

Inappropriate Use of Aztreonam

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Background: Aztreonam is not a preferred empiric antibiotic because of variable susceptibilities compared with alternative agents. In addition, it has no Gram-positive activity, necessitating coadministration with vancomycin when used empirically, and is more costly when compared with other Gram-negative active agents. Aztreonam is often given to patients with a reported penicillin allergy without further investigation into the reaction or other relevant allergy information.

Study Question: How frequently is aztreonam being used inappropriately?

Study Design: We conducted a retrospective chart review at an academic medical center to assess the appropriateness of our aztreonam use.

Measures and Outcomes: Our primary outcome was frequency of appropriate aztreonam use, based on a true IgE-mediated allergy reported for each patient. We evaluated whether the patients had tolerated a beta-lactam in the past, and what the reported allergic reaction was.

Results: We included 165 patients and found that 46.7% of our aztreonam use was inappropriate, based on previous use of a beta-lactam, or no documentation of an IgE-mediated response. Of the patients with a documented beta-lactam allergy, 63 (38.2%) patients had no allergy manifestation listed, and 37 (22.4%) patients had a non-IgE-mediated allergy manifestation. Of the total population, 61 (37%) patients had tolerated a beta-lactam in the past.

Conclusions: Aztreonam should be avoided, except in the case of a true IgE-mediated allergic reaction. Our goal was to reduce the inappropriate use of aztreonam at our institution by one or more of the following: educating providers, reviewing aztreonam orders, requiring answering of order questions, or requiring an indication for use. Penicillin skin testing and desensitization are options as well.

Keywords: antimicrobial stewardship, aztreonam, beta-lactam allergy

INTRODUCTION

Allergy to penicillin is reported in up to 10% of patients, making it the most commonly reported medication allergy.^{1,2} There is a proven risk of

serious hypersensitivity to penicillin and other beta-lactams, but ample literature suggests that patient self-reporting overestimates the true incidence of IgE-mediated allergic reactions. More than 90% of patients who report a penicillin allergy do not have a positive response to penicillin skin testing.^{1–3} Previous studies have demonstrated the importance of clarifying beta-lactam allergies, and the presence of a beta-lactam allergy in a patient's medical record has been associated with worse patient outcomes.^{4–6} However, many of the documented allergies are incomplete, unverified, or insignificant.¹

According to Infectious Diseases Society of America guidelines, beta-lactam antibiotics are first-line agents

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for a variety of infections including but not limited to pneumonia, intra-abdominal infections, urinary tract infections, and skin and skin structure infections.^{7–10} Owing to concerns of IgE-mediated hypersensitivity reactions and cross-reactivity among penicillins, cephalosporins, and carbapenems, these classes of antibiotics are often avoided in patients with any listed beta-lactam allergy.¹ Older studies have reported the incidence of penicillin cross-reactivity to cephalosporins and carbapenems to be upward of 40%, primarily because of impurities within the compounds themselves. However, newer data suggest the true incidence is much lower (<5% and <1%, respectively). In addition, later-generation cephalosporins such as ceftriaxone and cefepime are much less likely to cross-react with penicillins.^{1,2}

Aztreonam, a monobactam antibiotic, is recommended in patients with beta-lactam allergies because it has shown virtually no cross-reactivity with beta-lactam antibiotics.^{2,3} However, based on a patient's allergy history and antibiotic indication, aztreonam is not always the most appropriate agent. Aztreonam lacks Gram-positive activity, has variable Gram-negative activity, and is more costly than other alternative agents.^{11–14} These limitations can lead to use of suboptimal therapy and increased cost of antibiotics. Ideally, aztreonam should be reserved for patients with a confirmed IgE-mediated beta-lactam allergy with a suspected Gram-negative infection.¹¹

At our institution, aztreonam is frequently prescribed for patients with a reported beta-lactam allergy, regardless of the type or severity of the reaction. The purpose of this evaluation was to assess the appropriateness of aztreonam usage in adult patients with reported beta-lactam allergies at Cooper University Hospital (CUH).

