

Initiative to reduce aztreonam use in patients with self-reported penicillin allergy: Effects on clinical outcomes and antibiotic prescribing patterns

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Purpose. Evaluation of the clinical impact of a pharmacist led-penicillin allergy assessment initiative to enhance antibiotic selection is reported.

Methods. A retrospective analysis was conducted on patients with a self-reported penicillin allergy (SRPA) at a 529-bed community teaching hospital and compared clinical response rate before and after implementation of a penicillin allergy assessment initiative, consisting of pharmacy staff education and pocket card development. Patients admitted with SRPA who received antibiotics with gram-negative coverage for at least 48 hours were included. The primary outcome was the clinical response rate of penicillin-allergic patients determined preimplementation and postimplementation of the initiative and was based upon improvement in signs and symptoms of infection. Secondary outcomes included antibiotics used, antibiotic durations, length of stay, survival rate, antibiotic discontinuation rate, and *Clostridium difficile* infection rate.

Results. A total of 280 patients were reviewed. Clinical response rate improved after implementation of the initiative ($p = 0.047$). There were significant differences in the type of antibiotics prescribed between the preimplementation group and the postimplementation group: increased cephalosporin use ($p < 0.001$), decreased aztreonam use ($p = 0.017$), and lower fluoroquinolone use ($p = 0.008$). Median length of stay ($p = 0.943$), in-hospital mortality rate ($p = 0.173$), and *C. difficile* infection rate ($p = 0.426$) were similar before and after implementation of the initiative.

Conclusion. After implementation of an initiative to encourage the use of cephalosporins rather than aztreonam in patients with SRPA, the rate of clinical response and cephalosporin use increased and rates of exposure to aztreonam and fluoroquinolones decreased.

Keywords: antibiotics, antimicrobial stewardship, aztreonam, beta-lactam, drug allergy, infectious disease

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Penicillin allergy is one of the most commonly reported antibiotic allergies, with a reported frequency of 8–12% across the United States.¹⁻⁴ However, 85–90% of patients who report a penicillin allergy are found to have a negative penicillin skin test, and fewer than 1% of patients who report a penicillin allergy have a true immunoglobulin E-mediated allergic reaction. Self-reported penicillin allergy (SRPA)

presents a challenge to treatment and impacts optimal antibiotic selection. Penicillin and other β -lactams are first-line treatment options for many infections requiring gram-negative coverage, but penicillin-allergic patients may be treated with alternative antibiotics.⁵⁻⁸ The consequences of avoiding β -lactams include higher rates of treatment failure, risk of infections with resistant organisms, and

increased costs.⁹⁻¹¹ Furthermore, the cross-reactivity between penicillins and cephalosporins is associated with similarities in the side-chain group of the β -lactam ring.¹² This finding suggests that many penicillin-allergic patients may still be safely treated with a cephalosporin with less structural similarity to penicillin and that alternative antibiotics such as aztreonam and fluoroquinolones may be avoided.

Local institution susceptibility patterns showing increased resistance rates of *Pseudomonas aeruginosa*, with a susceptibility rate to aztreonam as low as 45%, prompted a pharmacist-led initiative at our institution. Reduction in aztreonam use was chosen as the target of this antimicrobial stewardship initiative, while focusing on improving empirical antibiotic therapy. This initiative was implemented to optimize antibiotic selection in penicillin-allergic patients and reduce the use of high-cost and less-effective antibiotics.

Similar antimicrobial stewardship initiatives, which have included penicillin allergy assessment and pharmacist intervention, have demonstrated reductions in the use of alternative antibiotics such as aztreonam.¹²⁻¹⁶ In fact, various penicillin allergy assessment initiatives have demonstrated a 36-76% decrease in aztreonam use, resulting in cost savings of \$297 per patient in 1 study.¹⁵ Although studies have found that reduced aztreonam use provides economic benefits, further studies are needed to evaluate whether clinical outcomes are maintained or improved when reducing the use of alternative antibiotics.

Methods

This single-center, retrospective, observational study was reviewed and approved by the institutional review board at St. Vincent's HealthCare, where the study was conducted. The initiative, which had 2 main components, was implemented in May 2015. The first component of this initiative involved education



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of the pharmacy staff. Pharmacists were educated about the low risk of penicillin-cephalosporin cross-reactivity and instructed to clarify all SRPAs when receiving an order for aztreonam. After clarification of the allergy and review of a patient's tolerance of previous cephalosporin use, pharmacists were expected to contact the prescriber to switch the order from aztreonam to a cephalosporin when possible. The second part of the initiative involved the development of a penicillin-allergy guidance pocket card. This card was distributed hospitalwide and explained the low frequency of cross-reactivity and listed the β -lactams with similar side chains.

