

Impact of an Antimicrobial Stewardship Initiative on Ertapenem Use and Carbapenem Susceptibilities at Four Community Hospitals

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Abstract

Background: After observed widespread use of ertapenem at four community hospitals, antimicrobial stewardship initiatives (ASIs) were undertaken to minimize ertapenem use. Our objective was to evaluate the impact of ASIs on antibiotic utilization and *Pseudomonas aeruginosa* and *Enterobacteriaceae* susceptibility patterns.

Methods: This was a retrospective pre-post implementation study conducted at four Methodist Healthcare System hospitals in San Antonio, Texas from July 2013 to July 2015. A multilevel ASI to reduce ertapenem utilization was implemented in July 2014. The ASI comprised of a clinical decision support notification for prescribers, order set modification, formal provider education, and retrospective/prospective audit. Monthly ertapenem use was expressed in days of therapy (DOT)/1,000 adjusted patient days (APD). The rates of carbapenem nonsusceptible *P. aeruginosa*, *Escherichia coli* and *Klebsiella pneumoniae* were calculated monthly. A segmented regression analysis for interrupted time series was used to evaluate ertapenem usage pre- and post-intervention.

Results: Overall ertapenem utilization decreased across the study period (18.3 DOT/1,000 APDs in July 2013 vs. 5.1 in July 2015). The mean ertapenem DOT/1,000 APDs declined approximately 60% from the pre vs. post intervention period (17.6 vs. 7.0, $p < 0.001$). Rates of group-2 carbapenem nonsusceptible *P. aeruginosa* isolates decreased in the post intervention period (4.9 per 10,000 APDs vs. 3.7 per 10,000 APDs; $p = 0.03$), while carbapenem nonsusceptible *E. coli* and *K. pneumoniae* or remained stable across the study period.

Conclusion: This multilevel ASI aimed at minimizing ertapenem utilization resulted in substantial declined use. Susceptibilities of *P. aeruginosa* and *Enterobacteriaceae* isolates to group 2 carbapenems remained stable in the post-intervention period.

Keywords: Antimicrobial stewardship; Carbapenems; Ecology; Ertapenem; Carbapenem resistance

Abbreviations: APD: Adjusted Patient Days; ASI: Antimicrobial Stewardship Initiatives; CIRE: Carbapenem-Intermediate or-Resistant *Enterobacteriaceae*; CRE: Carbapenem Resistant *Enterobacteriaceae*; DOT: Days of Therapy; ESBL: Extended Spectrum Beta-lactamase; MUE: a Medication use Evaluation; MHS: Methodist Healthcare System; MIC: Minimum Inhibitory Concentration.

Introduction

Antimicrobial resistance is one of the largest healthcare threats in the United States, with roughly 2,000,000 illnesses and 23,000 deaths due to resistant pathogens each year [1]. In 2011, U.S. antibiotic resistance resulted in \$20 billion in excess healthcare expenditures, \$35 billion in societal costs, and 8 million excess hospital days [2]. In addition to facing increased costs and duration of hospitalization, patients with resistant infections may undergo treatment with more toxic agents, including those with limited efficacy data to support optimal outcomes. While the number of resistant organisms continues to grow, the number of antimicrobial agents in development has

declined, bolstering the argument for more responsible antimicrobial usage and infection prevention strategies.

Although antibiotics are among the most frequently prescribed drugs, therapy is not optimized in as much as 50% of the time, increasing selective pressure and bacterial resistance development [1]. Antimicrobial stewardship programs, which often track antibiotic prescribing trends and assess for optimal use, have demonstrated the ability to improve patient safety, reverse antimicrobial resistance rates, and decrease healthcare expenditures [3-17]. With the urgent threat from carbapenem-resistant organisms, the utilization of carbapenems and other broad-spectrum antibiotics has drawn attention [18]. Ertapenem is an appropriate target for drug use review and stewardship initiatives, given its broad spectrum activity, multiple approved indications, potential impact on collateral resistance, and economic cost.