METHODS

This was a single-center, retrospective evaluation of all adult patients treated with aztreonam from January 1, 2017, to February 28, 2018, at CUH in Camden, NJ. This study was approved as a performance improvement project by the Research Determination Committee at CUH.

The primary end point was the frequency of inappropriate aztreonam usage in adult patients with a reported beta-lactam allergy. The determination of appropriateness was made based on each patient's documented beta-lactam allergy manifestation and/or previous beta-lactam usage, when applicable. Aztreonam was considered inappropriate if the patient had a non-IgE-mediated allergy manifestation or if the

patient had tolerated a beta-lactam antibiotic in the past based on documented administration of the drug in the medical record. Our institution does not offer penicillin skin testing; therefore, an IgE-mediated allergy history was determined solely by documentation in the chart, which is typically provided by the patient or a family member. Aztreonam was regarded as appropriate if the patient had a listed IgE-mediated beta-lactam allergy and had not previously received a beta-lactam antibiotic. If the patient did not fulfill the criteria for either group, aztreonam appropriateness was deemed "unclear." A secondary end point was to assess the difference in inappropriate aztreonam usage before and after the implementation of the antimicrobial stewardship program (ASP) initiative. Based on our collective clinical experience at our institution, we hypothesized that aztreonam was being used inappropriately >50% of the time and that there would be less inappropriate aztreonam usage after the start of the ASP initiative compared with before. Additional data that were collected included patient age and sex, estimated creatinine clearance (CrCl), antibiotic indication, determination if therapy was empiric or definitive, the primary medical service that initiated aztreonam, duration of aztreonam therapy, use of concomitant antimicrobials, duration of concomitant antimicrobial therapy, beta-lactam allergy manifestation, history of beta-lactam use, microbiological data including organism growth and susceptibilities, ID consultation, and recommendations and ASP interventions.

Aztreonam orders were identified through the TheraDoc clinical surveillance system. Patients were divided into 2 groups based on the date of their aztreonam order. Adult patients who were ordered aztreonam from January 1, 2017, to September 30, 2017, were included in the preintervention group. On October 1, 2017, a new ASP initiative targeting aztreonam usage was started as a stewardship and cost-saving measure. As part of the initiative, all aztreonam orders were reviewed retrospectively 3 times per week by a member of the ASP team. Adult patients who received aztreonam from October 1, 2017, until February 28, 2018, for at least 24 hours were included in the post-intervention group.

Descriptive statistics were used to summarize patient characteristics and end points. Inappropriate usage of aztreonam was tested against the hypothesized value using a one-sample Z test for proportions. The difference in frequency of aztreonam use before and after the implementation of the ASP initiative was analyzed using the chi-squared test or Fisher exact test (bivariate analysis) and a multiple stepwise logistic regression model (multivariate approach) to control for potential confounders. A *P* value of 0.05 was

considered statistically significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc, Cary, NC).

RESULTS

A total of 272 patients were screened, and 165 patients were included in this evaluation. The primary reason that patients were excluded from our analysis was receipt of aztreonam for less than 24 hours. Ninety-five patients were included in the preintervention group, whereas 70 were included in the postintervention group. Statistically significant differences between the 2 groups in regard to demographic and clinical characteristics included: duration of antimicrobials other than aztreonam, incidence of positive culture, and number of ASP interventions (Table 1).

One-hundred one (61.2%) patients were women. Aztreonam was initiated by an internal medicine service in 71 (43%) patients, a critical care service in 52 (31.5%) patients, and a surgical service in 25 (15.2%) patients. Forty-five (27.3%) patients were treated for sepsis, 38 (23%) patients were treated for pneumonia, 26 (15.8%) patients were treated for an intra-abdominal infection, and 20 (12.2%) patients were treated for a urinary tract infection.

