58,048 (28,399–118,501)                   | 0.160    |

<sup>a</sup>ASQI = antimicrobial stewardship quality initiative, IQR = interquartile range, LOS = length of stay, I-LOS = infection-related length of stay. All costs based on average wholesale price.

py among those who may experience a more severe adverse reaction without appropriate assessment.

Since recommended alternatives were often less expensive than aztreonam, the ASQI proved valuable even in cases where a  $\beta$ -lactam use was deemed inappropriate. Aztreonam expenditure was significantly decreased among anaphylactic patients, and while aztreonam cost was not significantly decreased among nonanaphylactic patients, the institution substantiated an annual savings of \$28,134, based on hospital acquisition cost. Further, a significant decrease in total antimicrobial costs per patient was seen across the entire study population.

A standardized algorithm for the treatment of patients with self-reported  $\beta$ -lactam allergies has yet to be determined. PST may be an option to help guide therapy, but the need for clinical evaluation of a patient's medication allergy and reaction history remains. Salkind et al.<sup>8</sup> endorsed a thorough history of allergy details prior to skin testing, because a majority of patients are not truly allergic to penicillin. The ASQI used similar questioning during the patient interview, assessing all patients with self-reported allergies and not excluding patients with vague histories or non-type-I reactions. If this ASQI study applied the same inclusion and exclusion criteria for PST as Salkind et al.,<sup>8</sup> only 4 of the 10 patients continued on aztreonam may have qualified for PST, because they reported a rash that could have been immunoglobulin E mediated.

Although cephalosporins and carbapenems are recommended as primary and secondary options in many national infectious diseases guidelines, PST provides little guidance in predicting patient response to these agents. With cephalosporin cross-reactivity ranging from 2% to 5% and skin testing only using penicillin as a reagent, PST does not predict patient response to  $\beta$ -lactam derivatives.<sup>6</sup> Despite evidence demonstrating that

PST may minimally aid in the safe use of a first-generation cephalosporin, the clinical utility of PST with later-generation cephalosporins or carbapenems and patients reporting allergies to  $\beta$ -lactam derivatives has not been established.<sup>11</sup> Although not all patients were switched to  $\beta$ -lactams in this study, less expensive alternatives were consistently selected with no adverse effects reported, and fewer patients were continued on aztreonam therapy.

This study had several limitations. The full impact of the ASQI may not have been realized because a greater percentage of aztreonam orders were placed after hours in the post-ASQI group than in the pre-ASQI group. Also, given the hospital's known suboptimal susceptibilities of aztreonam to *P. aeruginosa*, use may have been lower than at other institutions. This may suggest the potential for a greater impact at institutions with higher aztreonam use. In addition, the retrospective nature of the study demanded a reliance on the accuracy and completeness of the EMR. Minor adverse reactions may have gone undetected if they did not require physician or pharmaceutical intervention. The interventions detailed in this study appear to result in similar clinical outcomes; however, the study group was likely insufficient to detect small changes in rare secondary clinical outcomes such as death and clinical failure. Detailed assessment of clinical impact would require further research.

Critical evaluation of patient-reported  $\beta$ -lactam allergies among patients prescribed aztreonam proved financially beneficial in this ASQI. The results of the study suggest that this stewardship initiative may serve as a low-cost, effective alternative to PST among patients with self-reported  $\beta$ -lactam allergies.

## Conclusion

An ASQI that included critical evaluation of patient-reported

$\beta$ -lactam allergies led to decreased aztreonam use, reduced antimicrobial expenditure, and similar clinical outcomes to those observed before implementation.

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## Disclosures

The authors have declared no potential conflicts of interest.

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