Analysis of an outbreak of *Clostridium difficile* infection controlled with enhanced infection control measures

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Background: In October 2004, our *Clostridium difficile* infection (CDI) rate increased (relative risk, 3.51; 95% confidence interval: 2.96-4.16) from a baseline rate of 1.35 per 1000 patient-days. We describe the outbreak, the relationship between antibiotic use and CDI, and the effect of enhanced infection control measures (EICM) on CDI.
Methods: Rates were calculated as positive *C difficile* toxin A or B tests among patients with nosocomial diarrhea per 1000 patient-days (duplicates removed). Antibiotic use was calculated as defined daily dose per 1000 patient-days. EICM consisted of (1) placing patients with diarrhea into empiric Contact Precautions, (2) cleaning with a bleach product in areas with CDI patients, and (3) requiring soap and water hand hygiene when caring for CDI patients. CDI rates were analyzed by χ^2 for trend. Time series methodology was used to examine the association between CDI and antibiotic use.
Results: During the outbreak (October 2004-May 2005), we observed 144 excess cases of CDI. The CDI rate decreased after EICM were implemented ($P < .0001$) and has been maintained for 36 months beyond the outbreak. Multivariate analysis revealed positive associations between CDI rates and cefazolin use ($P = .008$) and levofloxacin/gatifloxacin use ($P = .015$).
Conclusion: Despite an association between some antibiotic use and CDI rates, we achieved sustained control of an outbreak using EICM without formulary changes or new antibiotic control policies. This suggests that patient-to-patient spread may be a more important cause of increased CDI rates.
Key Words: *Colostridium difficile*; infection control; antibiotic use.

(Am J Infect Control 2009;37:458-64.)

Historically, an estimated 3 million new cases of *Clostridium difficile* infection (CDI) have been reported to occur annually in US hospitals, and CDI has affected as many as 10% of patients hospitalized for more than 2 days.[1] CDI has also been associated with significant morbidity, increased costs of care, and sometimes mortality.[2-6] For example, in a prospective, case control study, patients who developed CDI during hospitalization stayed an average of 3.6 days longer and had excess hospital costs of $3669 compared with patients who did not develop CDI.[2] More recently, the incidence of CDI has been increasing and a new strain of *C difficile* with increased virulence has caused outbreaks of severe disease in North America.[7-9]

Many risk factors for the development of CDI have been identified such as age greater than 65 years, severe underlying illness, nasogastric intubation, antiulcer medications, and lengthy hospital stay; however, exposure to antibiotics has been considered the preeminent risk factor[10,11] with more than 90% of nosocomial CDI occurring during or shortly after antibiotic therapy.[12,13] In addition to the commonly associated cephalosporins and clindamycin, recent studies have suggested an association between fluoroquinolone use and increased rates of *C difficile*.[7,14-16]

Nosocomial transmission of *C difficile* in hospitals can occur via the contaminated hands, clothing, and equipment of health care providers, and guidance regarding control for CDI in hospitals has been offered.[10,17] In 1995, Gerding et al described 2 distinct approaches when considering control of CDI in a health care facility: (1) efforts directed at interrupting horizontal spread of *C difficile* such as the use of Barrier Precautions and environmental cleaning and (2) efforts to minimize the possibility that organism exposure will result in clinical infection such as antimicrobial use restriction.[10] The authors concluded that the most successful control measure directed at reduction of symptomatic disease was antimicrobial restriction. More

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Conflicts of interest. None to report.

0196-6553/$36.00

doi:10.1016/j.ajic.2008.11.010

recently, Muto et al described control of a CDI outbreak due to the hypervirulent BI strain by use of a comprehensive ''bundle'' approach.[17] This consisted of education, increased and early case finding, expanded infection control measures (environmental cleaning, electronic flags and alerts, hand hygiene with soap and water, prolonged duration of isolation, and infection control audits), development of a *C difficile* management team, and targeted antimicrobial restriction.

