ORIGINAL ARTICLE

Decreased Resistance of *Pseudomonas aeruginosa* with Restriction of Ciprofloxacin in a Large Teaching Hospital's Intensive Care and Intermediate Care Units

G. Jonathan Lewis, DO;[1] Xiangming Fang, PhD;[2] Michael Gooch, RPh;[2] Paul P. Cook, MD[1]

OBJECTIVE. To examine the effect of restricting ciprofloxacin on the resistance of nosocomial gram-negative bacilli, including *Pseudomonas aeruginosa*, to antipseudomonal carbapenems.

DESIGN. Interrupted time-series analysis.

SETTING. Tertiary care teaching hospital with 11 intensive care and intermediate care units with a total of 295 beds.

PATIENTS. All nosocomial isolates of *P. aeruginosa*.

INTERVENTION. Restriction of ciprofloxacin.

RESULTS. There was a significant decreasing trend observed in the percentage ($P = .0351$) and the rate ($P = .0006$) of isolates of *P. aeruginosa* that were resistant to antipseudomonal carbapenems following the restriction of ciprofloxacin. There was also a significant decreasing trend observed in the percentage ($P = .0017$) and the rate ($P = .0001$) of isolates of ciprofloxacin-resistant *P. aeruginosa*. The rate of cefepime-resistant *P. aeruginosa* isolates declined ($P = .004$) but the percentage of cefepime-resistant *P. aeruginosa* isolates did not change. There were no significant changes observed in the rate or the percentage of piperacillin-tazobactam-resistant *P. aeruginosa* isolates. There were no significant changes observed in the susceptibilities of nosocomial Enterobacteriaciae or *Acinetobacter baumannii* isolates that were resistant to carbapenems. Over the study period there was a significant increase in the use of carbapenems ($P = .0134$); the use of ciprofloxacin decreased significantly ($P = .0027$). There were no significant changes in the use of piperacillin-tazobactam or cefepime.

CONCLUSION. Restriction of ciprofloxacin was associated with a decreased resistance of *P. aeruginosa* isolates to antipseudomonal carbapenems and ciprofloxacin in our hospital's intermediate care and intensive care units. There were no changes observed in the susceptibilities of nosocomial Enterobacteriaciae or *A. baumannii* to carbapenems, despite increased carbapenem use. Reducing ciprofloxacin use may be a means of controlling multidrug-resistant *P. aeruginosa*.

Infect Control Hosp Epidemiol 2012;33(4):368-373

Excessive use of broad-spectrum antimicrobials in intensive care units (ICUs) has been directly correlated with the emergence of antimicrobial-resistant gram-negative bacteria.[1] Infections with antimicrobial-resistant organisms have consistently been associated with increased attributable lengths of stay, mortality, and costs.[2] As much as 30%–50% of antibiotic use in hospitals is unnecessary or inappropriate.[3,4] Over 50% of patients in the ICU receive antimicrobials; not surprisingly, this is the area of greatest antimicrobial use[5,6] and the core of antimicrobial resistance in most hospitals.[7]

Nosocomial infections affect up to 33% of patients in the ICU, with a 5–10-times greater risk among ICU patients compared with non-ICU patients.[8,9] Up to 60% of nosocomial gram-negative infections are caused by organisms that are resistant to 3 drug classes.[10] Annual costs due to ICU infections are approximated at $4.5–$5.7 billion.[11] Increased antimicrobial use leads to selective pressure on normal flora, resulting in the emergence of resistant pathogens. Withdrawal of this pressure through strategies to restrict antimicrobial use has been studied as a method to combat emerging resistance.[12]

Pseudomonas aeruginosa is one of the most common nosocomial gram-negative pathogens.[13,14] Although antipseudomonal carbapenems (also called the group-2 carbapenems) remain among the most reliable agents for treating *P. aeruginosa* infections, isolations of carbapenem-resistant *P. aeruginosa* have been steadily increasing.[15-17] A delay in appropriate antimicrobial therapy has been shown to be associated with *P. aeruginosa* infection–related mortality. However, selection of appropriate therapy has become increasingly dif-

Affiliations: 1. Vidant Medical Center (formerly Pitt County Memorial Hospital), Greenville, North Carolina; 2. East Carolina University, Greenville, North Carolina.

