Hand Hygiene, and Not Ertapenem Use, Contributed to Reduction of Carbapenem-Resistant *Pseudomonas aeruginosa* Rates

Rodrigo Pires dos Santos, MD, PhD;[1,2] Thalita Jacoby, PharmD, MSc;[1] Denise Pires Machado, MSc;[3]
Thiago Lisboa, MD, PhD;[1] Sandra Ludwig Gastal, MD;[1] Fabiano Márcio Nagel, MD;[1] Nádia Mora Kuplich, RN, MSc;[1]
Loriane Konkewicz, RN, MSc;[1] Carem Gorniak Lovatto, RN;[1] Márcia Rosane Pires, RN;[1]
Luciano Zubaran Goldani, MD, PhD[2]

OBJECTIVE.   To evaluate the impact of ertapenem use in *Pseudomonas aeruginosa* carbapenem resistance, taking into account the volume of antimicrobial consumption, the consumption by the entire hospital of alcohol-based antiseptic hand rub, and the density rate of invasive practices.

DESIGN.   Before-and-after trial.

SETTING.   A tertiary care university hospital in southern Brazil.

METHODS.   Ertapenem was first added to the hospital formulary in June 2006, and it was excluded in February 2009. We evaluated *Pseudomonas aeruginosa* resistance rates through 3 study periods: period 1, before ertapenem use (17 months); period 2, during ertapenem use (33 months); and period 3, after exclusion of ertapenem (15 months).

RESULTS.   After introduction of ertapenem, there was a significant decrease in median consumption of imipenem or meropenem, from 2.6 to 2.2 defined daily doses (DDDs) per 100 patient-days (level change from 0.04 to −1.08; $P < .01$), and an increase in the use of these medications after ertapenem exclusion, from 2.2 to 3.3 DDDs per 100 patient-days (level change from −0.14 to 0.91; $P < .01$), by segmented regression analysis. There was no difference in the incidence density of carbapenem-resistant *P. aeruginosa* infection related to ertapenem use throughout the study periods. However, by multiple regression analysis, the reduction in the rate of carbapenem-resistant *P. aeruginosa* infection correlated significantly with the increase in the volume of alcohol used as hand sanitizer, which was from 660.7 mL per 100 patient-days in period 1 to 2,955.1 mL per 100 patient-days in period 3 ($P = .04$). Ertapenem use did not impact the rate of carbapenem-resistant *P. aeruginosa* infection.

CONCLUSIONS.   Use of alcohol-based hand gel, rather than ertapenem, was associated with a reduction in the rates of carbapenem-resistant *P. aeruginosa* infection. Measures to reduce resistance must include factors other than just antimicrobial stewardship programs alone.

In hospitals, the prescription of antimicrobial drugs is an exercise of balance between the benefits of an immediate and aggressive empirical therapy and the risk of the emergence of antimicrobial-resistant pathogens.[1] Antimicrobial stewardship programs have been implemented to promote the rational use of antimicrobial drugs.[2]

A lack of activity of ertapenem against *Pseudomonas aeruginosa* has raised some issues concerning the induction of resistance by or even the lack of protection against carbapenem-resistant *P. aeruginosa*. Few studies have addressed the impact of the use of ertapenem on carbapenem-resistant *P. aeruginosa*, but the results are conflicting.[3-7] Factors other than antimicrobial consumption may contribute to the rise of resistance, and infection control programs must address all of these issues in order to control for the emergence of resistance.[8] We evaluated the use of ertapenem and the rates of carbapenem-resistant *P. aeruginosa* infection in a university-affiliated hospital, taking into account the volume of antimicrobials consumed, the volume of alcohol-based hand gel consumed, and the density rate of invasive practices.

METHODS

Setting and Study Design

Hospital de Clínicas de Porto Alegre, a 749-bed, university-affiliated, tertiary level public hospital, is located in the city

of Porto Alegre, in southern Brazil. The hospital has 22 non-critical wards and 3 intensive care units (adult, neonatal, and pediatric). The adult and pediatric intensive care units have 42 and 13 beds, respectively, for medical and surgical patients. The neonatal intensive care unit comprises 20 beds.