This analysis included all patients 18 years of age or older with an SRPA who received antibiotics with gram-negative coverage for at least 48 hours. Data were gathered for periods before (December 2013 through December 2014) and after (June 2015 through June 2016) implementation of the initiative. Antibiotics with gram-negative coverage were examined, reducing

aztreonam use should not affect the use of antibiotics not used for gram-negative infections. Patients with a history of allergy to cephalosporin, penicillin desensitization, antibiotics for prophylaxis or before admission, pregnancy, or incarceration were excluded. Patients were divided into groups based on whether they were treated before or after the initiative was implemented.

The primary outcome was to compare the clinical response rate of patients with SRPA who were treated with antibiotics before and after implementation of the initiative. Clinical response rate, which was based on a modified version of the clinical stability definition from the 2007 Infectious Diseases Society of America community-acquired pneumonia guidelines,⁵ was defined as documentation of resolution or improvement in signs and symptoms of infection, survival at discharge, and criteria for clinical failure were not met.

Clinical failure was defined as prolonged clinical instability of at least 48 hours occurring after 2 days of antimicrobial therapy. Clinical instability criteria included any 1 of the following: temperature of ≥ 37.8 °C, heart rate of ≥ 100 beats/min, respiratory rate of ≥ 24 breaths/min, systolic blood pressure of < 90 mm Hg, inability to maintain oral intake, and altered mental status. Secondary outcomes included length of stay, survival rate, intensive care unit admission rate, aztreonam use, aztreonam drug cost, *Clostridium difficile* infection rate, antibiotic selected, rate of discontinuation due to an adverse reaction, and appropriate antibiotic use. Appropriate antibiotic use was defined as (1) the use of an administered antibiotic regimen that is active against the identified pathogen based on the results of in vitro antimicrobial susceptibility testing or (2) the patient had a clinical response to guideline-recommended antibiotics without the need for changing antibiotic therapy. Antibiotics with at least 1 dose administered were recorded. If an antibiotic was discontinued or

switched during the patient's hospital stay, documentation was examined. If it was determined that the change in antibiotic regimen was due to dosage de-escalation, the antibiotic was defined as appropriate.

All data analyses were performed using SAS OnDemand for Academics, version 9.4 (SAS Inc., Cary, NC). All patients were randomized using a random-number generator and evaluated until the sample size to obtain 80% power was achieved. Fisher's exact test or chi-square test was used to analyze nominal data, and Student's *t* test or Mann-Whitney *U* test was used to analyze continuous data. Based on an estimated 90% clinical response rate after implementation of the initiative, a total of 140 patients would be required in each group to detect a 12.5% absolute risk reduction with a power of 80% and an α of 0.05.

Results

After randomization and exclusions, the study included 280 patients, 140 each in the preimplementation and postimplementation groups. For the preimplementation group, randomization led to the review of 386 of 4,610 medical records. Of the 386 records reviewed, 140 remained after those for 246 patients were excluded—188 with less than 48 hours of antibiotic treatment, 30 with prophylactic antibiotic treatment, 25 with pregnancy, 2 with a reported cephalosporin allergy, and 1 with antibiotic treatment before admission. For the postimplementation group, randomization led to the review of 343 of 4,397 medical records. Of the 343 records reviewed, 140 remained after those for 203 patients were excluded—143 with less than 48 hours of antibiotic treatment, 47 with prophylactic antibiotic treatment, 10 with pregnancy,

and 3 with a reported cephalosporin allergy. Baseline characteristics were similar between both groups except that there were significantly more patients with hypertension and diabetes mellitus in the postimplementation group (Table 1). The most common infections treated were respiratory and urinary tract infections.