Ertapenem is a 1 β -methyl carbapenem approved for complicated intra-abdominal infections (cIAI), prophylaxis of surgical site infection in elective colorectal surgery, amongst other indications [19-21]. This agent has a broad-spectrum coverage, including activity against extended spectrum beta-lactamase (ESBL) and AmpC producing bacterial pathogens, with evidence supporting carbapenems as superior agents [19-21]. However, it is generally accepted that

widespread use of any antibiotic will eventually lead to the development of resistance, supporting the reservation of broad-spectrum, last-line agents [22]. *In vitro* studies have shown that ertapenem may select for resistant *Pseudomonas* isolates and lead to cross-resistance to imipenem and meropenem, although this has never been proven *in vivo* [23-26]. Carbapenem use has been shown to increase the risk of carbapenem-resistant *Klebsiella pneumoniae* infections in inpatients, further illustrating the need for prudent utilization [27,28].

Many institutions have reported improvement in carbapenem susceptibilities after implementing ASIs to restrict carbapenems as a class; however, the impact of ASIs to decrease ertapenem is not known. After observed widespread prescribing of ertapenem at four community hospitals, antimicrobial stewardship initiatives (ASIs) were undertaken to minimize its use. Our objective was to evaluate the impact of ASIs on antimicrobial use and *Pseudomonas aeruginosa* and *Enterobacteriaceae* susceptibility patterns.

Methods

Study setting: This study was conducted in four community hospitals in the Methodist Healthcare System (MHS) in San Antonio, TX. The hospitals consisted of Methodist Hospital (845 beds), Methodist Specialty and Transplant Hospital (267 beds), Methodist Metropolitan Hospital (388 beds), and Northeast Methodist Hospital (169 beds).

Implementation of ASI: In late 2013, a medication use evaluation (MUE) was completed across the Methodist Healthcare System (MHS) to review the use of ertapenem. Results of this MUE showed extensive use of ertapenem in a variety of patient populations from a wide range of prescribers [29]. In January 2014 (Phase I of ASIs), a robust educational initiative was implemented across the four MHS hospitals to minimize ertapenem use and provide awareness of alternatives. Several groups were targeted for the education including hospitalists, emergency medicine physicians, intensivists, multiple surgery groups, and pharmacists.

In June 2014, additional measures to minimize indiscriminate use of ertapenem were implemented including targeted education and removal of ertapenem from all MHS order sets. Physicians who frequently prescribed ertapenem were targeted for further education. An automated alert was developed within the electronic medical record that would notify the prescribing physicians of appropriate indications for ertapenem use. The ertapenem alert was implemented in July 2014 (Phase II of ASI). Targeted education continued throughout the study period.

Study design: This was a retrospective pre-post implementation study from July 2013 to July 2015. A multilevel ASI to reduce ertapenem utilization was implemented over 6 months January-July 2014. The post-ASI phase I period included 19 months (January 2014 to July 2015) from the start of ASI with a pre-ASI period of 6 months (July 2013 to December 2013). The post-ASI phase II period included 12 months (August 2014 to July 2015) with a pre-ASI period of 7 months (January 2014 to July 2014).

Drug utilization data and analysis: Drug consumption data was collected *via* central mining software (MEDITECH; Westwood, MA). Ertapenem consumption was measured as number of days of therapy (DOT) per 1,000 patient days [30]. To identify other temporal changes

to other antimicrobials during the post-implementation phase, consumption data for the following antibiotics were evaluated: ampicillin/sulbactam, aztreonam, cefepime, ceftriaxone, fluoroquinolones, aminoglycosides, and carbapenems. Only antibiotics intended for systemic use were evaluated; antibiotics prescribed as an ophthalmic solution, ointment, irrigation, or enema were not included. DOT were aggregated monthly for all antibiotics at each facility and across all sites.

