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Antimicrobial Stewardship Lessons: Do *Pseudomonas*-Sparing Agents, Such as Ertapenem, Effectively Improve Bacterial Resistance?

Goldstein et al. addressed the issue of antimicrobial stewardship programs for reducing bacterial resistance in hospitals (2). In their study, they concluded that the introduction of ertapenem into a hospital formulary improved the *in vitro* susceptibility of *Pseudomonas aeruginosa* to imipenem. Previous studies (5) have concluded that although ertapenem can select *in vitro* carbapenem resistance in *P. aeruginosa*, this phenomenon occurs only briefly *in vivo*.

Goff et al. have concluded that susceptibility to imipenem in *P. aeruginosa* did not change after the addition of ertapenem and the continuous use of ertapenem for 5 years did not select for *P. aeruginosa* resistance to imipenem (1). Recently, another study in Brazil showed a probable decrease in carbapenem resistance in *P. aeruginosa* after the introduction of ertapenem, instead of imipenem, for the treatment of infections with extended-spectrum beta-lactamase-producing *Enterobacteriaceae*, but these results did reach statistical significance (4).

Goldstein et al. (2) stated that ". . . After the introduction of ertapenem (months 10 to 19), susceptibility continued to increase and was above 80% for the last 4 months; the increasing trend was significant (slope = 1.74; $P < 0.001$); however, the change in the rate of increase (the change in the slope was 1.14) was not statistically significant ($P = 0.36$) . . ." What did they mean by that?

Segmented regression models are the best methodological approach for analyses of temporal series in quasiexperimental studies. This type of analysis is used to determine significant changes in level (immediate change after the intervention) and the trend (slope after the intervention) of a series, measuring the impact of one or more interventions, taking into account the data before (baseline trend) and after the intervention. For this type of study, data from at least 10 observations before and 10 after the intervention are recommended to capture potential seasonal changes (6–8). From what we understood by the results presented by Goldstein et al., there was a trend of susceptibility that "continued" to increase despite the intervention and was not affected by the intervention *per se*, by segmented regression analysis, as stated afterwards, ". . . the change in the rate of increase (the change in the slope was 1.14) was not statistically significant ($P = 0.36$) . . .." In conclusion, there was an improvement in *P. aeruginosa* susceptibility that coincided with the increase in the use of ertapenem, and we can only speculate about this relationship, but definitely we cannot state that ertapenem influenced this change by interpreting the results of the segmented regression analysis.

Many factors may impact on bacterial resistance: multiple comorbidities, invasive procedures, poor hand hygiene practices and cross-transmission of resistant bacteria, intensive care unit (ICU) stay, length of hospitalization, and antimicrobial selective pressures. Jacoby et al. have shown that more than 30% of the bacterial resistance in an ICU was related to invasive procedures outside the ICU (3). These covariates were not controlled for or addressed by the authors.

The authors conclude that the addition of ertapenem was an important component and helped to improve *P. aeruginosa* susceptibility, but this is not supported by the segmented regression analysis. We believe that because of the methodological problems, the authors' conflicts of interest in relation to the studied drug, ertapenem, so far does not effectively improve *P. aeruginosa* susceptibility in relation to carbapenems. This study does not answer this question, although it seems to confirm that ertapenem usage does not select imipenem-resistant *P. aeruginosa* strains.

We have no conflicts of interest to declare.

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Rodrigo Pires dos Santos*
Thalita Jacoby
Infection Control Committee
Hospital de Clínicas de Porto Alegre
Ramiro Barcelos 2350
Porto Alegre, 90035-003 RS, Brazil

Luciano Zubaran Goldani
Infectious Disease Service
Hospital de Clínicas de Porto Alegre
Ramiro Barcelos 2350
Porto Alegre, 90035-003 RS, Brazil

*Phone: 55 51 33598644
Fax: 55 51 33598001
E-mail: rpsantos@hcpa.ufrgs.br

Authors' Reply

We are glad that Santos et al. agree that segmented regression analyses are the best approach to the analysis of quasiexperimental studies of antimicrobial resistance. One concern was that the optimal period of data collection suggested by guidelines should contain at least 10 observations prior to and 10 observations postintervention (Shardell et al., their reference 6). We have 9 months of data prior to the

introduction of ertapenem and >10 months postintervention and don't believe that this would be considered a significant drawback of our analysis.

Their primary concern seems to be with the interpretation of the results. Our results showed that after ertapenem was added (months 10 to 19), the susceptibility of *P. aeruginosa* to imipenem continued to increase; however, the change in the rate of increase in the susceptibility of *P. aeruginosa* to imipenem was not significant (change of slope was 1.14, *P* value = 0.36). Subsequently, in months 20 to 48 (after a policy change), there was no consistent increasing or decreasing trend in susceptibility. In the Discussion, we stated that "... The increased ertapenem usage per se did not show a statistically significant impact on the imipenem susceptibility of *P. aeruginosa*; however, the increased ertapenem use was simultaneous with a decline in imipenem usage, and this decreased imipenem use paralleled the improved imipenem susceptibility of *P. aeruginosa*." (We show in the paper that for 1 U of decrease in imipenem usage, there was a significant increase of 0.38% [*P* = 0.008] in susceptibility.) Thus, we clearly pointed out the relationship between ertapenem and imipenem usage and susceptibility without stating causality.

Lastly, they comment that there are a variety of covariates, such as hand hygiene practices and cross-contamination, as well as length of stay and comorbidities, etc., that could have been controlled for in our model. While we did not address their concerns specifically, we did report that there were no outbreaks or other changes in antimicrobial selective pressures during the study period. We also noted some limitations of our analysis in our Discussion. Like all U.S. hospitals, we monitor our hand hygiene practices, as well as length of stay, and verify that they remained constant throughout the study periods. We agree that fuller analysis of more covariates might improve the paper but do not think their inclusion would alter our findings.

Ellie J. C. Goldstein*
Department of Infectious Diseases
St. John's Health Center
Santa Monica, California 90404

Diane M. Citron
R. M. Alden Research Laboratory
Santa Monica, California

Victoria Peraino
Department of Microbiology
St. John's Health Center
Santa Monica, California 90404

Tanya Elgourt
Department of Pharmacy
St. John's Health Center
Santa Monica, California 90404

Anne R. Meibohm
Shuang Lu
Merck & Co., Inc.
North Wales, Pennsylvania

*Phone: (310) 315-1511
Fax: (310) 315-3662
E-mail: ejcgmd@aol.com