Study Design and Definitions

We conducted a before-and-after trial to assess the impact of ertapenem consumption on rates of carbapenem-resistant *Pseudomonas aeruginosa* infection. Ertapenem was first introduced into our antimicrobial panel in June 2006. This drug was then removed from the antimicrobial panel in March 2009. Thus, we analyzed this time series in the following 3 periods: period 1, from January 2005 to May 2006 (17 months, the pre-ertapenem period); period 2, from June 2006 to February 2009 (33 months, the ertapenem period); and period 3, from March 2009 to May 2010 (15 months, the postertapenem period).

Risk factors, including the consumption of antibiotics by the entire hospital, invasive practices (endotracheal intubation, use of a urinary tract catheter, use of a central venous catheter [CVC]), and the total volume of alcohol used as hand sanitizer were considered as covariates for antibiotic drug resistance. We excluded the pediatric units from the analysis, because the consumption of antibiotics by this population is not standardized in our hospital.

On a monthly basis, data on the consumption of antimicrobial drugs were recorded as the number of defined daily doses (DDDs) per 100 patient-days, as recommended by the Anatomical Therapeutic Chemical Classification System and the DDD index.[9] Data were collected on the consumption of aminoglycosides (gentamicin, amycacin, tobramycin), third-generation cephalosporins (ceftriaxone, ceftazidime), fluoroquinolones (norfloxacin, ciprofloxacin, and levofloxacin), broad-spectrum penicillins (piperacillin-tazobactam, ticarcillin-clavulanate), carbapenems (imipenem and meropenem), and ertapenem.

For measurement of invasive practices, data were extracted from the hospital electronic database every month. As recommended by the National Healthcare Safety Network, the rate of use of invasive practices was reported as the number of days of endotracheal intubation, urinary catheter, or CVC use divided by the total number of patient-days.[10]

The consumption of alcohol-based hand gel by the entire hospital (excluding the pediatric units) was recorded monthly in milliliters per 100 patient-days. This included the use of alcohol-based formulations from 100-mL bottles and from wall dispensers.

In this study, for each patient, information about only the first microbiological isolate was recorded, irrespective of the body site from which it was obtained or the antimicrobial susceptibility pattern.[11] Microbiological isolates from patients who received a diagnosis of a community-acquired infection were excluded. Bacteria species identification was performed according to the protocols of the clinical microbiology laboratory. Susceptibility testing was performed by the disk-diffusion method: Isolates were suspended in saline to create a 0.5 McFarland turbidity standard. This suspension was used to inoculate Mueller-Hinton agar plates, and antibiotic disks were applied to the agar surface. The inhibition zones of the antibiotic disks were interpreted according the recommendations of the Clinical and Laboratory Standards Institute guideline.[12] Bacterial multiresistance was classified according to the recommendations of the Centers for Disease Control and Prevention (CDC) and Infection Control Committee criteria,[13] and it included the following organisms: extended-spectrum β-lactamase (ESBL)–producing *Klebsiella* species, *Escherichia coli*, *Proteus mirabilis*, carbapenem-resistant *Acinetobacter baumanii*, vancomycin-resistant *Enterococcus* species, methicillin-resistant *Staphylococcus aureus* (MRSA), and carbapenem-resistant *P. aeruginosa*. On a monthly basis, bacterial resistance rate was calculated by dividing the number of resistant isolates of each species by the number of patient-days, multiplied by 1,000.

Statistical Analysis

Time-series segmented regression analysis was used to determine significant changes in the level and trend of antibiotic use and resistance patterns throughout the study periods.[1-16] By this analysis, estimates of changes in level (immediate change after intervention) and trend (changes that occurred after months of intervention) were determined.

For normally distributed variables, one-way ANOVA analysis with Tukey multiple comparisons adjustment was performed to compare mean differences among the period groups. For the nonparametric variables (quinolone, ertapenem, and CVC use rates, and the volume of alcohol-based hand antiseptic used), the median differences among these periods were assessed by Kruskal-Wallis test.

