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RESEARCH ARTICLE

Short and long term impact of combining restrictive and enabling interventions to reduce aztreonam consumption in a community hospital

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Abstract
Background Antimicrobial stewardship initiatives combining restrictive and enabling components may be an effective strategy to achieve short- and long-term objectives. Aztreonam, a relatively high-cost antipseudomonal antibiotic, is an appropriate target for stewardship initiatives based on propensity for overuse in penicillin allergy, an activity profile often warranting additional empiric gram-negative and gram-positive coverage, and a unique durability to Ambler class B metallo-beta-lactamases. *Objective* Analyze the immediate and long-term impact on aztreonam prescribing of combining restrictive and enabling interventions. *Setting* Single 233-bed community hospital with 45 adult intensive care unit beds in Nashville, Tennessee. *Method* Retrospective, interrupted time series analysis comparing all patients receiving aztreonam prior to intervention between January 1, 2010 and September 30, 2011 and following intervention between October 1, 2011 and September 30, 2019. Quarterly defined daily doses/1000 adjusted patient days and microbiology laboratory annual surveillance data were utilized for analysis. *Main outcome measure* Post-intervention change in trend of aztreonam consumption. *Results* Following intervention, a significant decline in aztreonam consumption was observed (− 1.97 defined daily doses/1000 adjusted patient days; $p = 0.003$) resulting in a sustained decrease in aztreonam consumption from 2011 (3rd quarter) to 2019 (3rd quarter) from 15.2 to 0.26 defined daily doses/1000 adjusted patient days. Short-term group 2 carbapenem consumption increased ($p = 0.044$). *Pseudomonas aeruginosa* susceptibility to aztreonam improved from 2011 to 2018 (72% vs. 84%; $p = 0.0004$) without deleterious effects to alternative antipseudomonal beta-lactams. *Conclusion* Combining restrictive and enabling interventions had immediate and sustained impact on aztreonam consumption with *P. aeruginosa* susceptibility improvement.

Keywords Antimicrobial stewardship · Aztreonam · Community hospitals · Enabling restriction · Interrupted time-series analysis

Impacts on practice

- In resource-limited settings such as community hospitals, implementing pharmacist-driven interventions combining restrictive and enabling strategies can produce immediate and sustained impacts on antimicrobial consumption.
- Sustained antimicrobial stewardship initiatives that do not involve strict restriction or prior authorization requirements can lead to improvement in long-term exigencies such as *P. aeruginosa* susceptibility rates.

Introduction

Formal strategies to improve antibiotic use are a core component of antimicrobial stewardship programs (ASPs) and can be categorized as restrictive or persuasive [1]. According to Infectious Diseases Society of America (IDSA)/Society for Healthcare Epidemiology of America ASP guidelines, a conventional restrictive strategy is preauthorization, defined as the requirement for clinicians to get approval before prescribing certain antimicrobials. Advantages of preauthorization are noted to include an immediate impact on antibiotic consumption, cost and favorable outcomes on measures

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such as gram-negative susceptibility. Disadvantages include loss of prescriber autonomy, need for effective, accessible resources such as physicians or pharmacists with infectious diseases (ID) training, potential delays in therapy, and potential for simply redirecting antibiotic consumption from restricted agents to alternatives. The classic persuasive, or enabling, strategy is prospective audit and feedback (PAF) in which regimens are reviewed after initiation with subsequent clinical recommendations combined with education for improvement of future prescribing. Advantages of this approach have been noted to include preserved prescriber autonomy and more flexibility in regards to accessibility of the service but with the trade-off that this approach is generally more labor-intensive and requires more time to achieve significant reductions in targeted antibiotics.

The determination of which strategy(ies) to employ is likely multifactorial and includes hospital infrastructure, available resources, and urgency and nature of the perceived need. These approaches are likely not mutually exclusive, however. In fact, a meta-analysis of 29 interrupted time series (ITS) analyses of restrictive interventions in a Cochrane review demonstrated that addition of an enabling component, which was included in 13 (45%) of the studies, consistently enhanced the effect of interventions on antibiotic prescribing measured as either compliance with antibiotic guidelines or policies, duration of antibiotic treatment, decision to treat, or total duration of treatment (+38.36%; 95% CI, 18.94–57.78%) [2]. Data also suggests that the effects of combining enablement with restriction may be more sustainable than either intervention alone. Although not statistically significant, restrictive interventions that included enablement trended towards these effects being more sustained at 12 months (+30%; 95% CI, − 7% to 66%) [2].