In October of 2004, the Department of Infection Prevention and Control at our hospital began receiving inquiries from health care providers regarding a perceived increase in the occurrence of nosocomial diarrhea due to *C difficile* among patients in adult inpatient units. Monthly comparison of nosocomial CDI rates from January 2002 through October 2004 revealed a significant increase from a steady 33-month baseline rate of 1.35 cases per 1000 patient-days to 4.74 cases per 1000 patient-days (relative risk, RR 3.51; 95% confidence interval [CI]: 2.96-4.16; $P < .0001$). This prompted us to investigate the outbreak including the potential association between antimicrobial use patterns and CDI rates. Here, we describe the outbreak, the relationship between antibiotic use and CDI rates, and the effect of enhanced infection control measures (EICM) on the rate of nosocomial CDI in adults in our academic, tertiary care hospital.

METHODS

Study setting and data collection

The Medical University of South Carolina Hospital is a 610-bed, tertiary care, academic institution that cares for patients from South Carolina as well as referral areas from neighboring states. The hospital offers all medical and surgical subspecialty services including solid organ and bone marrow transplantation. The study was approved by the university's Institutional Review Board. For this study, only CDI cases considered to be nosocomial in nature among adults being cared for in our hospital were included. These cases were defined as any patient with a positive *C difficile* toxin A or B test in the setting of diarrhea that developed after 72 hours of admission or was present on admission if the patient had been hospitalized within the previous 30 days. This information was supplied to us by the Department of Infection Prevention and Control and the Department of Clinical Microbiology. Duplicate patient results were removed, and results were entered into an electronic database. Antibiotic usage data for each adult inpatient unit was supplied by the Department of Pharmacy Services. For this analysis, antibiotic usage included that of cefazolin, cefepime, ceftriaxone (as well total cephalosporin use), ciprofloxacin, levofloxacin, gatifloxacin (as well as total fluoroquinolone use), clindamycin, and piperacillin/tazobactam.

Enhanced infection control measures

Historically at our institution, patients with diarrhea were routinely placed into Contact Precautions once they were diagnosed with CDI, and the type of hand hygiene preferred when caring for these patients was not routinely discussed with health care workers. Similarly, the type of disinfectant used for environmental cleaning was not closely monitored. EICM implemented during the outbreak consisted of (1) placing patients with diarrhea into empiric Contact Precautions until CDI was ruled out as the cause of diarrhea, (2) cleaning equipment and the environment with a bleach product in areas occupied by CDI patients, and (3) requiring soap and water for hand hygiene among health care providers when caring for patients with CDI (rather than alcohol hand gel). All elements of the EICM were fully implemented at once. When CDI was diagnosed as the cause of a patient's diarrheal illness, the patient was kept in Contact Precautions for the duration of hospitalization and their status flagged in the electronic medical record to place them into Contact Precautions upon readmission if they were symptomatic. Contact Precautions at our facility include placing the patient into a private room and requiring health care workers to don a gown and pair of gloves prior to entering the room to care for the patient. Memos describing EICM were sent to all patient care areas of the hospital and detailed in-services were conducted in areas with high CDI rates just prior to full implementation.

Data treatment and statistical analysis

Quarterly CDI rates from the first quarter of 2000 through the second quarter of 2005 were calculated for the entire adult hospital as the number of nosocomial CDI cases per 1000 patient-days. Similarly, antibiotic use data for the same time period were converted to defined daily doses (DDD) and normalized by census data (ie, DDD/1000 patient-days). Levofloxacin and gatifloxacin were analyzed as a single variable rather than as individual agents because our antibiotic formulary changed from levofloxacin to gatifloxacin during the period of interest (third quarter of 2001). CDI rates after implementing EICM (December 2004) were analyzed by χ^2 test for trend (EpiInfo 3.4.3, 2007; CDC, Atlanta, GA). A P value $\leq .05$ was considered statistically significant.