Received September 30, 2011; accepted December 17, 2011; electronically published March 15, 2012.

 0899-823X/2012/3304-0009$15.00. DOI: 10.1086/664763

ficult because of increasing rates of resistance.[18,19] This resistance is also associated with higher hospital costs.[15,17]

The use of fluoroquinolones[15,17,20-22] and group-2 carbapenems[17,20,23-25] is a known risk factor for infections with carbapenem-resistant *P. aeruginosa*. We examined the effect of restricting ciprofloxacin use on the resistance of nosocomial gram-negative bacilli, including *P. aeruginosa*, to group-2 carbapenems in our hospital's intensive care and intermediate care units.

METHODS

Pitt County Memorial Hospital is an 861-bed tertiary care teaching hospital affiliated with the Brody School of Medicine at East Carolina University. This study encompassed 11 intensive care and intermediate care units (cardiac intensive care and intermediate care, cardiovascular intensive care and intermediate care, medical intensive care and intermediate care, respiratory intermediate care, surgical intensive care and intermediate care, and neurosurgical intensive care and intermediate care units) with a total of 295 beds. Renal transplantations but no bone marrow transplantations are performed at the hospital, and there are no burn units. This was an observational study using aggregate data from January 1, 2004, until December 31, 2010. Our antibiotic stewardship program was established in 2001 and has been described elsewhere.[26] Ciprofloxacin use was restricted hospital wide in July 2007; after this restriction, preapproval by the on-call infectious diseases fellow was required for its use.

In vitro bacterial susceptibilities to group-2 carbapenems, ciprofloxacin, piperacillin-tazobactam, and cefepime were determined using the MicroScan system (Dade Behring). Gram-negative bacilli were tested for susceptibility to imipenem between 2004 and 2006; because of a change in the hospital's formulary, they were tested for susceptibility to meropenem between 2006 and 2010. Beginning in 2008, meropenem-resistant isolates were tested for susceptibility to doripenem by the E-test method (bioMérieux). Nosocomial gram-negative data sets were created by querying Carefusion (Medmined). All clinical intensive care and intermediate care unit specimens (blood, sterile fluid, sputum, urine, wounds, and anaerobic specimens) with test results that were positive for *Pseudomonas aeruginosa, Enterobacter aerogenes, Enterobacter cloacae, Acinetobacter baumannii,* and *Stenotrophomonas maltophilia* between January 1, 2004, and December 31, 2010, that had been collected at Pitt County Memorial Hospital were included in the database. Results of surveillance and environmental sample cultures were excluded. Only nosocomial cases, defined as involving patients who had a hospital length of stay that was greater than 2 days, were included in this study. Duplicate isolates collected from the same patient within the same hospital stay were counted only once. Percent resistance was defined as the percentage of total isolates that were resistant to the selected antimicrobial. Intermediately susceptible isolates were classified as resistant. Rates of nosocomial carbapenem-resistant gram-negative cases were expressed as the number of bacterial isolates per 10,000 patient hospital-days. Before July 2007, the data source for antimicrobial usage was obtained from the pharmacy database, and this rate was determined as doses sent minus doses returned. After July 2007, the data source for antimicrobial usage was the patients' electronic medication administration records. Antimicrobial drug use was measured in defined daily doses per 1,000 patient-days (DDD/1,000PD), using the standards of the World Health Organization (http://www.whocc.no/atcddd/).