As alluded to, strict preauthorization is likely incongruous with clinical settings in which 24-h accessibility of skilled personnel providing approval is not practicable and timely initiation of agents in question may be prudent. ASPs have demonstrated effective workarounds to this problem including providing access to restricted agents during off-hours and using computerized antimicrobial approval systems [3, 4]. When confronted with a pressing need, ASPs must balance availability of resources with requisites for rapid improvement.

Aztreonam, a relatively high-cost antipseudomonal antibiotic, may be predisposed to unnecessarily large consumption due to a safety profile that includes no cross-reactivity to penicillins and cephalosporins with the exception of ceftazidime [5]. Susceptibility rates for *P. aeruginosa* are often lower with aztreonam compared with other commonly used β-lactams, therefore empiric use can lead to potentially suboptimal therapy or need for double-coverage [6, 7]. Of note, aztreonam is not hydrolyzed by Ambler class B metallo-β-lactamases (MBL's) leading to renewed interest, particularly in combination with newer β-lactamase inhibitors [8, 9].

Swearingen et al. describe a multidimensional intervention targeting aztreonam use at a 550-bed academic teaching hospital [10]. An aztreonam restriction to patients with a history of anaphylactic penicillin allergy resulted in a decrease of two (4.0 vs. 2.0; $p=0.0001$) median days of therapy (DOT) over a 3-month period. Median DOT per 1000 patient days was significantly reduced (14.5 vs. 9.3; $p=0.0001$) and this reduction was sustained after one year (18.5 vs. 6.5; $p=0.0001$). Phan et al. describe an enabling strategy that included formal pharmacist PAF and education to providers to target aztreonam use in patients with self-reporting penicillin allergies at a 529-bed community teaching hospital [11]. Following this intervention, defined clinical response rates improved (83.6% vs. 91.4%; $p=0.0468$) over a one-year period. Significantly fewer patients received aztreonam (12.1% vs. 4.3%; $p=0.017$) and fluoroquinolones (50.7% vs. 35.0%; $p=0.008$) following implementation.

Aim of the study

Based on the paucity of evidence regarding combination restrictive-enabling strategies at community hospitals with high utilization of aztreonam, the purpose of this study was to evaluate the immediate and long-term impact on aztreonam utilization of such an intervention in a setting with limited resources.

Setting

The study was conducted at a 233-bed community nonteaching hospital with 45 adult intensive care unit (ICU) beds in Nashville, Tennessee. The ASP includes an ID physician and ID pharmacist during weekday daytime hours. On-site verifying pharmacist coverage extends to 24 h every day.

Method

Following a medication use evaluation (MUE) of aztreonam which was prompted by trends of increased consumption during routine ASP surveillance, aztreonam prescribing was deemed inappropriately high and subsequently restricted to certain criteria in October 2011. Prescribers were instructed to restrict aztreonam to empiric or targeted treatment of infections in patients with serious β-lactam allergies. In particular, prescribers were instructed to determine the nature and severity of allergies as well as history of tolerance of cephalosporins and/or carbapenems. In addition, combination with other β-lactams was discouraged. Education,

including MUE findings, institutional susceptibility rates, and cross-reactivity of penicillin allergies with cephalosporin and carbapenem alternatives, was provided to all relevant prescribers (e.g., hospitalists and intensivists) along with implementation of the restriction. The restriction criteria were also posted in prominent areas. In addition, restriction criteria were included in an ASP educational package that is provided to all new prescribers and redistributed annually with updated (e.g., antibiogram) data. No restriction was placed on disciplines that can prescribe aztreonam. Verifying pharmacists were given authority to deny the order based on the criteria with the caveat that denial must be communicated in real-time and cannot result in a delay of appropriate therapy. Likewise, the ID pharmacist reviewed aztreonam regimens through PAF on weekdays and could retroactively deny courses provided acceptable alternatives could be mutually agreed upon with the provider. Prior to this intervention, no restrictions had been placed on aztreonam prescribing.