Microbiological data and analysis: All isolates were obtained from clinical cultures from January 2014 to July 2015. Only the first isolate per patient per month was included in the analysis. Antimicrobial susceptibility testing was conducted using the VITEK2 system (bioMérieux, Durham, NC). Antimicrobial minimum inhibitory concentrations (MICs) were interpreted according to the Clinical and Laboratory Standards Institute document M100-S14 (2014) [31]. Monthly *E. coli* and *K. pneumoniae* susceptibilities to carbapenems were collected to indicate the prevalence of carbapenem-non susceptible *Enterobacteriaceae*. Carbapenem non-susceptibility in *E. coli* and *K. pneumoniae* was defined as isolates for which the imipenem and meropenem MIC was $>2 \mu\text{g/mL}$ or ertapenem MIC was $>1 \mu\text{g/mL}$ [32]. Susceptibilities for *P. aeruginosa* to meropenem and imipenem were collected. Nonsusceptible rates were measured as the proportion of isolates non-susceptible to carbapenems and incidence density on a monthly basis. The incidence density was calculated as the number of non-susceptible isolates per 10,000 patient days.

Statistical analysis: Data were summarized by means and compared by Student's t-test for pre and post intervention groups. Segmented regression analysis for interrupted time series was used to determine the significance of the differences in levels and slopes of ertapenem utilization over time after implementation of the two intervention phases in July 2014. Estimations were made of the change in ertapenem utilization and isolation of carbapenem non-susceptible *E. coli*, *K. pneumoniae*, and *P. aeruginosa* following phase II, the difference between the pre- and post-intervention slopes of the outcome, and the 12 month intervention effect after the intervention. Significance was determined at the 0.05 level, and SPSS 23.0 (IBM Corp, Armonk, NY, USA) was used for all statistical analyses. The Appendix contains detailed description of the model.

Results

Impact of ASIs on ertapenem utilization: Overall ertapenem use declined from 18.3 to 5.1 DOT/1,000 APDs between July 2013 and July 2015. This represented a reduction from 841 doses administered during the first month and 253 doses in the last month of the study period. Among the four participating facilities, Northeast Methodist Hospital experienced the highest reduction in utilization, with a decline from 38.6 to 0.4 DOT/1,000 APDs across the study period. This reduction was followed by Methodist Specialty & Transplant Hospital, Methodist Hospital, and Methodist Metropolitan Hospital with decreased utilization from 26.6 to 9.2, 14.2 to 5.0, and 10.7 to 4.9 DOT/1,000 APDs, respectively.

The mean ertapenem DOT/1,000 APDs declined by approximately 68% compared to the pre-ASI phase I (14.2 vs. 4.6, $p < 0.001$). The implementation of the ASIs was associated with a decline in ertapenem utilization from an already downward trend (Figure 1). While there was an immediate relative level effect (-7%), the rate of decline leveled off in ertapenem utilization by 12 months post-intervention ($p = 0.04$).

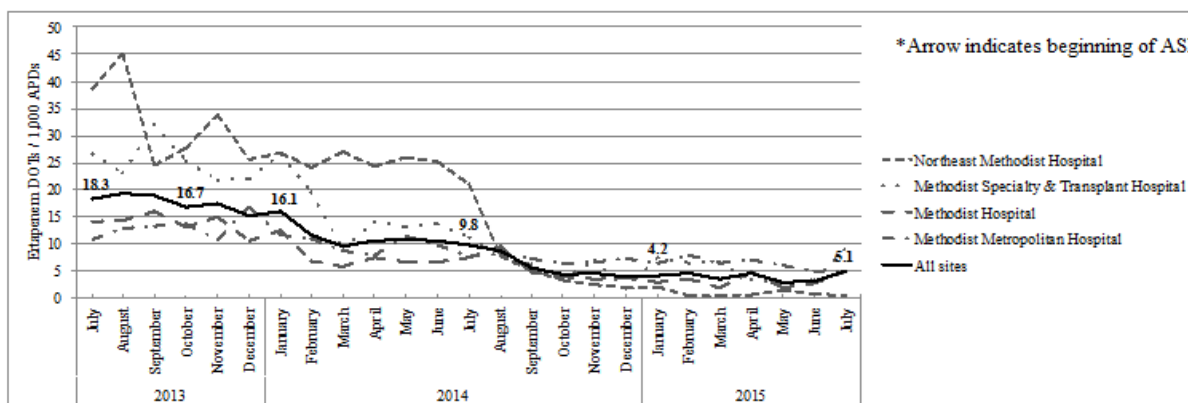


Figure 1: Impact of ASI on ertapenem DOT per 1,000 APDs across all sites*.