The clinical response rate improved from 83.6% of patients in the preimplementation group to 91.4% of patients in the postimplementation group ($p = 0.0468$). Overall, there were significant differences in the distribution of antibiotics prescribed between groups ($p < 0.001$). There was significantly less frequent aztreonam use, less frequent fluoroquinolone use, and more frequent cephalosporin use in the preimplementation group (Table 2). Secondary outcomes were similar between groups except that there were significantly more patients

Table 1. Baseline Characteristics of Study Patients

Characteristic	Before Initiative Implementation (<i>n</i> = 140)	After Initiative Implementation (<i>n</i> = 140)	<i>p</i>
Mean $\pm$ S.D. age, yr	60.4 $\pm$ 20.6	65.0 $\pm$ 16.0	0.159
No. (%) women	103 (73.6)	99 (70.7)	0.807
Mean $\pm$ S.D. height, cm	166.0 $\pm$ 14.6	167.0 $\pm$ 10.9	0.323
Mean $\pm$ S.D. weight, kg	80.2 $\pm$ 28.8	81.8 $\pm$ 27.3	0.413
Comorbidities, no. (%)			
Diabetes mellitus	41 (29.3)	57 (40.7)	0.045
Chronic kidney disease	6 (4.3)	14 (10.0)	0.063
Atrial fibrillation	14 (10.0)	16 (11.4)	0.699
Congestive heart failure	7 (5.0)	6 (4.3)	0.776
Coronary artery disease	22 (15.7)	31 (22.1)	0.170
Hypertension	72 (51.4)	101 (72.1)	<0.001
Chronic obstructive pulmonary disease	39 (27.9)	41 (29.3)	0.791
Malignancy	29 (20.7)	22 (15.7)	0.357
Infection type, no. (%)			
Pulmonary	57 (40.7)	61 (43.5)	0.400
Intraabdominal	26 (18.6)	18 (12.9)	0.190
Genitourinary	33 (23.6)	33 (23.6)	0.677
Sepsis, bacteremia	9 (6.4)	15 (10.7)	0.277
Skin or soft tissue	20 (14.3)	26 (18.6)	0.420

Table 2. Outcomes Before and After Initiative Implementation

Outcome	Before Initiative Implementation (n = 140)	After Initiative Implementation (n = 140)	p
Specific antibiotic type received, no. (%) pts			
Aminoglycoside	7 (5.0)	2 (1.4)	0.090
Carbapenem	7 (5.0)	7 (5.0)	>0.999
Cephalosporin	56 (40.0)	106 (75.7)	<0.001
Fluoroquinolone	71 (50.7)	49 (35.0)	0.008
Macrolide	11 (7.9)	24 (17.1)	0.019
Monobactam	17 (12.1)	6 (4.3)	0.017
Mean $\pm$ S.D. length of stay (days)	7.2 $\pm$ 5.7	7.3 $\pm$ 6.7	0.943
No. (%) pts surviving	133 (95.0)	138 (98.6)	0.173
No. (%) pts admitted to intensive care unit	45 (32.1)	49 (35.0)	0.268
No. (%) pts with <i>Clostridium difficile</i> infection	9 (6.4)	6 (4.3)	0.426
No. (%) pts receiving appropriate antibiotics	94 (67.1)	108 (77.1)	0.062
Mean $\pm$ S.D. antibiotic duration (days)	4.3 $\pm$ 2.9	4.1 $\pm$ 3.2	0.466
No. (%) pts with antibiotic discontinued due to adverse reaction	6 (4.3)	0	0.030

who discontinued antibiotics due to an adverse reaction in the preimplementation group (4.3% versus 0%, $p = 0.03$) (Table 2). The majority of adverse reactions in these patients were swelling and rash in patients receiving a fluoroquinolone; however, direct causation could not be determined. In addition, the hospital total acquisition cost of aztreonam decreased from \$7,903 preimplementation to \$1,092 postimplementation.

Discussion

Selecting optimal antibiotics in patients with an SRPA is challenging. Improper interpretation of this allergy and its associated cross-reactivity with cephalosporins may limit treatment options for many types of infections. Penicillin allergy assessment initiatives aim to identify candidates for alternative antibiotics such as cephalosporins with different side-chain structure, which may not have been previously considered attributable to SRPA. Due to the high level of resistance observed at our institution and the high cost associated with alternative antibiotics, this study interven-

tion focused on improving empirical antibiotic therapy for patients with an SRPA.

The goal of this antimicrobial stewardship initiative was to provide more-appropriate antibiotic therapy by identifying candidates for cephalosporins in penicillin-allergic patients and minimizing the use of broad-spectrum antibiotics to limit resistance rates and adverse reactions. With this initiative, a high number of SRPAs were found to be inaccurate, as many patients were able to tolerate cephalosporin.