Aztreonam was determined to be inappropriate for 77 (46.7%) patients and appropriate for only 46 (27.9%) patients (Table 2). Nineteen of 65 (29%) patients with a listed IgE-mediated allergy and 21 of 63 (33%) patients with no listed allergy manifestation had tolerated a beta-lactam antibiotic in the past (Table 3). For the 77 patients where aztreonam was deemed inappropriate, the most common criteria to determine inappropriateness were toleration of a beta-lactam in the past for 61 (79.2%) patients and documentation of a non-IgE-mediated allergy manifestation for 37 (48.1%) patients. Overall, 63 of 165 (38%) patients who received aztreonam did not have any allergy manifestation documented, whereas 61 (37%) patients had tolerated a beta-lactam antibiotic in the past. IgE-mediated reactions and non-IgE-mediated manifestations were common in both groups. Aztreonam was used in combination with other antimicrobials for 155 (93.9%) patients and as empiric treatment for 148 (89.7%) patients. The duration of other antimicrobial therapy was significantly reduced in the postintervention group (3.11 vs. 3.86 days, $P = 0.0169$). The ID service was consulted for 63 (38%) patients. There were 14 total ASP interventions related to aztreonam use in the postintervention group. There was a reduction in aztreonam

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Table 1. Baseline characteristics.

Characteristic	N = 165
Age, yrs, median (IQR)	60 (51, 72)
Female sex, n (%)	101 (61)
ID consult, n (%)	63 (38)
ID team continued aztreonam, n/N (%)	27/63 (43)
Antimicrobial characteristics, n (%)	
Gram-positive activity	43 (60.6)
Gram-negative activity	22 (31)
Other	6 (8.5)
Stewardship intervention, n (%)	
Yes	14 (8.5)
Empiric aztreonam, n (%)	
Yes	155 (94)
Concomitant antibiotics, n (%)	148 (90)
Vancomycin	130 (79)
Daptomycin	4 (2)
Linezolid	5 (3)
Metronidazole	68 (41)
Fluoroquinolone	5 (3)
Clindamycin	2 (1)
Other	7 (4)
Positive culture, n (%)	71 (43)
Antibiotic indication, n (%)	
Sepsis	45 (27)
Pneumonia	38 (23)
Abdominal infection	26 (16)
Urinary tract infection	20 (12)
Skin/skin structure infection	14 (9)
Febrile neutropenia	13 (8)

duration in the postintervention group compared with the preintervention group in all patients (3.41 vs. 4.03 days, $P = 0.1455$) and in the 77 patients where aztreonam was deemed inappropriate (3.23 vs. 3.83 days, $P = 0.2743$), but neither reduction was statistically significant.

DISCUSSION

Aztreonam is a frequently used alternative for patients with listed beta-lactam allergies even when the allergy documentation is incomplete or the manifestation is unknown. Patient self-reporting of beta-lactam allergies likely overestimates the true incidence of IgE-mediated allergic reactions. This overestimation along with concern of cross-reactivity among beta-lactam antibiotics can lead to suboptimal antimicrobial treatment and increased cost of therapy.¹⁻³

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Table 2. Primary outcome—aztreonam inappropriateness.

	All patients, N = 165	Preintervention, N = 95	Postintervention, N = 70	P
Frequency of appropriateness, n (%)				
Inappropriate	77 (47)	42 (44)	35 (50)	0.76
Unclear	42 (25)	25 (26)	17 (23)	
Appropriate	46 (27)	28 (29)	18 (25)	
Aztreonam duration (d)	N = 165	N = 95	N = 70	
All patients, median (IQR)	3 (2, 4)	3 (2, 5)	3 (2, 4)	0.146
Inappropriate aztreonam (d), median (IQR)	N = 77	N = 42	N = 35	
	3 (2,4)	3 (2,5)	3 (2,4)	0.274