Multiple regression analysis was used to assess the relationship among explanatory variables (antimicrobial drug use, invasive practices, and consumption of alcohol-based hand antiseptic) and the outcome variable rate of carbapenem-resistant *P. aeruginosa* infection. Antibiotics included in the analysis are those that are related to the risk of resistance by *P. aeruginosa*.[17]

All *P* values less than .05 were considered to be statistically significant. All collected data were analyzed using SPSS, version 18.0. The study was approved by the institution's Review and Ethics committee.

RESULTS

There was a significant overall decrease in mean consumption of aminoglycosides, third-generation cephalosporins, and quinolones in the ertapenem and postertapenem periods compared with in the pre-ertapenem period. The mean consumption of aminoglycosides in DDDs per 100 patient-days was 4.3 (95% confidence interval [CI], 3.9–4.8), 3.2 (2.9–3.5; *P* < .01), and 2.0 (1.7–2.2; *P* < .01) in periods 1–3, respectively; for third-generation cephalosporins, the mean rate of

consumption was 1.1 (0.9–1.2), 0.8 (0.7–0.9; $P < .01$), and 0.5 (0.4–0.6; $P < .01$) in periods 1–3, respectively; and for quinolones, the median consumption rate was 10.1 (8.7–10.8), 10.0 (9.3–10.9; $P = 1.0$), and 3.6 (2.7–4.0; $P < .01$) in periods 1–3, respectively. For broad-spectrum penicillins, there was an increase in use: the mean consumption rate was 2.4 (2.2–2.7), 3.3 (3.1–3.5; $P < .01$), and 4.2 (3.8–4.5; $P < .01$) in periods 1–3, respectively.

The median rate of consumption of ertapenem in period 2 was 0.5 DDDs per 100 patient-days (95% CI, 0.4–0.7). For other carbapenems, the mean consumption rate was 2.6 (2.2–3.0), 2.2 (2.1–2.4; $P = .08$), and 3.3 (3.1–3.6; $P < .01$) in periods 1–3, respectively. Ertapenem consumption was associated with changes in the use of imipenem or meropenem. By a segmented regression model, the introduction of ertapenem in the hospital antibiotic panel resulted in an immediate decrease in the use of other carbapenems (level change from 0.04 to –1.08; $P < .01$). Furthermore, the exclusion of ertapenem resulted in an immediate increase in the use of other carbapenems (level change from –0.14 to 0.91; $P < .01$; fig. 1).

Throughout the 3 study periods, the median rate of use of CVCs per 1,000 patient-days was 152.2 (95% CI, 144.4–155.8), 174.2 (162.5–182.8; $P < .01$), and 209.6 (202.8–223.4; $P = .01$) in periods 1–3, respectively. For urinary catheters, the mean rate of use per 1,000 patient-days was 157.6 (144.0–171.1) in period 1, 178.4 (171.2–185.4; $P < .01$) in period 2, and 203.4 (193.8–213.0; $P < .01$) in period 3. For mechanical ventilation, the mean rate of use was 31.3 (28.9–33.6), 36.2 (34.4–37.9; $P < .01$), and 40.3 (37.2–43.4; $P = .02$) ventilation-days per 1,000 patient-days in from periods 1–3, respectively.

There was a significant increase in the consumption of alcohol-based hand gel throughout the study period. In period 1, the median consumption was 685.4 mL per 100 patient-days (95% CI, 531.7–735.3), in period 2 it was 1,548.8 (1,434.2–1,706.2; $P < .01$), and in period 3 it was 2,995.8 (2,558.0–3,251.3; $P < .01$; fig. 2).

There was a significant decrease in the rate of multidrug-resistant bacteria. The mean incidence rate of multidrug-resistant bacteria was 5.0 per 1,000 patient-days (95% CI, 4.6–5.3) in period 1, 4.9 (4.6–5.2; $P = .9$) in period 2, and 4.0 (3.6–4.4; $P < .01$) in period 3. The mean rate per 1,000 patient-days of ESBL-producing organisms was 2.4 (2.1–2.6) in period 1, 2.5 (2.3–2.7; $P = .69$) in period 2, and 2.5 (2.1–2.8; $P = 1.0$) in period 3.