To the best of our knowledge, this is 1 of the first studies of SRPA to examine clinical response rate as a primary outcome with an adequately powered sample size. Our study findings demonstrate that the initiative was associated with a significant improvement in clinical response rate, with rates similar to previous findings.¹⁵ There was also a decrease in the use of aztreonam and other alternative antibiotics, which was consistent with previous findings.¹²⁻¹⁶ Evidently, this antimicrobial stewardship initiative successfully facilitated a decreased

use of the broad-spectrum antibiotic treatment by prescribers. Overall, this initiative can serve as an effective tool that can be expanded to other institutions and allow for reduced exposure to and adverse effects associated with less favorable alternative antibiotics while providing clinically effective and less costly care.

One limitation of this study was the variable use of antibiotics selected for each type of infection, which may have confounded the results for the primary outcome. Further, there were other concurrent antimicrobial stewardship initiatives, including fluoroquinolone and carbapenem use restriction and antibiotic de-escalation, during the time frame of this study that may have affected antibiotic selection. In addition, this study was a retrospective chart review and relied on accurate and proper documentation in the electronic medical record. A final limitation was that patients' antibiotic use after discharge and readmission rates were not captured.

Aztreonam was targeted as a high-cost antibiotic. Since the implementation of this initiative, pharmacists

made interventions on aztreonam orders sooner, leading to a reduction of aztreonam use and increased use of less-expensive alternatives. This was associated with a decrease in aztreonam expenditure by \$6,811 for the 140 patients studied after implementation of the initiative.

Conclusion

After implementation of an initiative to encourage the use of cephalosporins rather than aztreonam in patients with SRPA, the rate of clinical response and cephalosporin use increased and rates of exposure to aztreonam and fluoroquinolones decreased.

Disclosures

The authors have declared no potential conflicts of interest.

References

1. Chang C, Mahmood MM, Teuber SS, Gershwin ME. Overview of penicillin allergy. *Clin Rev Allergy Immunol*. 2012; 43:84-97.
2. Solensky R, Khan DA. Drug allergy: an updated practice parameter. *Ann Allergy Asthma Immunol*. 2010; 105:259-73.
3. Macy E, Poon K-Y T. Self-reported antibiotic allergy incidence and prevalence: age and sex effects. *Am J Med*. 2009; 122:778.e1-7.
4. Albin S, Agarwal S. Prevalence and characteristics of reported penicillin allergy in an urban outpatient adult population. *Allergy Asthma Proc*. 2014; 35:489-94.
5. Mandell LA, Wunderink RG, Anzueto A et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis*. 2007; 44(suppl 2):S27-72.
6. Kalil AC, Metersky ML, Klompas M et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis*. 2016; 63:e61-111.
7. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf (accessed 2016 Jul 30).
8. Freifeld AG, Bow EJ, Sepkowitz KA et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2011; 52:e56-93.
9. 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; 133:790-6.
10. Lee CE, Zembower TR, Fotis MA et al. The incidence of antimicrobial allergies in hospitalized patients: implications regarding prescribing patterns and emerging bacterial resistance. *Arch Intern Med*. 2000; 160:2819-22.
11. Pichichero ME, Zagursky R. Penicillin and cephalosporin allergy. *Ann Allergy Asthma Immunol*. 2014; 112:404-12.
12. Swearingen SM, White C, Weident S et al. A multidimensional antimicrobial stewardship intervention targeting aztreonam use in patients with a reported penicillin allergy. *Int J Clin Pharm*. 2016; 38:213-7.
13. King EA, Challa S, Curtin P et al. Penicillin skin testing in hospitalized patients with β -lactam allergies. Effect on antibiotic selection and cost. *Ann Allergy Asthma Immunol*. 2016; 117:67-71.
14. Staicu ML, Brundige ML, Ramsey A et al. Implementation of a penicillin allergy screening tool to optimize aztreonam use. *Am J Health-Syst Pharm*. 2016; 73:298-306.
15. Estep PM, Ferreira JA, Dupree LH et al. Impact of an antimicrobial stewardship initiative to evaluate β -lactam allergy in patients ordered aztreonam. *Am J Health-Syst Pharm*. 2016; 73(suppl 1):S8-13.
16. Jiang F, Jain R, Pottinger PS et al. Automated allergy and infectious disease pharmacy consult to limit the use of aztreonam in patients with reported beta-lactam allergy. *J Allergy Clin Immunol*. 2016; 137(suppl):B196.

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