Multivariate time series methodology was used to examine the association between CDI rates and antibiotic use within the entire adult hospital.[18] Pearson correlation coefficients (Prob $>$ |r| under H_0: Rho = 0)

were used for univariate analysis and to test for multicollinearity among the independent variables in the multivariate analysis. P values $\leq .05$ were considered significant. For the multivariate time series analysis, proper estimations of standard errors and significance were made through the detection of and correction for autocorrelation. The Durbin-Watson statistic was used to test for autocorrelation in the residuals.[19] If significant autocorrelation was detected, maximum likelihood estimation with first-or second-order differencing was used to correct the problem. A backward selection process was used to determine the final model for multivariate analysis (SAS 9.0; SAS Institute, Inc, Cary, NC). Statistical significance for the multivariate analysis was determined at the .05 level.

RESULTS

Description of the outbreak and effect of enhanced infection control measures

During the outbreak period (October 2004 through May 2005), we observed 307 cases of nosocomial CDI, 144 excess cases above the expected baseline, and 9 deaths (mortality rate of 2.9%) among patients with CDI. The overall mean outbreak CDI rate was 3.90 per 1000 patient-days, and the peak outbreak CDI rate (November 2004) was 5.52 per 1000 patient-days. The highest CDI rates occurred among patients on the hematology/oncology ward (5.94 per 1000 patient-days), the general medicine ward (5.83 per 1000 patient-days), and the gastrointestinal surgery ward (4.04 per 1000 patient-days). Based on estimates from Kyne et al,[2] the excess CDI cases that occurred during the outbreak accounted for 518.4 excess hospital days and $528,336 excess hospital costs.

EICM were implemented during the third week of November 2004. The CDI rate decreased significantly over the subsequent 6 months after EICM were implemented ($P < .0001$). We observed the greatest absolute as well as relative decrease in CDI rates over the first 3 months after implementing EICM (a 2.50 per 1000 patient-days rate decrease and 45.3% decrease, respectively). Our immediate postoutbreak CDI rate was 1.84 per 1000 patient-days, and our mean postoutbreak rate, maintained for 36 months beyond the outbreak, has been 1.24 per 1000 patient-days (Fig 1).

Antibiotic usage data and association with CDI

Over the study period (January 2000 through June 2005), total fluoroquinolone use (quarterly mean 127.8 DDD per 1000 patient-days prior to outbreak vs 159.4 quarterly mean during outbreak), total cephalosporin use (quarterly mean 157.9 DDD per 1000 patient-days prior to outbreak vs 222.4 quarterly mean during outbreak), and piperacillin/tazobactam use (quarterly mean 77.4 DDD per 1000 patient-days prior to outbreak vs 105.9 quarterly mean during outbreak) significantly increased (all P values $< .0001$). Clindamycin use did not change significantly (quarterly mean 30.3 DDD per 1000 patient-days prior to outbreak vs. 34.2 quarterly mean during outbreak). Univariate analysis revealed positive associations between the hospital-wide CDI rate (Table 1) and cefazolin use, as well as with levofloxacin/gatifloxacin use, which was primarily driven by gatifloxacin use over the last 3.5 years of the period of analysis. Ciprofloxacin use was negatively correlated with the CDI rate as was clindamycin use. Cefepime, ceftriaxone, total cephalasporin, and piperacillin/tazobactam did not have significant correlations with the CDI rate. The correlation coefficients revealed a strong positive association between the 2 independent variables cefazolin use and levofloxacin/gatifloxacin use (84%; $P < .0001$), suggesting multicollinearity. Because there is no obvious reason for this high correlation (eg, combination therapy), dropping one of the drugs from the multivariate equation was not justified. Therefore, 2 equations were regressed: the first excluding levofloxacin/gatifloxacin and the second excluding cefazolin. After controlling for each of the variables from the univariate analysis, multivariate analyses (Tables 2 and 3) revealed significant positive associations between hospital-wide CDI rates and cefazolin use (equation 1; $P = .008$) as well as with the use of levofloxacin/gatifloxacin (equation 2; $P = .015$). The multivariate effects from ciprofloxacin use were negative in both equations (equation 1, $P < .0001$; equation 2, $P = .0006$). Interestingly, after controlling for the effect of covariates, the negative association between clindamycin use and the CDI rate became nonsignificant in both equations. Second-order autocorrelation was present and corrected for in the analysis. The R^2 for the multivariate equations were calculated as 0.67 (equation 1) and 0.64 (equation 2).