A retrospective, interrupted time series analysis was conducted to review the impact of the aztreonam intervention. The pre-intervention period spanned all available pre-intervention data and consisted of January 1, 2010 through September 30, 2011. The intervention period encompassed October 1, 2011 through September 30, 2019. The primary endpoint was quarterly aztreonam consumption based on purchasing data measured in defined daily doses per 1,000 adjusted patient-days (DDD/1000 APD). DDD of 4gm was utilized for the measurement of aztreonam consumption according World Health Organization standards which did not change over the course of the study [12]. APD, number of patients times their lengths of stay plus estimated outpatient days of care, was utilized according to facility measurement protocols. Secondary endpoints included consumption of alternative antipseudomonal β-lactams and susceptibility rates of *P. aeruginosa* to aztreonam and alternatives. *Pseudomonas aeruginosa* was chosen for evaluation due to its prevalence and clinical relevance, particularly as it relates to prescribing aztreonam both as monotherapy and in double coverage. Of note, a pharmacodynamic (PD) dosing scheme for alternative antipseudomonal β-lactams, not including aztreonam, was implemented in September 2012. This included utilizing extended (4-h) infusions for piperacillin-tazobactam and shorter dosing intervals for cefepime and meropenem [13]. The result was decreased daily doses for standard regimens for all agents. Since this would affect antibiotic consumption, analysis of alternative agents only included a parallel monthly analysis of the pre-intervention period of January 2011 through August 2011 with the intervention period of the corresponding months in 2012. Also noteworthy, the formulary group 2 carbapenem was changed from doripenem to meropenem in July 2011. Susceptibility rates were obtained from microbiology laboratory annual surveillance and encompassed the first isolate of *P. aeruginosa* from each patient; irrespective of source [14].

The electronic medical record was utilized to describe all patients age 18 years or older that received at least one dose of aztreonam in the pre- and post-intervention periods, assessing the following parameters: age, gender, demographics, status of β-lactam allergy, ICU admission, mechanical ventilation, infectious diagnosis, and pertinent positive cultures.

Statistical analysis

The impact on aztreonam use was analyzed using a linear regression model that incorporated both slope and level change after the intervention. A total of 7 quarterly data points were analyzed in the pre-intervention period and 32 quarterly data points were analyzed in the intervention period. The model was checked for autocorrelation issues using autocorrelation and partial-autocorrelation plots. The model can be formulated as follows:

$$Y_t = \beta_0 + \beta_1 * Time_t + \beta_2 * Intervention_t + \beta_3 * Time\ after\ intervention_t + \varepsilon_t$$

where Y_t is aztreonam use in DDD/1000 APD at time t, β_0 is the intercept estimating the baseline level at the beginning of the time series, β_1 estimates the slope before the intervention, β_2 estimates the intercept change in DDD/1000APD after the intervention, β_3 estimates the slope after the intervention, and ε_t is random error.

Alternative antibiotic consumption (DDD/1000 APD) was analyzed using a paired t-test accounting for seasonality. Changes in susceptibility of *P. aeruginosa* to aztreonam and alternatives secondary to the intervention were compared using Chi-square tests.

Results

Aztreonam was initiated in 324 patients during the 7 quarters of the pre-intervention period and 738 patients during the 32 quarters of the intervention period. Patient characteristics are described in Table 1. Compared with the pre-intervention group, there were significantly fewer patients age 65 years and older (64.8% vs. 57.4%; $p = 0.0243$) and fewer male patients (40.7% vs. 33.3%; $p = 0.0202$). More patients in the intervention group had β-lactam allergies (77.8% vs. 89.57%; $p < 0.0001$) and cephalosporin and/or carbapenem allergies (19.8% vs. 30.2%; $p = 0.0017$). Fewer patients in the intervention group received concomitant β-lactam antibiotics (9.6% vs. 3.25%; $p < 0.0001$). ICU admissions (29.0%