The first time period included the 42 months prior to the restriction of ciprofloxacin; the second time period was the 42 months following the restriction of ciprofloxacin. Statistical analysis was performed using SAS (ver. 9.2; SAS Institute). Simple linear regression models were used to investigate the trend of antimicrobial drug use in time. To control for the serial correlation among the data, interrupted time-series models were adopted to compare the percentages and rates per 10,000 patient-days of *P. aeruginosa* isolates that were resistant to antipseudomonal drugs before and after the restriction of ciprofloxacin. Results indicated that a first-order autoregressive (AR[1]) model or a first-order autoregressive moving average (ARMA[1,1]) model could sufficiently account for the autocorrelation among the data. The model can be formulated as follows:

$$Y_t = \beta_0 + \beta_1 \times \text{time}_t + \beta_2 \times \text{intervention}_t + \beta_3 \times \text{time after intervention}_t + e_t,$$

where Y_t is the percentage or rate per 10,000 patient-days of *P. aeruginosa* resistance at time t, e_t is random error with the AR(1) or ARMA(1,1) autocorrelation structure, and "intervention" is an indicator variable whose value is 0 for time points before the restriction of ciprofloxacin and 1 for time points after the restriction of ciprofloxacin. In this model, β_0 estimates the baseline level (intercept) of the outcome at the beginning of the time series, β_1 estimates the preintervention trend (slope), β_2 estimates the change in level (intercept) after the intervention, and β_3 estimates the change in postintervention trend (slope). Thus, testing the effect of the restriction of ciprofloxacin is equivalent to testing the significance of β_2 and β_3.

RESULTS

Antimicrobial Drug Use

Following the restriction of ciprofloxacin there was a significant decreasing trend ($P = .0027$) in its use, from 87.09 DDD/1,000PD in 2004 to 8.04 DDD/1,000PD in 2010. Use of the group-2 carbapenems significantly increased ($P = .0134$), from 11.96 DDD/1,000PD in 2004 to 28.19 DDD/1,000PD in 2010. The use of other antipseudomonal drugs was variable following the restriction of ciprofloxacin. There was an insignificant increasing trend in cefepime usage

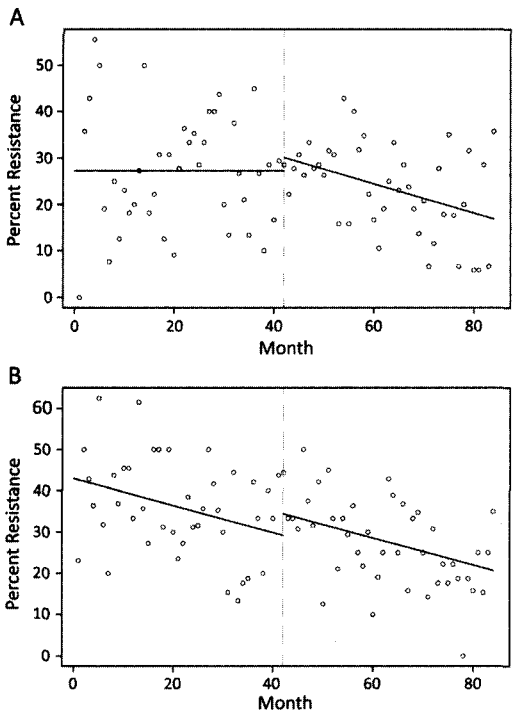

FIGURE 1. Percentage of carbapenem-resistant *Pseudomonas aeruginosa* (*A*) and ciprofloxacin-resistant *P. aeruginosa* (*B*) infections by month, with the restriction of ciprofloxacin starting at month 42. We observed a significant decreasing trend in the percentage of carbapenem-resistant *P. aeruginosa* infections that occurred after the restriction of ciprofloxacin ($P = .0351$) and a significant decreasing trend in the percentage of ciprofloxacin-resistant *P. aeruginosa* infections that occurred over the entire study period ($P = .0017$).

($P = .0756$) and an insignificant decreasing trend in piperacillin-tazobactam usage ($P = .4194$). Overall, there was a hospital-wide decrease of 18.4% ($P < .0001$) in the use of antibacterials during the study time (data not shown).