The mean incidence of carbapenem-resistant *P. aeruginosa* infections per 1,000 patient-days was 0.51 (95% CI, 0.41–0.60) in period 1, 0.43 (0.36–0.49; $P = .33$) in period 2, and 0.33 (0.26–0.41; $P = .34$) in period 3. Comparing the mean rate in periods 1 and 3, there was a statistically significant decrease in the incidence of carbapenem-resistant *P. aeruginosa* infection ($P = .04$).

By segmented regression analysis, there was no difference in the incidence density of carbapenem-resistant *P. aeruginosa* infections throughout the study period in relation to ertapenem use. Comparing the pre-ertapenem use period and the period following the introduction of ertapenem, there was a change in slope from −0.003 to −0.002 ($P = .87$). Comparing periods 2 and 3, there was a change in slope from −0.002 to 0.13 ($P = .28$).

By multiple regression analysis, the use of antibiotics (ie, aminoglycosides, third-generation cephalosporins, fluoro-quinolones, broad-spectrum penicillins, carbapenems, and ertapenem) and invasive practices (endotracheal intubation, use of urinary catheter, use of CVC) did not impact the rate of carbapenem-resistant *P. aeruginosa* infection. Alcohol-based antiseptic hand gel use was associated with a decrease in the incidence of carbapenem-resistant *P. aeruginosa* infection ($P = .04$; table 1). Furthermore, the use of alcohol-based hand gel correlated significantly to the decrease in the rate of carbapenem-resistant *P. aeruginosa* infection ($P < .01$; Spearman correlation $r = −0.40$).

DISCUSSION

To the best of our knowledge, this is the first study to assess the impact of ertapenem use on the rate of carbapenem-
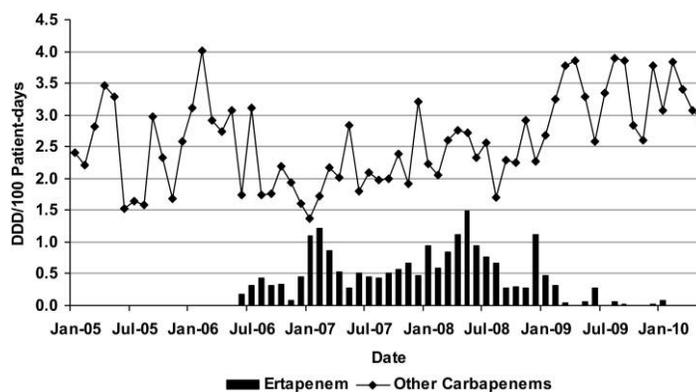

FIGURE 1. Consumption of ertapenem (*bars*) and other carbapenems (*line*), in defined daily doses (DDDs) per 100 patient-days, from January 2005 to May 2010.
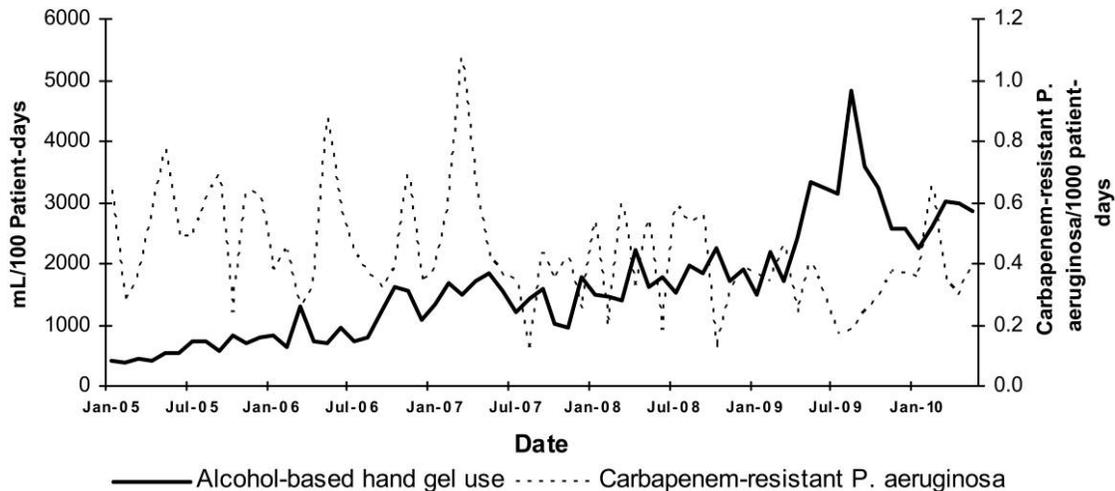
FIGURE 2. Rates of alcohol-based hand gel consumption in milliliters per 100 patient-days (*solid line*) and carbapenem-resistant *Pseudomonas aeruginosa* infection per 1,000 patient-days (*dashed line*), from January 2005 to May 2010.