DISCUSSION

C difficile is shed in feces. Any surface, device, or material that becomes contaminated with feces may serve as a reservoir for the *C difficile* spores. Spores are transferred to patients via the hands of health care personnel who have touched a contaminated surface or item. To control nosocomial CDI, the Centers for Disease Control and Prevention (CDC) recommends judicious use of antibiotics, use of Contact Precautions for patients known or suspected of having CDI, hand hygiene with soap and water when caring for CDI patients, and implementation of an environmental cleaning and disinfection strategy, including use of an

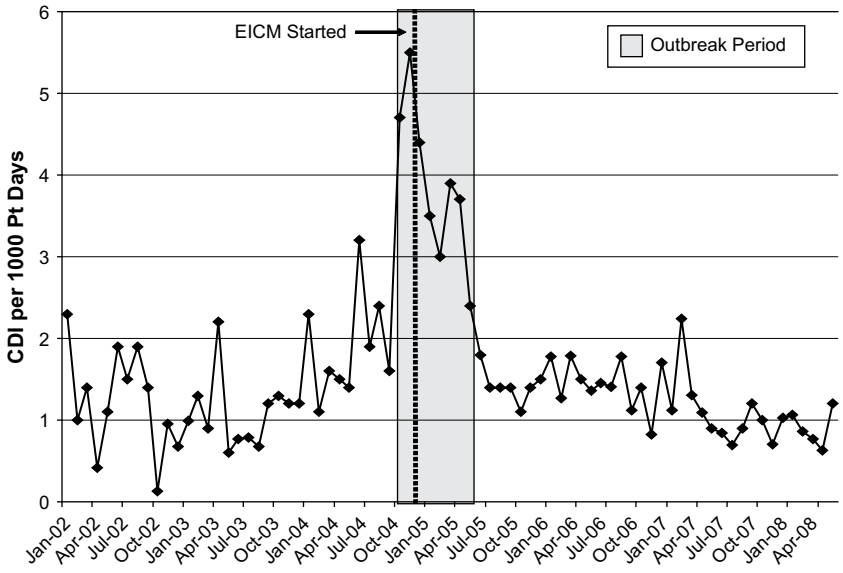

Fig 1. Monthly CDI rates before, during, and after the outbreak period. CDI rates decreased significantly after EICM were implemented, χ^2 for trend $P < .0001$.

Environmental Protection Agency-registered hypochlorite-based disinfectant for environmental surface disinfection after cleaning. Generic sources of hypochlorite (eg, household chlorine bleach) also may be appropriately diluted and used (http://www.cdc.gov/ncidod/dhqp/id_CdifficileFAQ_HCP.html#7).

Without instituting a targeted antibiotic control program or any formulary changes, we were able to achieve sustained control of nosocomial CDI in our hospital with use of EICM as recommended by the CDC. This would suggest that patient-to-patient spread of the organism plays an important role in outbreaks of CDI and that interruption of this spread can be an effective control measure. There has been debate regarding whether or not infection control measures alone are adequate for control of CDI outbreaks and whether antibiotic stewardship is needed. Because multiple antibiotic agents have reportedly increased the risk for CDI, it seems prudent that good antibiotic stewardship in general should help in the control of CDI, and this approach may be more beneficial in a facility in which specific agents are identified as having an association with increased rates of CDI. Two recent studies have used sophisticated statistical analysis to assess the effect of antibiotic stewardship on CDI rates.[20,21] Fowler et al described the effect of a narrow-spectrum antibiotic policy on antibiotic prescription practices and CDI rates in their large United Kingdom teaching hospital caring for elderly individuals.[20] The policy was reinforced by an auditing program of feedback from pharmacists to physicians regarding antibiotic usage and CDI rates. The goal of the program was to reduce the use of broad-spectrum antibiotics (amoxicillin/clavulanate and cephalosporins) and increase the use of narrow-spectrum antibiotics (benzyl penicillin, trimethoprim, and amoxicillin). Over the study period, there were significant reductions in the acute and long-term use of all targeted broad-spectrum antibiotics, and this phenomenon was associated with a significant decrease in CDI rates (incidence rate ratio, 0.35 [95% CI: 0.17-0.73], $P = .009$). Accompanying infection control measures that were implemented included isolating patients with CDI into side rooms where aprons and gloves were worn for contact. These measures notably did not change throughout the study period. A study by Valiquette et al from a Canadian hospital reported similar results.[21] The effects of multiple measures used to control a CDI outbreak because of the hypervirulent strain of *C difficile* were assessed, including development of a nonrestrictive antimicrobial stewardship program. The program consisted of developing guidelines for antimicrobial use aimed to decreased consumption of agents known to be