Susceptibility of *Pseudomonas aeruginosa* to Antipseudomonal Drugs

A total of 1,664 nonduplicate clinical nosocomial isolates of *P. aeruginosa* were collected from our hospital's intermediate care and intensive care units over the 7-year period. Prior to the restriction of ciprofloxacin, an average of 18 ± 5 *P. aeruginosa* isolates were collected per month; following the restriction of ciprofloxacin, an average of 22 ± 6 *P. aeruginosa* isolates were collected per month. Prior to the restriction of ciprofloxacin, the percentage of carbapenem-resistant *P. aeruginosa* isolates collected was stable; after the restriction of ciprofloxacin, there was a decrease of 13.2% in the percentage of carbapenem-resistant *P. aeruginosa* isolates that were collected (Figure 1*A*), which equates to a decrease of 3.8% per year ($P = .0351$). Prior to the restriction of ciprofloxacin, the rate of carbapenem-resistant *P. aeruginosa* isolates that were collected increased by 0.54 per year; after the restriction, the rate decreased by 7.1 cases per 10,000 patient-days, equating to a decrease of 2 cases per 10,000 patient-days per year ($P = .0006$; Figure 2*A*). Over the entire study period there was a decrease of 13.7% in the percentage of ciprofloxacin-resistant *P. aeruginosa* isolates that were collected (Figure 1*B*), which equates to a decrease of 3.9% per year ($P = .0017$). The decreasing slope of the percentage of ciprofloxacin-resistant *P. aeruginosa* did not change before or after the restriction of ciprofloxacin. Prior to the restriction of ciprofloxacin, the rate of ciprofloxacin-resistant *P. aeruginosa* isolates remained constant; after the restriction, the rate de-

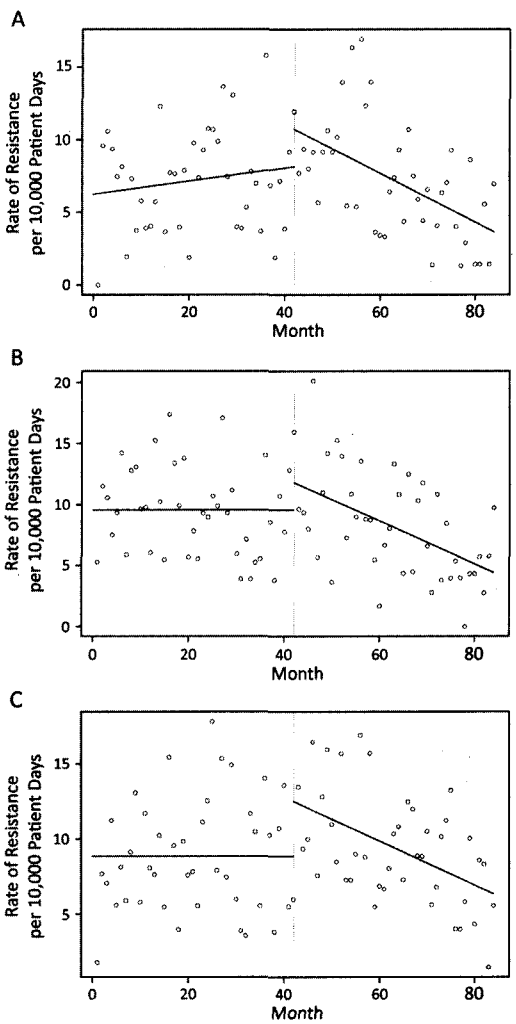

FIGURE 2. Rate of carbapenem-resistant *Pseudomonas aeruginosa* (*A*), ciprofloxacin-resistant *P. aeruginosa* (*B*), and cefepime-resistant *P. aeruginosa* (*C*) infections per 10,000 patient-days by month, with the restriction of ciprofloxacin starting at month 42. We observed a significant decreasing trend in the rate of carbapenem-resistant *P. aeruginosa* infections ($P = .0006$), a significant decreasing trend in the rate of ciprofloxacin-resistant *P. aeruginosa* infections ($P = .0001$), and a significant decreasing trend in the rate of cefepime-resistant *P. aeruginosa* infections ($P = .0004$) that occurred after the restriction of ciprofloxacin.