Table 1 Baseline characteristics of patients receiving aztreonam before and after the criteria of use restriction

Variable	Pre-intervention[a] n = 324	Intervention[b] n = 738	*p*
Age ≥ 65 years, n (%)	210 (64.8)	424 (57.4)	0.0243
Male, n (%)	132 (40.7)	246 (33.3)	0.0202
β-lactam allergy, n (%)	252 (77.8)	662 (89.7)	< 0.0001
Penicillin only, n (%)	202 (80.2)	462 (62.7)	0.0017
Ceph/carbapenem, n (%)	50 (19.8)	200 (30.2)	0.0017
Regimen			
Concomitant β-lactam, n (%)	31 (9.6)	24 (3.25)	< 0.0001
DOT, mean	4.56	4.18	0.0829
ICU admission, n (%)	94 (29.0)	213 (28.9)	0.9603
Mech vent, n (%)	51 (15.7)	130 (17.6)	0.4545
Infectious diagnosis			
Pneumonia, n (%)	164 (50.6)	332 (45)	0.0904
Empiric, n (%)	93 (28.7)	171 (23.2)	0.0547
Sepsis, n (%)	29 (9.0)	93 (12.6)	0.0858
UTI, n (%)	18 (5.6)	63 (8.5)	0.0920
COPD/bronchitis, n (%)	10 (3.1)	23 (3.1)	0.9792
SSTI, n (%)	7 (2.2)	39 (5.3)	0.0213
Bone/joint infection, n (%)	3 (0.9)	10 (1.3)	0.7645
CNS infection, n (%)	0 (0)	4 (0.5)	0.3198
GI, n (%)	0 (0)	2 (0.3)	1.0000
Endovascular, n (%)	0 (0)	1 (0.1)	1.0000
Microbiology			
Positive culture, n (%)	145 (44.8)	278 (37.7)	0.0299
Gram negative, n (%)	79 (24.4)	164 (22.2)	0.4403

Ceph cephalosporin, *DOT* duration of therapy, *ICU* intensive care unit, *Mech vent* mechanical ventilator, *UTI* urinary tract infection, *COPD* chronic obstructive pulmonary disease, *SSTI* skin/soft tissue infection, *CNS* central nervous system, *GI* gastrointestinal

[a]January 1, 2010 through September 30, 2011

[b]October 1, 2011 through September 30, 2019

vs. 28.9%; $p = 0.9603$) and mechanical ventilation rates (15.7% vs. 17.6%; $p = 0.4545$) were similar between groups.

Quarterly aztreonam consumption and trends are reported in Fig. 1. During the 7 quarters prior to the intervention, there was a significant increasing trend ($\beta_1 = 1.54$ DDD/1000 APD; $p = 0.0037$) of aztreonam use, from 13.76 DDD/1000 APD in the 1st quarter of 2010 to 19.94 DDD/1000 APD in the 3rd quarter of 2011. During the 32 quarters following implementation, there was a significant decreasing trend ($\beta_2 = -0.43$ DDD/1000 APD; $p < 0.001$) of aztreonam use, from 15.22 DDD/1000 APD in the 4th quarter of 2011 to 0.26 DDD/1000 APD in the 3rd quarter of 2019. The overall effect on aztreonam consumption was significant ($\beta_3 = -1.97$ DDD/1000 APD; $p = 0.003$). Consumption of alternative antipseudomonal β-lactams was variable (Fig. 2). There was a significant increase in group 2 carbapenems (9.84 DDD/1000 APD; $p = 0.044$) but no significant difference in piperacillin-tazobactam or cefepime. As rates of ESBL *E. coli* did not significantly change from 2011 (n = 225; 14.7%) to 2012 (n = 239; 14.4%), it is likely that a shift from empiric aztreonam to group 2 carbapenems in patients with penicillin allergies accounts for a significant portion of this increase. *Pseudomonas aeruginosa* susceptibility to aztreonam trended downwards in the period preceding (72% in 2011) and immediately following (65% in 2012) the intervention but then improved significantly as consumption rates continued to decline (84% in 2018; $p = 0.008$; Fig. 3). There were no deleterious effects on susceptibility to other antipseudomonal β-lactams (Fig. 4). In fact, *P. aeruginosa* susceptibilities significantly improved from 2011 to 2018 for cefepime (76% vs. 88%; $p = 0.0004$) and meropenem (78% vs. 92%; $p = 0.0001$), and only slightly decreased for piperacillin/tazobactam (91% vs. 90%; $p = 0.6609$). This is potentially due to additional ASP interventions including PAF for these agents and a criteria of use restriction on quinolones that was implemented in September 2014 that resulted in a substantial decrease in quinolone consumption from 2011 (158 DDD/1000 APD) to 2018 (35.63 DDD/1000 APD).