Overall antibiotic use: Between January 2014 and July 2015, overall antibiotic use decreased from 385 to 317 DOT/1,000 APDs (-17.8%). As shown in Figure 2, ceftriaxone maintained the highest utilization, but also decreased from 114.0 to 97.5 DOT/1,000 APDs (-14.5%) across the study period. This was followed by fluoroquinolones (declined from 109.9 to 83.7 (-23.8%) DOT/1,000 APDs) and piperacillin/tazobactam (declined from 64.1 to 49.3 (-23.1%) DOT/1,000 APDs) across the study period, respectively. Carbapenems as a class, aminoglycosides, ampicillin/sulbactam, and aztreonam utilization remained stable between January 2014 and July 2015.

Carbapenem nonsusceptibility: The percentage of *P. aeruginosa* isolates nonsusceptible to a group-2 carbapenem remained stable across the post-intervention period, with 16% nonsusceptible in January 2014 and 17% nonsusceptible in July 2015 (Figure 3A).

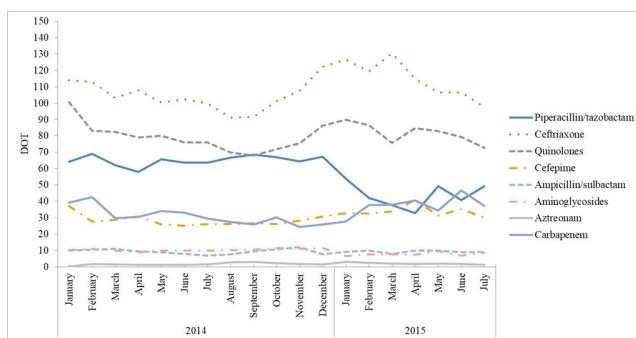


Figure 2: DOT per 1,000 APDs of other antibiotics across all sites.