https://doi.org/10.1086/664763 Published online by Cambridge University Press

creased by 7.4 cases per 10,000 patient-days, which equates to a decrease of 2.1 cases per 10,000 patient-days per year ($P = .0001$; Figure 2*B*). The rates of resistance to other antipseudomonal drugs following the restriction of ciprofloxacin were variable. Prior to the restriction of ciprofloxacin, the rate of cefepime-resistant *P. aeruginosa* isolates remained constant; after the restriction, this rate decreased by 6.2 cases per 10,000 patient-days over the study period, which equates to a decrease of 1.8 cases per 10,000 patient-days per year ($P = .0004$; Figure 2*C*). There was a nonsignificant downward trend observed in the percentage of *P. aeruginosa* isolates that were resistant to cefepime ($P = .5744$) following the restriction of ciprofloxacin (data not shown); there was a nonsignificant increased trend observed in the percentage and rate per 10,000 patient-days of *P. aeruginosa* isolates resistant to piperacillin-tazobactam ($P = .4783$ and $P = .1143$, respectively) following the restriction of ciprofloxacin (data not shown).

Susceptibility of Enterobacteriaceae and *Acinetobacter baumannii* to Group-2 Carbapenems

The effect on other gram-negative bacilli of increasing carbapenem use was examined. Over the 7-year time period, there were no significant changes observed in the susceptibilities of nosocomial Enterobacteriaceae or *A. baumannii* isolates to the group-2 carbapenems (data not shown).

Number of Isolates of *Stenotrophomonas maltophilia*

There were no changes observed in the number of nosocomial *S. maltophilia* isolates per 10,000 patient-days following the restriction of ciprofloxacin (data not shown).

DISCUSSION

We have described decreased resistance of *Pseudomonas aeruginosa* to group-2 carbapenems and ciprofloxacin in our hospital's intermediate care and intensive care units after the restriction of ciprofloxacin. Aubert et al[27] did not show a change in carbapenem sensitivity after restricting fluoroquinolone use in their ICU. However, that study was limited to a 15-bed ICU over 2.5 years, with a total of only 150 patients who were colonized or infected with *P. aeruginosa.* Our study encompassed 295 beds in intermediate care and intensive care units and 7 years of data including over 1,600 nonduplicate nosocomial *P. aeruginosa* isolates. Pakyz et al[28] reported a decreased resistance of *P. aeruginosa* to group-2 carbapenems following restriction of the use of group-2 carbapenems; however, ciprofloxacin use was noted to be a potential confounder in that study.

Previous studies have described ciprofloxacin use as a risk factor for the development of carbapenem-resistant *P. aeruginosa.*[15,17,20-22] Lautenbach et al found fluoroquinolone use to be the only independent risk factor for infections with imipenem-resistant *P. aeruginosa.* Patients infected with these organisms experienced longer lengths of stay, higher costs, and higher mortality rates.[15] Our results are similar to those of Meddadi et al, whose study was performed in a single intensive care burn unit.[22] In that study, restriction of ciprofloxacin was followed by a decreasing resistance of *P. aeruginosa* to both ciprofloxacin and group-2 carbapenems in spite of an increasing use of group-2 carbapenems. The duration of that study was only about 5 years, they collected just over 200 isolates, and their analysis was performed using Spearman rank correlation. Our results further support their conclusions, that the pressure of selection of group-2 carbapenem resistance was made more significant by the use of ciprofloxacin than by the use of group-2 carbapenems themselves.