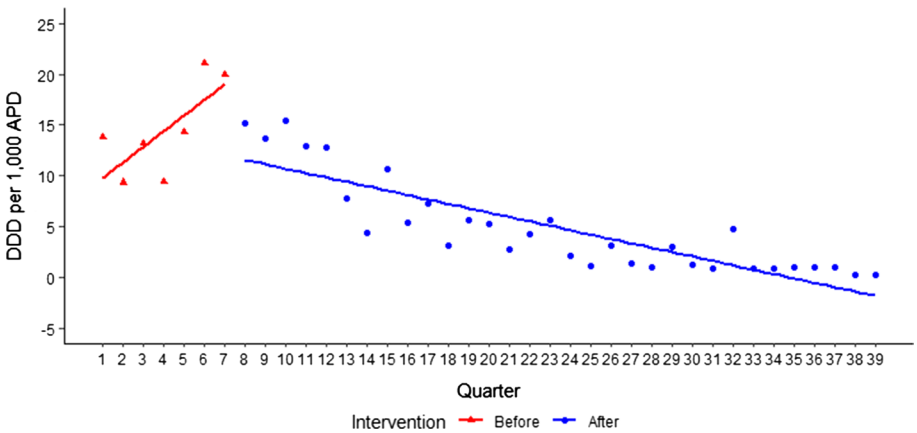

Fig. 1 Aztreonam usage before (quarters 1–7) and after (quarters 8–39) intervention. Pre-intervention, there was a significant increasing trend (1.54 DDD/1000 APD; $p = 0.0037$) from 13.76 to 19.94 DDD/1000 APD. Following implementation, there was a significant decreasing trend (-0.43 DDD/1000 APD; $p < 0.001$) from 15.22 to 0.26 DDD/1000 APD. The overall change in trend was significant ($\beta_3 = -1.97$ DDD/1000 APD; $p = 0.003$)

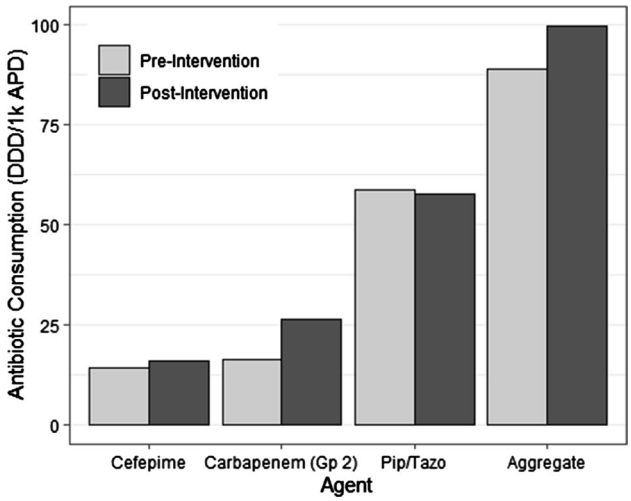

Fig. 2 Consumption of alternative antipseudomonal β-lactams (January–September 2011 vs. January–September 2012). Group 2 carbapenem use significantly increased (9.84 DDD/1000 APD; $p=0.0044$)