resistant *Pseudomonas aeruginosa* infection by taking into account risk factors for bacterial resistance other than antimicrobial pressure alone (ie, rates of use of invasive devices and hand hygiene compliance). This study demonstrates the association of hand hygiene, as measured by the use of alcohol-based gel, with a reduction in the rate of carbapenem-resistant *P. aeruginosa* infection. Furthermore, the introduction and subsequent exclusion of ertapenem from the hospital antimicrobial panel were not associated with changes in *P. aeruginosa* resistance.

In 2006, the hospital antimicrobial policy recommended the use of ertapenem only for the treatment of infections with ESBL-producing organisms, and it reserved the use of imipenem and meropenem for treatment of infections caused by other Gram-negative bacteria. The aim of the antimicrobial stewardship program was to diminish the rates of carbapenem-resistant *P. aeruginosa* infection by reducing the consumption of other carbapenems. Although we observed a significant and immediate reduction in the use of other carbapenems after the introduction of ertapenem, it did not correlate with a decrease in the rate of carbapenem-resistant *P. aeruginosa* infection. Ertapenem was excluded from the hospital antimicrobial panel for cost reasons in 2009; this resulted in a significant increase in the use of imipenem or meropenem, without changes in the rate of carbapenem-resistant *P. aeruginosa* infection.

Several studies have assessed the risk factors for carbapenem resistance in *P. aeruginosa*. The use of carbapenems, third-generation cephalosporins, ciprofloxacin, piperacillin-tazobactam, and aminoglycosides are all associated with multidrug or carbapenem resistance in *P. aeruginosa*. Other factors include prolonged hospital stay, intensive care unit stay, use of mechanical ventilation, use of Foley catheters, renal failure, history of chronic obstructive pulmonary disease, advanced age, and human immunodeficiency virus infection.[17-23]

Studies have been published examining the impact of an-

timicrobial programs on bacterial resistance.[24,25] Restrictions or decreases in the use of carbapenems have been responsible for reductions in the rates of carbapenem-resistant *P. aeruginosa* infection.[26,27] However, there are conflicting results concerning ertapenem use and improvement in the rates of carbapenem-resistant *P. aeruginosa* infection.[4-7] Goff et al[4] concluded that susceptibility to imipenem in *P. aeruginosa* did not change after the continuous use of ertapenem for 5 years. Lima et al[5] found a decrease in carbapenem resistance in *P. aeruginosa* after the introduction of ertapenem but not imipenem for the treatment of infections with ESBL-producing Enterobacteriaceae, but their results did not reach statistical significance. Goldstein et al[6] concluded that the addition of ertapenem was an important component and helped to improve susceptibility of *P. aeruginosa* mostly through decreased consumption of other carbapenems. Finally, Eagye et al,[7] in a recent multicenter study, showed that *P. aeruginosa* susceptibility rates did not change in relation to ertapenem use in 25 US hospitals. All of these studies evaluated antibiotic use and its relationship with *P. aeruginosa* resistance, but they did not include in their analyses other known risk factors for *P. aeruginosa* resistance.

In this study, other risk factors for carbapenem-resistant *P. aeruginosa* infection (ie, invasive devices and hand hygiene) and antibiotic use were included in the analysis. Furthermore, there was a significant increase in the rate of use of invasive devices during the study period. It could be assumed that this is an indicator of severity and might have contributed to an increase in antimicrobial resistance. In spite of this, the increase in use of alcohol-based hand gel was independently associated with a reduction in the rate of carbapenem-resistant *P. aeruginosa* infection.