Although the primary mechanisms of fluoroquinolone resistance are mutations in DNA gyrase and topoisomerase IV, fluoroquinolone resistance may also occur through alterations or reductions in outer-membrane proteins or through the overexpression of efflux pumps. Most clinical carbapenem resistance of *P. aeruginosa* occurs because of either the loss or decrease in levels of the outer membrane porin protein OprD or the overexpression of the MexAB-OprM efflux system.[29,30] Interestingly, meropenem is a substrate of the MexAB-OprM efflux system, whereas imipenem is not. Loss of OprD is associated with resistance to imipenem and reduced susceptibility to meropenem. Furthermore, OprD is coregulated with another efflux system, MexEF-OprN.[31] It is thought that exposure to fluoroquinolones may select for mutations that demonstrate upregulation of MexEF-OprN and reduced levels of OprD, with consequent resistance to both fluoroquinolones and the group-2 carbapenems.[31,32] Our results may support these conclusions; however, we did not perform the genetic testing that is required to confirm this mechanism in our isolates.

We have demonstrated a decrease in both the percentage (Figure 1) and the rate (Figure 2) of *P. aeruginosa* resistant to both carbapenems and ciprofloxacin as well as a decrease in the rate (Figure 2) of cefepime-resistant *P. aeruginosa* following the restriction of ciprofloxacin in our hospital's intensive care and intermediate care units. Our results that indicate a decrease in the percentage of *P. aeruginosa* isolates that are ciprofloxacin resistant are in opposition to those of the United States MYSTIC Program,[33] which showed an overall increase in the percentage of resistant from 1999 to 2008. That study showed a decreasing percentage of ciprofloxacin-resistant *P. aeruginosa* isolates from 2003 to 2008, but the authors did not comment on antibiotic usage. In our study, the restriction of ciprofloxacin was not limited to our intensive care and intermediate care units; similar results were found hospital wide.[34]

This study has several limitations. Because we were looking at aggregate data, we cannot ascribe a causal relationship between antibiotic exposure and antibiotic resistance. As this study did not involve reviews of the medical records of individual patients, we cannot account for previous antimicrobial use in the community and in hospitals from which pa-

tients may have been transferred. It is clear that antibiotic-resistant microorganisms can spread from patient to patient via hospital personnel. Nevertheless, we did not experience any outbreaks of *P. aeruginosa* infection. Our hospital instituted a policy in February 2007 of screening all incoming patients for nasal colonization with methicillin-resistant *Staphylococcus aureus*. All patients who had positive test results were placed in strict contact isolation according to infection control measures. It is possible that by placing more high-risk patients under contact precautions, a decrease occurred in the spread of several multidrug-resistant organisms including *P. aeruginosa*, *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia*. We analyzed our data accounting for this intervention at the time of the start of our universal MRSA screening program, and the results were unchanged (data not shown). Other infection control policies were implemented during the study period. These include ventilator-associated pneumonia and central line–associated blood stream infection bundles in 2005 and hand-hygiene campaigns in 2006 and 2009. There was an outbreak of *Acinetobacter* infection during the last year of the study. The data were analyzed with and without the outbreak data, and the results were unchanged by the outbreak (data not shown).

In conclusion, decreased ciprofloxacin usage was associated with a decrease in the resistance of *P. aeruginosa* to group-2 carbapenems and ciprofloxacin in our hospital's intermediate care and intensive care units. There were no changes observed in the susceptibilities of nosocomial Enterobacteriaciae or *A. baumannii* to carbapenems despite an increase in carbapenem use. We suspect that the reduction in ciprofloxacin use resulted in a decreased activity of MexEF-OprN. Since stimulation of MexEF-OprN is associated with a decrease in the number of OprD porin channels, restriction in the use of ciprofloxacin should result in an improved susceptibility of *P. aeruginosa* to group-2 carbapenems.

ACKNOWLEDGMENTS

We would like to thank Dr. Keith Ramsey for his help with obtaining the infection control initiatives performed during the study time.