Table 1. Correlations between antibiotic use and hospital-wide CDI rate

Variables*	Association with CDI	*P* value
Cefazolin	+43%	.043
Gatifloxacin/levofloxacin	+65%	.001
Ciprofloxacin	−62%	.002
Clindamycin	−45%	.037

*Cefepime, Ceftriaxone, total cephalosporins, and piperacillin/tazobactam were all nonsignificant.

Table 2. Significant associations from multivariate analysis comparing hospital-wide CDI rate with antibiotic use—gatifloxacin/levofloxacin excluded from equation

Variable	Association with CDI	*P* value
Intercept	+	.0004
Cefazolin	+	.0084
Ciprofloxacin	−	<.0001

NOTE. R^2 = .67; Akaike Information Criterion (AIC) = 46.76.

associated with CDI at the investigators' institution (second- and third-generation cephalosporins, ciprofloxacin, clindamycin, and macrolides). Recommendations were reinforced by telephone conversations between pharmacists and physicians. Interrupted time series analysis revealed that decreased consumption of targeted antibiotics was associated with a 60% reduction in the incidence of CDI. Interestingly, there was no change in CDI incidence after strengthening infection control measures; however, these infection control measures were implemented well into the outbreak period, after there was heavy environmental contamination, and thus their efficacy may have been affected. The success our interventions demonstrated with the use of EICM may have in part been due to the fact that we instituted these measures relatively early in the outbreak. Taken together, it seems that successful control of a nosocomial CDI outbreak may be institution dependent and may require EICM as well as antibiotic stewardship.

Our study is limited by the fact that we did not do strain typing of the organism responsible for our outbreak; thus, we do not know for certain that the epidemic hypervirulent strain of *C difficile* was a factor. However, clinicians caring for these CDI patients clearly communicated that there was increased morbidity and mortality associated with this outbreak, and, thus, we think that it is a reasonable assumption that this strain contributed. In addition, we did not formally require that compliance with the EICM be monitored. However, environmental services employees use a daily checklist to ensure proper cleaning techniques and use of proper products for patients with epidemiologic important organisms (such as *C difficile*), and this was reviewed in detail with the Department of Infection Prevention and Control. Additionally, the Department of Infection Prevention and Control received daily reports from the Clinical Microbiology Laboratory indicating the patients for which *C difficile* toxin tests were being performed, and this information was used to instruct the individual units regarding who to place into empiric Contact Precautions. Finally, to encourage the use of soap and water, signs were posted over the alcohol gel dispensers in the room of patients on Contact Precautions for *C difficile* stating that soap and water was the preferred method of hand hygiene. Overall hand hygiene compliance over the outbreak period ranged from 62% to 80%.

Our analysis of possible associations of antibiotic use with this outbreak of *C difficile* yielded some intriguing results. It has long been reported that antibiotics are the preeminent risk factor for development of CDI. Furthermore, penicillins, cephalosporins, and clindamycin are frequently listed among those presenting the greatest risk. A metaanalysis by Bignardi reported that essentially all antibiotics can be independent risk factors for CDI, but those that have broad-spectrum coverage and perhaps a greater effect on eliminating normal gut flora may be more likely to have an association with the disease.[12] It is notable, therefore, that we did not detect a relationship between third-generation cephalosporins or clindamycin use and rising CDI rates, as found by others, perhaps because of the time frame of the study but nonetheless suggesting other operative factors or more simply that the level of use of these agents was not changing just prior to or during the outbreak.