Alcohol-based antiseptic hand gel was introduced in our hospital in 2003. In 2006, campaigns to stimulate hand hygiene were started, which included continuous training, distribution of educational materials, and dissemination of dis-

TABLE 1. Multiple Regression Analysis of Explanatory Variables and Carbapenem-Resistant *Pseudomonas aeruginosa* as the Outcome Variable

	Coefficient (β)	95% CI	P
Central venous catheter rate of use	0.1×10^{-2}	-0.003 to 0.004	.77
Urinary catheter rate of use	-0.1×10^{-2}	-0.05 to 0.02	.43
Mechanical ventilation rate of use	1.2×10^{-2}	-0.002 to 0.025	.09
Aminoglycosides	2.4×10^{-2}	-0.053 to 0.1	.53
Quinolones	-0.2×10^{-2}	-0.03 to 0.03	.90
Third-generation cephalosporins	-0.15	-0.44 to 0.15	.33
Broad-spectrum penicillins	5.6×10^{-2}	-0.04 to 0.14	.26
Ertapenem	1.6×10^{-2}	-0.14 to 0.17	.84
Other carbapenems	1.5×10^{-2}	-0.07 to 0.10	.74
Alcohol-based hand gel use	-0.01×10^{-2}	-0.2×10^{-3} to -0.07×10^{-4}	.04
Hospital patient-days	-0.13	-0.09×10^{-3} to 0.004×10^{-2}	.46
ICU patient-days	-9.2×10^{-2}	-0.001 to 0.001	.69

NOTE. CI, confidence interval; ICU, intensive care unit.

pensers near each hospital bed. In 2008, the hospital adhered to the World Health Organization campaign "Clean Care is Safer Care" and introduced its methodology. In 2009, as is shown in figure 2, a significant increase in the use of alcohol-based antiseptic hand gel occurred during the H1N1 influenza pandemic.[28]

Adherence to hand hygiene practices can vary from 5% to 81%.[29] Pittet et al[30] demonstrated significant increases in hand hygiene adherence practices in Geneva, from 48% to 66%, with a subsequent reduction in healthcare-associated infections and transmission of MRSA. Others have found that even a modest increase in hand hygiene adherence (23% from baseline) resulted in control of multidrug-resistant organisms.[31] In a study by Eckmanns et al,[32] rates of nosocomial infection did not correlate with an increase in the rate of hand rub consumption, even though their increase in hand hygiene compliance was considered low. Because of the diversity in the results and methods of most relevant studies, the CDC's multidrug-resistant organism (MDRO) guidelines supports the use of combinations of various control interventions to reduce the burden of MDROs.[13] However, only the recommendations to monitor trends of MDROs or implement contact precautions and hand hygiene practices are supported by well-designed experimental, clinical, or epidemiologic studies. Crivaro et al[33] demonstrated that active surveillance and strict adherence to hand disinfection effectively stopped the spread of *P. aeruginosa* infections in a neonatal intensive care unit in Italy.

We have shown herein a significant 4-fold increase in the use of alcohol-based hand gel from period 1 to period 3. This was the only factor associated with a reduction in the rate of infection by carbapenem-resistant *P. aeruginosa* (fig. 2). Reduction in the use of other carbapenems during the period of ertapenem use (fig. 1) was modest, and this could have contributed to the nonsignificant association between ertapenem and resistance by *P. aeruginosa*.

The guidelines to control MDROs recommend bundles to overcome resistance. Isolation precautions, hand hygiene, and use of gowns, gloves, and masks are the measures that are most often recommended.[13,34] Which part of this bundle is the most important is yet to be determined. One limitation of our study is that we did not evaluate adherence to isolation precaution measures. As well, direct observation is the gold standard for monitoring hand washing. However, we used consumption of alcohol-based hand gel as a surrogate marker of hand hygiene, as it would be impractical to observe the hand-washing behavior of the entire hospital continuously for 65 months.

Our results emphasize the recommendations of the CDC in the MDRO guidelines. The simple introduction of a new drug or any isolated intervention may be insufficient to prevent bacterial resistance. Antimicrobial stewardship programs are essential but are not enough for resistance control, and hand-washing protocols must be extensively sought after in order to achieve results in the reduction of rates of drug resistance. As Pagani stated, in reference to antimicrobial stewardship programs, "there is no such thing as too much."[8] We would like to add, to control resistance, too much is not enough, and efforts must go beyond the use of antimicrobial stewardship programs.

