Carbapenem stewardship – positive impact on hospital ecology

ABSTRACT

Introduction: Excessive group 2 carbapenem use may result in decreased bacterial susceptibility. **Objective:** We evaluated the impact of a carbapenem stewardship program, restricting imipenem and meropenem use. **Methods**: Ertapenem was mandated for ESBL-producing *Enterobacteriaceae* infections in the absence of non-fermenting Gram-negative bacilli (GNB) from April 2006 to March 2008. Group 2 carbapenems were restricted for use against GNB infections susceptible only to carbapenems and suspected GNB infections in unstable patients. Cumulative susceptibility tests were done for nosocomial pathogens before and after restriction using Clinical and Laboratory Standards Institute (CLSI) guidelines. Vitek System or conventional identification methods were performed and susceptibility testing done by disk diffusion according to CLSI. Antibiotic consumption (t-test) and susceptibilities (McNemar's test) were determined. **Results**: The defined daily doses (DDD) of group 2 carbapenems declined from 61.1 to 48.7 DDD/1,000 patient-days two years after ertapenem introduction ($p = 0.027$). Mean ertapenem consumption after restriction was 31.5 DDD/1,000 patient-days. Following ertapenem introduction no significant susceptibility changes were noticed among Gram-positive cocci. The most prevalent GNB were *P. aeruginosa*, *Klebsiella pneumoniae*, and *Acinetobacter* spp. There was no change in *P. aeruginosa* susceptibility to carbapenems. Significantly improved *P. aeruginosa* and *K. pneumoniae* ciprofloxacin susceptibilities were observed, perhaps due to decreased group 2 carbapenem use. *K. pneumoniae* susceptibility to trimethoprim-sulfamethoxazole improved. **Conclusion**: Preferential use of ertapenem resulted in reduced group 2 carbapenem use, with a positive impact on *P. aeruginosa* and *K. pneumoniae* susceptibility.

Keywords: carbapenems; drug resistance; bacterial ecology.

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INTRODUCTION

Susceptibility to the group 2 carbapenems, imipenem and meropenem, remains high even after decades of use.[5] The more recently introduced group 1 carbapenem ertapenem has a different spectrum of activity, with minimal activity against *Pseudomonas aeruginosa*; ertapenem has been described as a *Pseudomonas*-sparing carbapenem.[2,12,16] The premise that ertapenem has minimal activity against *P. aeruginosa* and is thus less likely to select for resistance has been substantiated *in vitro* and in clinical settings.[4,6,10,11] Still, the question of the long-term impact of ertapenem on hospital ecology lingers as overall concerns about antibiotic resistance become more pervasive.

Ertapenem is appropriate for the treatment of extended spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae*, and thus provides a good weaponry to combat an increasingly important problem, particularly in an era when few new antibiotics are being introduced. The widespread use of ertapenem is likely to depend on long-term clinical evidence of the effect of ertapenem on the susceptibility of Gram-negative bacteria to the spectrum of antibiotics used.

ESBL-producing *Enterobacteriaceae* are a growing problem in Brazil as they are elsewhere; this problem can result in increased, and not always appropriate, carbapenem use.[10,15] Antibiotic consumption and the prevalence of antibiotic resistance are linked, giving institutional antibiotic use policies an important role in reducing the selective pressure for resistance.[9,15] The goal of this study was to evaluate the long-term impact of a carbapenem stewardship program on the hospital ecology at our facility, where ertapenem use was mandated for appropriate infections while group 2 carbapenems were restricted.

MATERIALS AND METHODS

Study design

This single-center study was conducted at the Institute of Orthopedics and Traumatology of Hospital das Clínicas, School of Medicine, *Universidade de São Paulo*, a 200-bed tertiary care facility that treats orthopedic and trauma patients. A mandatory antibiotic restriction policy was put in place in March 2006. Ertapenem use was mandated for infections caused by ESBL-producing *Enterobacteriaceae* for patients who did not have co-infection with non-fermenting Gram-negative bacilli. Before the restriction, group 2 carbapenems were used to treat infections caused by ESBL-producing *Enterobacteriaceae* and infections caused by non-fermenting Gram-negative bacilli that were shown to be susceptible only to carbapenems. Following the restriction group 2 carbapenems were used only to treat infections caused by non-fermenting Gram-negative bacilli infections sensitive to carbapenems alone and to treat suspected Gram-negative infections in hemodynamically unstable patients who did not respond to other agents. Meropenem was not used from March 2005 to March 2006, but was used in the other periods of time included in the present study.