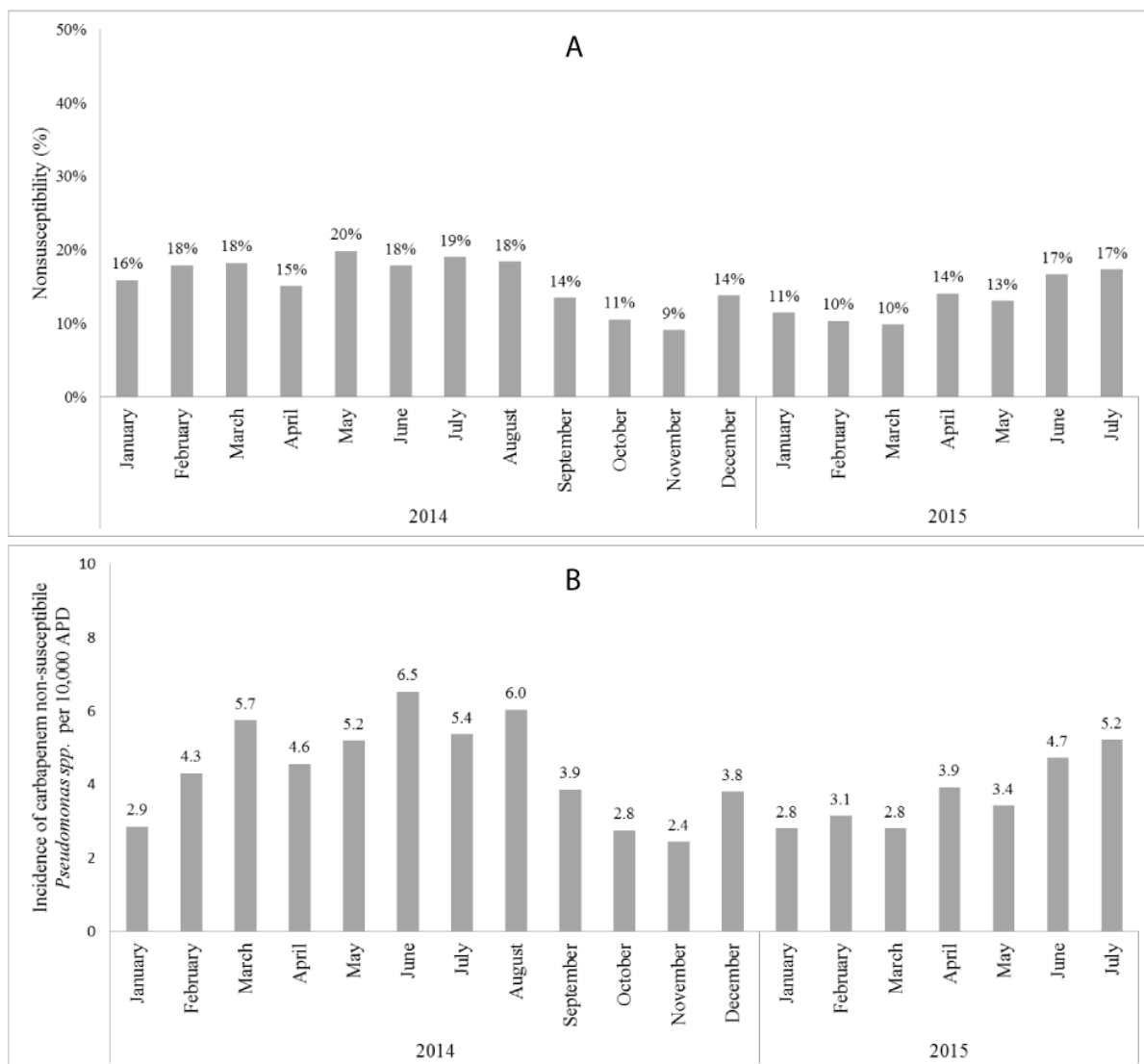


Figure 3: *P. aeruginosa* isolates nonsusceptible to group 2 carbapenems across all sites.

Figure 3B shows the incidence of carbapenem non-susceptible *Pseudomonas spp.* per 10,000 APDs. In the post-ASI phase II, the average incidence of carbapenem non-susceptible *Pseudomonas spp.* per 10,000 APDs significantly decreased compared to the pre-ASI

phase II (4.9 vs. 3.7; $p=0.03$). However, no significant trend of carbapenem non-susceptible *Pseudomonas spp.* was observed in the regression model ($p=0.81$).