Address correspondence to Rodrigo Pires dos Santos, MD, PhD, Rua Ramiro Barcelos 2350, CEP: 90035-903, Porto Alegre, RS, Brazil (rpsantos@hcpa.ufrgs.br).

REFERENCES

1. Kollef MH. Broad-spectrum antimicrobials and the treatment

of serious bacterial infections: getting it right up front. *Clin Infect Dis* 2008;47(suppl 1):S3–S13.

2. Dellit TH, Owens RC, McGowan JE Jr, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin Infect Dis* 2007;44:159–177.

3. Livermore DM, Mushtaq S, Warner M. Selectivity of ertapenem for *Pseudomonas aeruginosa* mutants cross-resistant to other carbapenems. *J Antimicrob Chemother* 2005;55:306–311.

4. Goff DA, Mangino JE. Ertapenem: no effect on aerobic gram-negative susceptibilities to imipenem. *J Infect* 2008;57:123–127.

5. Lima ALL, Olivera PR, Paula AP, Dal-Paz K, Rossi F, Zumiotti AV. The impact of ertapenem use on the susceptibility of *Pseudomonas aeruginosa* to imipenem: a hospital case study. *Infect Control Hosp Epidemiol* 2009;30:487–490.

6. Goldstein EJ, Citron DM, Peraino V, Elgourt T, Meibohm AR, Lu S. Introduction of ertapenem into a hospital formulary: effect on antimicrobial usage and improved in vitro susceptibility of *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother* 2009;53:5122–5126.

7. Eagye KJ, Nicolau DP. Absence of association between use of ertapenem and change in antipseudomonal carbapenem susceptibility rates in 25 hospitals. *Infect Control Hosp Epidemiol* 2010;31:485–490.

8. Pagani L. Antimicrobial stewardship: there's no such thing as too much. *Am J Respir Crit Care Med* 2010;181:94.

9. Natsch S, Hekster YA, de Jong R, Heerdink ER, Herings RM, van der Meer JW. Application of the ATC/DDD methodology to monitor antibiotic drug use. *Eur J Clin Microbiol Infect Dis* 1998;17:20–24.

10. Edwards JR, Peterson KD, Andrus ML, et al. National Healthcare Safety Network (NHSN) report, data summary for 2006. *Am J Infect Control* 2007;35:290–301.

11. Hindler JF, Stelling J. Analysis and presentation of cumulative antibiograms: a new consensus guideline from the Clinical and Laboratory Standards Institute. *Clin Infect Dis* 2007;44:867–873.

12. Clinical Laboratory Standards Institute. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. Approved standard M7-A7. 7th ed. Wayne, PA: CLSI; 2006.

13. Siegel JD, Rhinehart E, Jackson M, Chiarello L. Healthcare infection control management of multidrug-resistant organisms in health care settings, 2006. *Am J Infect Control* 2007;35(suppl 2):S165–S193.

14. Shardell M, Harris AD, El-Kamary SS, Furuno JP, Miller RR, Perencevich EN. Statistical analysis and application of quasi experiments to antimicrobial resistance intervention studies. *Clin Infect Dis* 2007;45:901–907.

15. Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. *J Clin Pharm Ther* 2002;27:299–309.

16. Zhang F, Wagner AK, Soumerai SB, Ross-Degnan D. Methods for estimating confidence intervals in interrupted time series analyses of health interventions. *J Clin Epidemiol* 2009;62:143–148.

17. Falagas ME, Kopterides P. Risk factors for the isolation of multidrug-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa*: a systematic review of the literature. *J Hosp Infect* 2006;64:7–15.

18. Tacconelli E, De Angelis G, Cataldo MA, et al. Antibiotic usage and risk of colonization and infection with antibiotic-resistant bacteria: a hospital population-based study. *Antimicrob Agents Chemother* 2009;53:4264–4269.

19. Lodise TP, Miller CD, Graves J, et al. Clinical prediction tool to identify patients with *Pseudomonas aeruginosa* respiratory tract infections at greatest risk for multidrug resistance. *Antimicrob Agents Chemother* 2007;51:417–422.