Antimicrobial susceptibility tests were obtained for nosocomial pathogens (e.g. *Enterobacteriaceae*, *Acinetobacter* spp., and *P. aeruginosa*) isolated as the cause of nosocomial infection, according to the definitions of the Centers for Disease Control and Prevention (CDC)[3], for the 24 months before and the 24 months after ertapenem introduction in March 2006. Cumulative susceptibility tests were done for nosocomial pathogens before and after restriction using Clinical and Laboratory Standards Institute (CLSI) guidelines. Strains were identified by Vitek 1 automated microbial identification system. *Enterobacteriaceae* susceptibility tests were done using the GNS 655 card. Susceptibility to ertapenem was extrapolated from imipenem results, according to CLSI standards during the time this study was performed.[13] Susceptibility tests for non-fermenting bacteria were done by disk diffusion (CLSI M100-S16).Quality control followed the CLSI standards.

Data analysis

Antimicrobial susceptibility was measured as the proportion of susceptible isolates of each bacterium to the antimicrobials tested. The statistical significance susceptibility changes before and after the restriction was assessed using the Chi-square test. Consumption of antimicrobial agents was measured as the number of defined daily doses (DDD) per 1,000 patient-days, calculated for each month before and after the restriction. The mean consumptions before and after the restriction were compared using t-tests on the log-transformed data. Generally concordant results were obtained using a t-test performed on the raw data. Stability of the number of patient-days, length of stay, the numbers of deaths, and the hospital mortality index were also evaluated using these methods. The Durbin-Watson test for autocorrelation was used to rule out the possibility of false positive results that might have been caused by autocorrelation of the monthly data series. The p-values < 0.05 were considered to be indicative of statistically significant comparisons; these tests are observational, however, and should be interpreted in conjunction with clinical judgment.

RESULTS

The average defined daily doses (DDD) of group 2 carbapenems declined from 61.1 to 48.7 DDD/1,000 patient-days two years after ertapenem was mandated for treatment of susceptible infections caused by ESBL-producing *Enterobacteriaceae* ($p = 0.027$).This represented a 20.2% decrease in group 2 carbapenem average consumption from the 24 months before the restriction to the 24 months after. Imipenem use decreased by 58.7%; meropenem was used only sporadically during the 24 months prior to the restriction thus the mean change in use was not assessed. The mean ertapenem consumption after the restriction was 31.5 DDD/1,000 patient-days.

No significant antibiotic susceptibility changes were noticed among Gram-positive cocci following ertapenem introduction (Table 1). The most prevalent Gram-negative bacteria that caused infection were *P. aeruginosa*, *Klebsiella pneumoniae*, and *Acinetobacter* spp. There were no changes in *P. aeruginosa* susceptibility to imipenem before and after the restriction (55% and 57%, respectively). Improved *P. aeruginosa* (from 28% to 57%) and *K. pneumoniae* (from 12% to 40%) ciprofloxacin susceptibilities were observed before and after the restriction, although ciprofloxacin use did not change significantly (before: 41.7 ± 17.4 DDD, after: 70.7 ± 34.5 DDD; $p = 0.057$). Although *K. pneumoniae* susceptibility to trimethoprim-sulfamethoxazole improved from 24% before the restriction to 60%, trimethoprim-sulfamethoxazole consumption was low before and after the restriction (0.92 ± 2.27 DDD before to 2.35 ± 2.97 DDD after, $p = 0.001$), so the increase may not be clinically relevant. *Acinetobacter* spp. susceptibility to carbapenems decreased, a trend also seen in the other departments within our hospital complex that did not have an ertapenem policy use (F Rossi and J N Almeida Jr, unpublished data).

In the 24 months before ertapenem introduction, 45% of all *P. aeruginosa* isolates were imipenem resistant. In the 24 months after restriction, 43% of isolates were resistant to imipenem, suggesting that ertapenem did not impact *P. aeruginosa* susceptibility to imipenem.

The mortality index slightly lower after the restriction was observed (mean $\pm$ SD 0.95 ± 0.39 before and 0.71 ± 0.45 after the restriction, $p = 0.035$). There were no clinically relevant changes in other outcomes. The median length of stay

Table 1. Antimicrobial susceptibilities for the most frequent agents related to nosocomial infections before and after ertapenem introduction