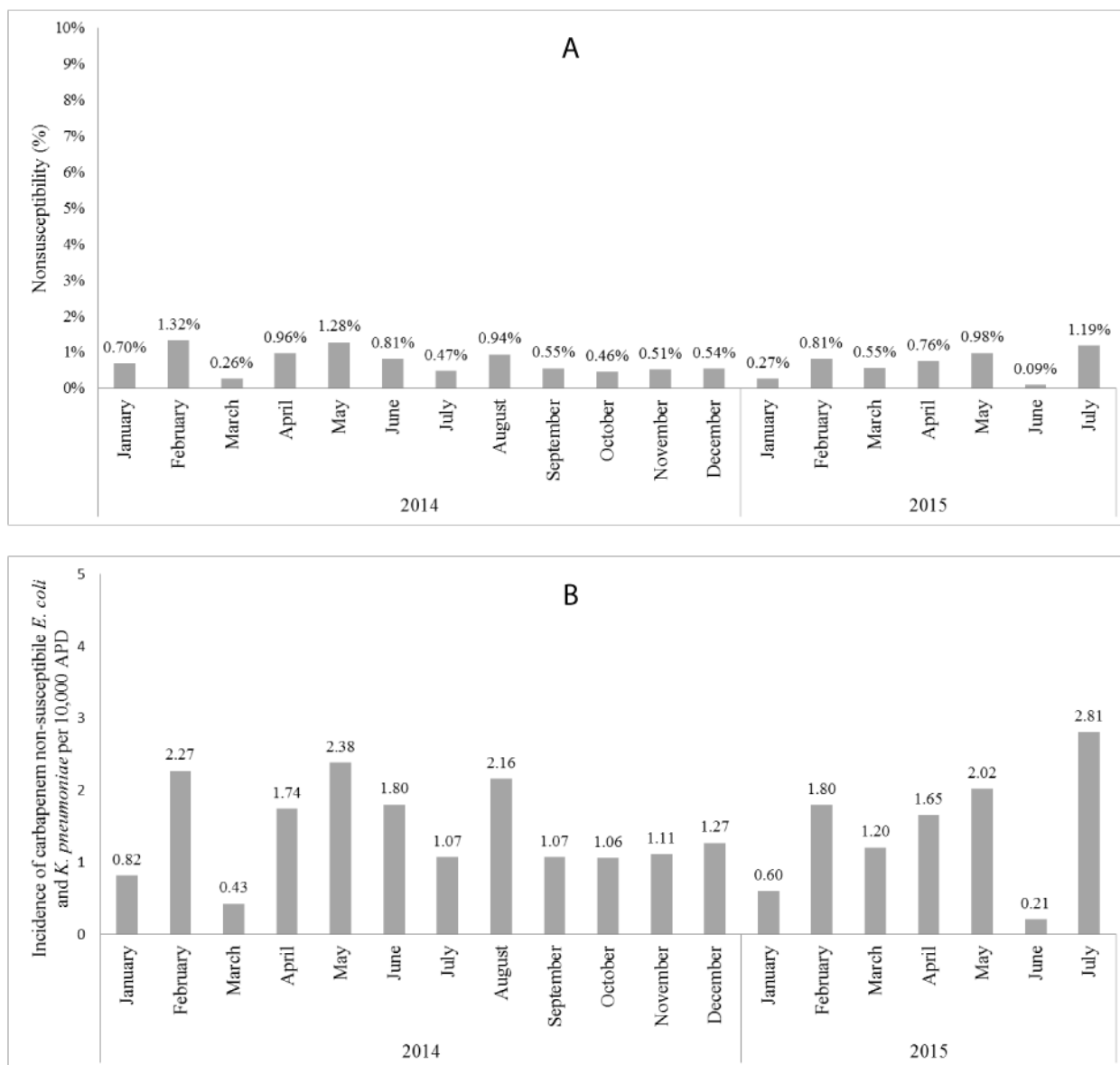


Figure 4: *K. pneumoniae* and *E. coli* nonsusceptible to carbapenems across all sites.

The percentage of *E. coli* and *K. pneumoniae* isolates nonsusceptible to a carbapenem remained stable across the post-intervention period, with 0.7% nonsusceptible in January 2014 and 1.19% nonsusceptible in July 2015, as shown in Figure 4A. The incidence of carbapenem non-susceptible *E. coli* and *K. pneumoniae* per 10,000 APDs, underwent slight fluctuations over the post-intervention period (Figure 3B). No associations on the nonsusceptibility rates of *E. coli* and *K. pneumoniae* per 10,000 APDs were observed related to the ASI implementation.

Discussion

Targeted ASI and restriction of broad-spectrum antimicrobial agents have emerged as important initiatives at many institutions due to the rise of multidrug-resistant *Enterobacteriaceae* across the United

States [33]. We described the short-term ecological results of restriction of ertapenem usage amongst multiple hospitals, specifically focused on *E. coli*, *K. pneumoniae*, and *Pseudomonas spp.* As a result of targeted education, removal of ertapenem from commonly used order sets across four community hospitals and an electronic alert for prescribers, ertapenem usage decreased substantially over the span of the study period of two years.