20. Lautenbach E, Weiner MG, Nachamkin I, Bilker WB, Sheridan A, Fishman NO. Imipenem resistance among *Pseudomonas aeruginosa* isolates: risk factors for infection and impact of resistance on clinical and economic outcomes. *Infect Control Hosp Epidemiol* 2006;27:893–900.

21. Fortaleza CM, Freire MP, Filho DC, de Carvalho Ramos M. Risk factors for recovery of imipenem- or ceftazidime-resistant *Pseudomonas aeruginosa* among patients admitted to a teaching hospital in Brazil. *Infect Control Hosp Epidemiol* 2006;27:901–906.

22. Lodise TP Jr, Miller C, Patel N, Graves J, McNutt LA. Identification of patients with *Pseudomonas aeruginosa* respiratory tract infections at greatest risk of infection with carbapenem-resistant isolates. *Infect Control Hosp Epidemiol* 2007;28:959–965.

23. Eagye KJ, Kuti JL, Nicolau DP. Risk factors and outcomes associated with isolation of meropenem high-level-resistant *Pseudomonas aeruginosa*. *Infect Control Hosp Epidemiol* 2009;30:746–752.

24. Carling P, Fung T, Killion A, Terrin N, Barza M. Favorable impact of a multidisciplinary antibiotic management program conducted during 7 years. *Infect Control Hosp Epidemiol* 2003;24:699–706.

25. Liebowitz LD, Blunt MC. Modification in prescribing practices for third-generation cephalosporins and ciprofloxacin is associated with a reduction in methicillin-resistant *Staphylococcus aureus* bacteraemia rate. *J Hosp Infect* 2008;69:328–336.

26. Pakyz AL, Oinonen M, Polk RE. Relationship of carbapenem restriction in 22 university teaching hospitals to carbapenem use and carbapenem-resistant *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother* 2009;53:1983–1986.

27. Fukushima Y, Fukushima F, Kamiya K, et al. Relation between the antimicrobial susceptibility of clinical isolates of *Pseudomonas aeruginosa* from respiratory specimens and antimicrobial use density (AUD) from 2005 through 2008. *Intern Med* 2010;49:1333–1340.

28. Pires Dos Santos R, Konkewicz LR, Nagel F, et al. The 2009 H1N1 influenza A pandemic and hand hygiene practices in a hospital in the south of Brazil. *Infect Control Hosp Epidemiol* 2010;31:1313–1315.

29. Boyce JM, Pittet D. Healthcare Infection Control Practices Advisory Committee. Guideline for hand hygiene in health-care settings: recommendations of the Healthcare Infection Control Practices Advisory Committee and the HICPAC/SHEA/APIC/IDSA Hand Hygiene Task Force. Society for Healthcare Epidemiology of America/Association for Professionals in Infection Control/Infectious Diseases Society of America. *MMWR Recomm Rep* 2002;51:1–45.

30. Pittet D, Hugonnet S, Harbarth S, et al. Effectiveness of a hospital-wide programme to improve compliance with hand hygiene. Infection control programme. *Lancet* 2000;356:1307–1312.

31. Apisarnthanarak A, Pinitchai U, Thongphubeth K, Yuekyen C, Warren DK, Fraser VJ. A multifaceted intervention to reduce pandrug-resistant *Acinetobacter baumannii* colonization and in-

fection in 3 intensive care units in a Thai tertiary care center: a 3-year study. *Clin Infect Dis* 2008;47:760–767.

32. Eckmanns T, Schwab F, Bessert J, et al. Hand rub consumption and hand hygiene compliance are not indicators of pathogen transmission in intensive care units. *J Hosp Infect* 2006;63:406–411.

33. Crivaro V, Di Popolo A, Caprio A, et al. *Pseudomonas aeruginosa* in a neonatal intensive care unit: molecular epidemiology and infection control measures. *BMC Infect Dis* 2009;9:70.

34. Pitten FA, Panzig B, Schröder G, Tietze K, Kramer A. Transmission of a multiresistant *Pseudomonas aeruginosa* strain at a German university hospital. *J Hosp Infect* 2001;47:125–130.