Potential conflicts of interest. P.P.C. is on the speakers' bureaus of Merck and Astellas and has research support from Merck, Pfizer, and Gilead. All other authors report no conflicts of interest relevant to this article. All authors submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest, and the conflicts that the editors consider relevant to this article are disclosed here.

Address correspondence to G. Jonathan Lewis, DO, Doctors Park 6A, Greenville, NC 27834 (lewisjon@ecu.edu).

REFERENCES

1. Neuhauser MM, Weinstein RA, Rydman R, Danziger LH, Karam G, Quinn JP. Antibiotic resistance among gram-negative bacilli in US intensive care units: implications for fluoroquinolone use. *JAMA* 2003;289:885–888.
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. Hecker MT, Aron DC, Patel NP, Lehmann MK, Donskey CJ. Unnecessary use of antimicrobials in hospitalized patients: current patterns of misuse with an emphasis on the antianaerobic spectrum of activity. *Arch Intern Med* 2003;163:972–978.
4. John JF Jr, Fishman NO. Programmatic role of the infectious diseases physician in controlling antimicrobial costs in the hospital. *Clin Infect Dis* 1997;24:471–485.
5. Erlandsson M, Burman LG, Cars O, et al. Prescription of antibiotic agents in Swedish intensive care units is empiric and precise. *Scand J Infect Dis* 2007;39:63–69.
6. Warren MM, Gibb AP, Walsh TS. Antibiotic prescription practice in an intensive care unit using twice-weekly collection of screening specimens: a prospective audit in a large UK teaching hospital. *J Hosp Infect* 2005;59:90–95.
7. Kaki R, Elligsen M, Walker S, Simor A, Palmay L, Daneman N. Impact of antimicrobial stewardship in critical care: a systematic review. *J Antimicrob Chemother* 2011;66:1223–1230.
8. Weber DJ, Raasch R, Rutala WA. Nosocomial infections in the ICU: the growing importance of antibiotic-resistant pathogens. *Chest* 1999;115(Suppl 3):S34–S41.
9. Eggimann P, Pittet D. Infection control in the ICU. *Chest* 2001;120:2059–2093.
10. Kallen AJ, Hidron AI, Patel J, Srinivasan A. Multidrug resistance among gram-negative pathogens that caused healthcare-associated infections reported to the National Healthcare Safety Network, 2006–2008. *Infect Control Hosp Epidemiol* 2010;31:528–531.
11. Njoku JC, Hermsen ED. Antimicrobial stewardship in the intensive care unit: a focus on potential pitfalls. *J Pharm Pract* 2010;23:50–60.
12. Cook PP, Das TD, Gooch M, Catrou PG. Effect of a program to reduce hospital ciprofloxacin use on nosocomial *Pseudomonas aeruginosa* susceptibility to quinolones and other antimicrobial agents. *Infect Control Hosp Epidemiol* 2008;29:716–722.
13. Pfaller MA, Jones RN, Doern GV, Kugler K. Bacterial pathogens isolated from patients with bloodstream infection: frequencies of occurrence and antimicrobial susceptibility patterns from the SENTRY antimicrobial surveillance program (United States and Canada, 1997). *Antimicrob Agents Chemother* 1998;42:1762–1770.
14. Jones RN. Microbial etiologies of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia. *Clin Infect Dis* 2010;51(Suppl 1):S81–S87.
15. 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.
16. King A, Shannon K, Phillips I. Resistance to imipenem in *Pseudomonas aeruginosa*. *J Antimicrob Chemother* 1995;36:1037–1041.
17. Lautenbach E, Synnestvedt M, Weiner MG, et al. Imipenem resistance in *Pseudomonas aeruginosa*: emergence, epidemiology, and impact on clinical and economic outcomes. *Infect Control Hosp Epidemiol* 2010;31:47–53.
18. Kang CI, Kim SH, Kim HB, et al. *Pseudomonas aeruginosa* bac-