Previous investigations on the impact of carbapenem restriction have revealed decreased rates of CRE; however, the studies focused primarily on the restriction of group 2 carbapenems, imipenem and meropenem, without measurement of ertapenem [34]. Ertapenem is a carbapenem antibiotic that lacks activity against *Pseudomonas* isolates, but retains activity against ESBL- and AmpC-producing organisms. It is known that ertapenem's favorable pharmacokinetics and broad

spectrum of activity leads to inappropriate prescribing practices, yet it is unknown whether its restriction results in decreased CRE.

Multiple studies have investigated the impact of ertapenem introduction to the overall hospital ecology, specifically focusing on *Pseudomonas spp.* [35-37]. In many instances, these investigations reported improved susceptibilities of *Enterobacteriaceae* and *Pseudomonas spp.* to other broad-spectrum antimicrobial agents, such as cefepime and piperacillin/tazobactam following the introduction of ertapenem to a hospital formulary. However, none have reported significant changes in carbapenem susceptibility following ertapenem usage alone, with many methodological problems cited in these studies [38-41].

The two-year ASI aimed at decreasing ertapenem utilization in this study revealed a corresponding decrease in the incidence of group-2 carbapenem resistant *Pseudomonas spp.* in the post-intervention period. Similar to other studies that identified significant decreases in the proportion of carbapenem resistant *P. aeruginosa* after carbapenem restriction, we observed this decrease with the restriction of ertapenem alone. Previous data regarding ertapenem use and susceptibility to *P. aeruginosa* have been inconsistent. In a long-term study, despite an increasing use of ertapenem over a 9 year period, no association was found between ertapenem and changes in pseudomonal susceptibility to carbapenems [37]. Other studies have reported an increased susceptibility to imipenem among *P. aeruginosa* after introduction of ertapenem, presumptively due to decrease in group 2 carbapenems [35,36]. While the present study detected an overall decrease in carbapenem non-susceptible *Pseudomonas* isolates in the post-intervention period, whether this is a direct impact of ertapenem or through indirect changes in other antimicrobials is unknown. The rates of carbapenem non-susceptible *Enterobacteriaceae* did not significantly change during the post-implementation period. Together, our findings demonstrate that future initiatives focused on eliminating unnecessary ertapenem usage may not come with untoward ecological consequences. Longer studies are likely needed to identify significant trends.

This study has many limitations. During the study period, multiple national drug shortages affected the supply of many commonly used anti-Pseudomonal antibiotics, such as cefepime and piperacillin/tazobactam. Although this study was performed at four hospitals, there were a limited number of isolates nonsusceptible to carbapenems over the study period, which might have limited the ability to identify significant trends in susceptibility patterns. Additionally, the short duration of the study limited the ability to detect any longer-term ecological effects.

In summary, this multilevel ASI aimed at decreasing ertapenem utilization resulted in substantially declined use. Susceptibilities of *P. aeruginosa* to group 2 carbapenems improved overall while *Enterobacteriaceae* isolates remained stable in the post-intervention period.

Appendix

Definitions: The coefficient for 'time'=slope of the regression line pre-intervention; the coefficient for 'phase'=the change in intercept; the coefficient for 'interact'=the change in slope pre and post intervention. The coefficient for time is β_1 , for phase is β_2 and for interact is β_3 . The regression model is: Outcome=constant+ β_1 time+ β_2 phase+ β_3 interact. Pre intervention: Outcome=constant+ β_1 time and post intervention: Outcome=constant+ β_1 time+ β_2 + β_3 interact=(constant+ β_2)+(β_1 + β_3)

time (as time and interact are the same post intervention). Therefore, the difference in constant (intercept) pre and post intervention is β_2 and the difference in slope is β_3 .

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