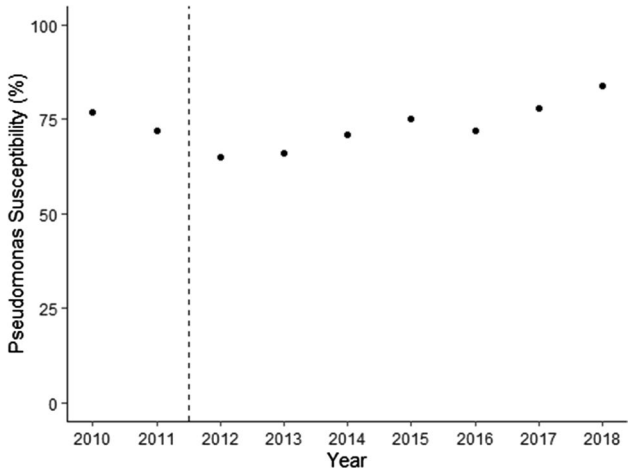

Fig. 3 *Pseudomonas aeruginosa* susceptibility to aztreonam. Trends in declining susceptibility reversed over time resulting in significant improvement (72% in 2011, 84% in 2018; $p=0.008$)

Discussion

Consistent with restrictive interventions, there was an immediate reduction of aztreonam consumption following implementation of the criteria of use intervention. This impact was more moderate than could be anticipated with a more austere restriction, however. Conversely, the trends were sustained over the span of 8 years and ultimately resulted in a profound decline in aztreonam consumption from 19.94 DDD/1000 APD in the 3rd quarter of 2011 to 0.26 DDD/1000 APD in the 3rd quarter of 2019. A recent Cochrane review included analysis of combining of restrictive and enabling antibiotic stewardship strategies and demonstrated that this

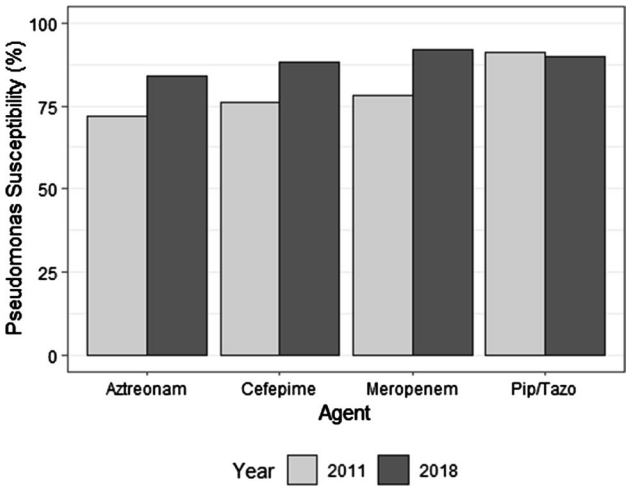

Fig. 4 *Pseudomonas aeruginosa* susceptibility to antipseudomonal β-lactams (2011 vs. 2018). Significant improvement for cefepime (76% vs. 88%; $p=0.0004$) and meropenem (78% vs. 92%; $p=0.0001$)

incorporation can enhance overall effects and may increase sustainability of the gains [2]. Our analysis was consistent with these findings.

A recent three-stage, multicenter, prospective nonrandomized clinical trial with crossover design analyzed the feasibility and impact of core ASP interventions on vancomycin, piperacillin-tazobactam, and antipseudomonal carbapenems at four community hospitals [15]. The authors noted the need for stewardship strategies in community hospitals with limited resources where the highest rates of antibiotics are consumed, contrasting with large tertiary care hospitals where most stewardship recommendations have been produced. Based on available resources, hospitals determined that strict preauthorization was not feasible. Instead a modified preauthorization intervention, in which prescribers had to receive pharmacist approval for continued use after the first dose was compared with a post-prescription audit and review, in which pharmacists would engage prescribers about antibiotic appropriateness after 72 h of therapy. Overall antibiotic use decreased during the post-prescription audit and review phase compared with historical controls (mean DOT per 1000 patient days: 925.2 vs. 965.3; mean difference, − 40.1; 95% CI, − 71.7 to − 8.6), but not during the modified preauthorization phase (mean DOT per 1000 patient-days, 931.0 vs. 926.6; mean difference, 4.4; 95% CI, − 55.8 to 64.7). The authors concluded that their findings "suggest that [post-prescription audit and review] is a better choice than [preauthorization] for stewardship teams in community hospitals with limited resources, particularly when stewardship interventions must be completed by a pharmacist." In our study, the criteria of use restriction enabled all disciplines to order aztreonam but sought to channel the prescribing through an educational, persuasive, and