Pathogen/Antibiotic (nº isolates collected before/ after ertapenem policy)	Susceptibility (%) 2 years before ertapenem use	Susceptibility (%) 2 years after ertapenem use
S. aureus **(100/76)**		
Cephalotin	30	32
Clindamycin	33	32
Methicillin	30	31
Trimethoprim-sulfamethoxazole	33	3
Vancomycin	100	100
A. baumanii **(64/36)**		
Amikacin	15	12
Cefepime	6	11
Ceftazidime	78	8
Ceftriaxone	14	3
Ciprofloxacin	3	11
Imipenem	64	33
Trimethoprim-sulfamethoxazole	6	17
P. aeruginosa **(51/42)**		
Amikacin	68	67
Cefepime	43	57
Ceftazidime	61	62
Ciprofloxacin	28	57
Imipenem	55	57
Coagulase-negative ***Staphylococci*** **(49/39)**		
Cephalotin	8	8
Clindamycin	20	20
Methicillin	8	8
Trimethoprim-sulfamethoxazole	43	8
Vancomycin	100	100
E. faecalis **(39/28)**		
Ampicillin	92	46
Gentamicin	61	25
Penicillin	4	86
Vancomycin	73	79
K. pneumoniae (25/35)		
Amikacin	76	97
Cefepime	16	17
Ceftazidime	20	11
Cefotaxime	8	11
Ceftriaxone	8	9
Ciprofloxacin	12	40
Imipenem	100	100
Trimethoprim-sulfamethoxazole	24	60

was 7.11 ± 0.74 days before and 6.89 ± 0.5 days after the restriction (p = 0.306); the number of deaths due to infection was 4.71 ± 2.05 before and 3.63 ± 2.41 after the restriction (p = 0.074). Overall, these data suggest that the severity of illness would have been similar during the two periods and that any observed decrease in *Pseudomonas*-resistant isolates would not be due to differences in the severity of illness.

DISCUSSION

Instituting ertapenem use for ESBL-producing *Enterobacteriaceae* infections in the absence of non-fermenting Gram-negative bacilli while restricting group 2 carbapenems had a positive effect on the overall hospital ecology at our institution. In particular, increased ertapenem use had, in an indirect way, positive impact on the susceptibility of *P. aeruginosa* to imipenem, perhaps related to decreased use of group 2 carbapenems. There was no evidence of carbapenem resistance development associated with ertapenem use. Ertapenem use heralded improvements in the susceptibilities of *P. aeruginosa* and *K. pneumoniae* to ciprofloxacin, again perhaps due to a decrease in group 2 carbapenem use. An improvement in *K. pneumoniae* susceptibility to trimethoprim-sulfamethoxazole was noticed. We observed a decrease in *Acinetobacter* susceptibility to imipenem. In the broader context of data collected from across our institution and analyzed by the Microbiology Laboratory of Hospital das Clinicas (F Rossi and J N Almeida Jr, unpublished data), a downward trend was also observed for susceptibility of *Acinetobacter* to group 2 carbapenems from 2005 to 2008 despite there being no ertapenem use policy in place. This could suggest that the *Acinetobacter* susceptibility trends were independent of ertapenem use.

Significant correlations between the consumption of specific antibiotics and resistance have been reported for Gram-negative bacteria including *P. aeruginosa* and *Acinetobacter*.[8,9,13] The rate of consumption of specific antibiotics is also related to the prevalence of resistance among nosocomial pathogens.[9] Examining correlations between consumption of specific antimicrobials and antibiotic resistance can assist in putting effective antimicrobial use policies in place in hospitals. Imipenem resistance, for example, has been linked to the use of amikacin, ciprofloxacin, and ceftazidime, but not to ertapenem.[9,11] Implementation of interventions such as the one we describe here can have a positive impact on antimicrobial resistance, because inappropriate antibiotic use is a main driver of resistance.[15] Goldstein *et al.* reported that adding ertapenem to the formulary in a 344-bed community hospital was an effective antimicrobial management tool.[7]

Apisarnthanarak *et al.* demonstrated that conducting surveillance and implementing prescribing policies resulted in reductions in antibiotic consumption and resistance in a tertiary care hospital in a developing country.[1] This is consistent with our experience. Our research was part of an ongoing close monitoring of antimicrobial resistance patterns in our hospital following ertapenem introduction. The data reported here were consistent with prior results detailing the impact of ertapenem on hospital ecology within our institution.[10,11]

The policies for rational use of carbapenems should always be encouraged, since it has been observed a worldwide dissemination of multidrug-resistant Gram-negative bacilli, with few therapeutic options. Indiscriminate use of carbapenems is one reason for this problem. It is also necessary to remember the rapidly increasing prevalence of *Enterobacteriaceae* harboring carbapenemases. From 2000 to 2007, the proportion of carbapenem-resistant *Klebsiella* spp. involved in nosocomial infections in the United States grew from less than 1% to 8% of the total *Klebsiella* spp. isolates.[17]

Our study provides long-term clinical data indicating that ertapenem is associated with a minimal risk of resistance, and that ertapenem use may improve overall hospital ecology by decreasing excess use of group 2 carbapenems. These results suggest that ertapenem may have an important place in the treatment of ESBL-producing *Enterobacteriaceae* infections in the absence of *Pseudomonas*, and that antibiotic use policies that promote stewardship may decrease antibiotic resistance.

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