Providers have a lack of awareness of the importance of a thorough allergy assessment and the limitations of aztreonam.^{11–14}

A number of antimicrobial stewardship studies have shown effective cost reduction and improved clinical outcomes by targeting aztreonam use.^{11–14} Swearingen et al used a pharmacist-led multidimensional antimicrobial stewardship intervention aimed at optimizing antimicrobial therapy and reducing unnecessary aztreonam use. The authors observed a significant reduction in median days of aztreonam therapy (4.0 vs. 2.0 days, $P = 0.0001$) and median days of therapy (DOT) per 1000 patient-days (14.5 vs. 9.3 days, $P = 0.001$) in the intervention group.¹⁴ Similarly, Staicu et al¹³ implemented a multifaceted stewardship intervention including the use of a penicillin allergy-screening tool, provider education, order set modification, and prospective order review by members of the ASP team to optimize aztreonam use. The total number of DOT with aztreonam was significantly decreased from 9.5 per 1000 patient-days preintervention to 4.4 per 1000 patient-days in the postintervention group ($P < 0.0001$). The number of inappropriate aztreonam DOT decreased from 4.0 per 1000 patient-days to 0.8 per 1000 patient-days ($P < 0.0001$). The study demonstrated cost savings of between \$60,000 and \$100,000.¹³ These studies have shown that a combination of provider education and prospective stewardship interventions can reduce unnecessary aztreonam use and optimize

antimicrobial regimens by promoting the use of preferred beta-lactam alternatives.

Our study showed that there is a significant issue with allergy documentation at our institution, as 63 (38.2%) patients with a documented beta-lactam allergy had no allergy manifestation listed. In addition, 37 (22.4%) patients who received aztreonam had a non-IgE-mediated allergy manifestation, whereas 61 (37%) patients had tolerated a beta-lactam in the past. Inadequate documentation along with insufficient investigation into allergy history likely contributed to the high percentage of aztreonam misuse. Although the frequency of inappropriate usage was slightly lower than our proposed estimate of 50%, 77 (47%) aztreonam orders were deemed inappropriate by our study definition, which is unacceptably high.

There were a number of limitations present within this study. This was a retrospective chart review evaluation at a single institution performed by a single reviewer. Owing to the retrospective nature, the results were largely dependent on patient allergy reporting and provider documentation. Second, the sample size was small. Although there were some trends in reduction of aztreonam use after the ASP instituted a thrice-weekly review, the difference did not reach statistical difference. This was likely because aztreonam orders could have been started on nonreview days or over the weekend when an ASP member was not present to review the patients. Obtaining a larger sample size through more frequent review

Table 3. Association between IgE-mediated allergy and previous tolerance of beta-lactam antibiotic.

	IgE-mediated allergy, n = 65	Non-IgE-mediated allergy, n = 37	None listed, n = 42	P
Beta-lactam tolerated in the past, n (%)	19 (29)	21 (57)	21 (33)	0.016

may have showed a difference. In addition, we feel that the intervention would be optimal at order verification instead of postprescription to initiate a full allergy assessment in real time. Finally, there was no prospective arm of the intervention. Retrospective review of aztreonam orders thrice weekly may not be frequent enough to see significant change.

Using provider education with an intervention targeting aztreonam at order entry with tighter restrictions for use would likely have had a greater impact. Owing to the low number of interventions that were capable with thrice-weekly review, we worked alongside medical informatics to implement mandatory order questions for providers. In addition, we have tightened the aztreonam restriction from 72 to 24 hours. We are hopeful that these 2 modifications will reduce some of the unnecessary prescribing.

Our findings are aligned with the previous literature demonstrating the importance of clarifying and properly documenting medication allergies, particularly those related to beta-lactam antibiotics. We encountered an unacceptably high rate of inappropriate usage of aztreonam at our institution. Ultimately, our data did show that retrospective review of aztreonam orders does have some utility, but there is a need for prospective measures.

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