judiciously restrictive intervention. The need for a restrictive component was determined to be evident by the ASP due to the relatively high overall consumption of aztreonam (reaching 21.03 DDD/1000 APD in the 2nd quarter of 2011) as well as the aforementioned increasing trend. The nature of the problem and structure of the ASP, however, precluded a more austere restriction to specific disciplines such as ID. Given its unique characteristics including a lack of cross-reactivity with β-lactam allergies and an activity profile that includes *P. aeruginosa*, timely initiation of aztreonam should not be hindered by the lack of ubiquitous ID or ASP coverage.

From a stewardship standpoint, the effect of improvement of *P. aeruginosa* susceptibilities could have significant clinical implications. Recent IDSA guidelines recommend a threshold of 10% resistance in ICU gram-negative isolates for empiric double antipseudomonal coverage in ventilator-associated pneumonia [16]. While not currently meeting this condition, trends suggest that aztreonam may be a viable monotherapy option for gram-negative coverage in the future.

Comparison of patient characteristics suggests that the principal reason for the decrease in aztreonam prescribing was added scrutiny of β-lactam allergies but also that discouragement of utilizing aztreonam in combination with other β-lactams had a significant impact. It is noteworthy that there is renewed interest in using aztreonam as an adjunctive agent with other β-lactams for a potential additive effect due to different bacterial cell wall targets [17]. The applicability of this component of the restriction likely depends on specific susceptibility patterns and individual patient characteristics.

Limitations of this study include the quasi-experimental design lacking randomization and the retrospective nature of the analysis. The actual decision-making process of the prescriber including the likelihood that aztreonam would have been chosen barring the restriction can only be inferred. Antibiotic consumption was measured by DDD using purchasing data although current recommendations from the IDSA are to measure DOT using antibiotic administrations as there can be dissimilarity between administered doses and the DDD recommended by the WHO as well as a lack of precision in utilizing purchasing data [1, 18]. While we presume that this variance would not lead to significant alterations in long-term trends of aztreonam consumption, it does have implications for analysis of alternative agents due to PD dosing schemes being implemented within a year of the studied intervention. In addition, this PD dosing scheme required an educational component to prescribers thus highlighting these agents and the strategies employed for enhancing their safety and efficacy. The possibility of this leading to preference of these agents over aztreonam and thus acting as a confounder cannot be ruled out. Similarly, the impact of additional ASP interventions such as the previously described fluoroquinolone restriction would also be anticipated to have an impact on aztreonam prescribing and thus act as a confounder. Also due to a lack of available data, consumption rates in the pre-intervention period only included 7 quarters compared with 32 quarters in the post-intervention period. While this is a substantial amount of time, it precludes long-term analysis of the trends of aztreonam prescribing prior to the intervention. A major limitation is lack of hospital readmission rates before and after the intervention. The study design thus measures the success of the intervention on consumption but not this important impact on patient care. Finally, this analysis took place at a single center. Applicability to other ASPs will be dependent on needs, infrastructure, and resources. Conversely, as smaller, nonacademic community hospitals may be underrepresented in ASP intervention studies, we feel these findings may be impactful for a significant portion of settings. In addition, the long-term nature of the analysis, spanning nine years, allowed for demonstration of the sustainability of the intervention and ultimate impact on *P. aeruginosa* susceptibility rates.

In conclusion, an ASP intervention combining restrictive and enabling strategies had an immediate and sustained impact on a determined critical need. The decline in aztreonam prescribing continued over 8 years and resulted in improvements in susceptibility of *P. aeruginosa* to aztreonam without deleterious effects to alternative antipseudomonal β-lactams.

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