teremia: risk factors for mortality and influence of delayed receipt of effective antimicrobial therapy on clinical outcome. *Clin Infect Dis* 2003;37:745–751.
19. Obritsch MD, Fish DN, MacLaren R, Jung R. National surveillance of antimicrobial resistance in *Pseudomonas aeruginosa* isolates obtained from intensive care unit patients from 1993 to 2002. *Antimicrob Agents Chemother* 2004;48:4606–4610.
20. Joo EJ, Kang CI, Ha YE, et al. Risk factors for mortality in patients with *Pseudomonas aeruginosa* bacteremia: clinical impact of antimicrobial resistance on outcome. *Microb Drug Resist* 2011;17:305–312.
21. Mohr JF, Jones A, Ostrosky-Zeichner L, Wanger A, Tillotson G. Associations between antibiotic use and changes in susceptibility patterns of *Pseudomonas aeruginosa* in a private, university-affiliated teaching hospital: an 8-year-experience: 1995–2002. *Int J Antimicrob Agents* 2004;24:346–351.
22. Messadi AA, Lamia T, Kamel B, Salima O, Monia M, Saida BR. Association between antibiotic use and changes in susceptibility patterns of *Pseudomonas aeruginosa* in an intensive care burn unit: a 5-year study, 2000–2004. *Burns* 2008;34:1098–1102.
23. Carmeli Y, Troillet N, Eliopoulos GM, Samore MH. Emergence of antibiotic-resistant *Pseudomonas aeruginosa*: comparison of risks associated with different antipseudomonal agents. *Antimicrob Agents Chemother* 1999;43:1379–1382.
24. Harris AD, Smith D, Johnson JA, Bradham DD, Roghmann MC. Risk factors for imipenem-resistant *Pseudomonas aeruginosa* among hospitalized patients. *Clin Infect Dis* 2002;34:340–345.
25. Lepper PM, Grusa E, Reichl H, Högel J, Trautmann M. Consumption of imipenem correlates with beta-lactam resistance in *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother* 2002;46:2920–2925.
26. Cook PP, Catrou PG, Christie JD, Young PD, Polk RE. Reduction in broad-spectrum antimicrobial use associated with no improvement in hospital antibiogram. *J Antimicrob Chemother* 2004;53:853–859.
27. Aubert G, Carricajo A, Vautrin AC, et al. Impact of restricting fluoroquinolone prescription on bacterial resistance in an intensive care unit. *J Hosp Infect* 2005;59:83–89.
28. 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.
29. Pai H, Kim J, Kim J, Lee JH, Choe KW, Gotoh N. Carbapenem resistance mechanisms in *Pseudomonas aeruginosa* clinical isolates. *Antimicrob Agents Chemother* 2001;45:480–484.
30. Köhler T, Michea-Hamzehpour M, Epp SF, Pechere JC. Carbapenem activities against *Pseudomonas aeruginosa*: respective contributions of OprD and efflux systems. *Antimicrob Agents Chemother* 1999;43:424–427.
31. Livermore DM. Multiple mechanisms of antimicrobial resistance in *Pseudomonas aeruginosa*: our worst nightmare? *Clin Infect Dis* 2002;34:634–640.
32. Ochs MM, McCusker MP, Bains M, Hancock RE. Negative regulation of the *Pseudomonas aeruginosa* outer membrane porin OprD selective for imipenem and basic amino acids. *Antimicrob Agents Chemother* 1999;43:1085–1090.
33. Rhomberg PR, Jones RN. Summary trends for the meropenem yearly susceptibility test information collection program: a 10-year experience in the United States (1999–2008). *Diagn Microbiol Infect Dis* 2009;65:414–426.
34. Cook PP, Gooch M, Rizzo S. Reduction in fluoroquinolone use following introduction of ertapenem into a hospital formulary is associated with improvement in susceptibility of *Pseudomonas aeruginosa* to group 2 carbapenems: a 10-year study. *Antimicrob Agents Chemother* 2011;55:5597–5601.