The results of this study would suggest a positive association between hospital-wide CDI rates and use of some antibiotics, including fluoroquinolones (specifically, gatifloxacin) and cephalosporins (specifically, cefazolin). Although it is possible that cefazolin could alter the bacterial flora of the gastrointestinal tract and thus predispose to CDI, others have not found this association. We believe the more likely explanation for the association we found between cefazolin use and CDI rates is a mathematical relationship driven by the consistently high use of this antibiotic in our hospital. On a gram/patient-day basis, it is the most frequently used injectable antibiotic at our institution. Other studies have reported increased CDI rates with fluoroquinolone use[7,8,14-16,22,23] and specifically gatifloxacin.[16] It is not clear, based on previously published literature, whether one fluoroquinolone is better or worse than the next in regard to its association with CDI with the exception of ciprofloxacin, which has been negatively associated with the condition. Our findings suggest

Table 3. Significant associations from multivariate analysis comparing hospital-wide CDI rate with antibiotic use—cefazolin excluded from equation

Variable	Association with CDI	*P* value
Intercept	+	.0023
Gatifloxacin/levofloxacin	+	.0150
Ciprofloxacin	−	.0006

NOTE. R^2 = 0.64; Akaike Information Criterion (AIC) = 48.51.

that there may be differences among class members because we often found a positive relationship between gatifloxacin and CDI case rates; however, these relationships were consistently weak, suggesting that other causes or risk factors were apparently operative. This conclusion would also be consistent with other relevant literature.[12] However, it is somewhat uncertain whether fluoroquinolones are now a leading cause of CDI or whether their popularity is simply a parallel but unrelated coincidence to rising CDI rates. One must be cognizant of the possibility of ecologic fallacy in interpreting such findings, although whether this risk applies to this type of analysis is questionable.[24,25] This is because both antibiotic exposure at the patient level and exposure/transmission at the environmental level are operative and important here. From our analysis, it is therefore unlikely that a change in fluoroquinolone or cefazolin use alone would have adequately addressed rising CDI case rates at our hospital, and, indeed, rates fell over the subsequent months in the absence of a formulary change, likely because of increased infection control measures.

The fact that our findings, in regard to associations with antibiotic use, were not entirely consistent with previous literature on this topic also merits discussion. Unlike earlier analyses of the association between antibiotic use and CDI occurrence/rates, multivariate time series methodology was used in the current study to examine the association between CDI rates and antibiotic use from a hospital-wide perspective. It can be argued that this is a more robust method to examine the presence and nature of such relationships. Unlike conventional statistical models that assume that observed data are culminations of independent random effects, time series analysis takes into account the possible relationship existing between consecutive observations. The major advantages of this approach are (1) proper estimation is performed controlling for correlated error terms between time periods and (2) the influence of other antibiotics can be controlled, which has generally not been fully assessed with previous analyses/reports. This is not to say that we have disproved previous findings and conclusions but certainly argues for further study of these relationships. Our findings of negative relationships between CDI and both ciprofloxacin and clindamycin should not be interpreted as indicating that either of these agents is somehow protective against this disorder and neither do our findings constitute an argument against the usual recommendation that antibiotics be discontinued, where possible, in affected patients.

In conclusion, even though there was an association between some antibiotic use and CDI rates in our hospital, we were able to achieve sustained control of a CDI outbreak using EICM without antibiotic control policies. This suggests that patient-to-patient spread may be an important cause of increased CDI rates and that, in some circumstances, an outbreak might be adequately addressed without changes in antibiotic use at the institutional level.

References

1. McFarland LV, Mulligan ME, Kwok RY, Stamm WE. Nosocomial acquisition of *Clostridium difficile* infection. N Eng J Med 1989;320:204.
2. Kyne L, Hamel MB, Polavaram R, Kelly CP. Health care costs and mortality associated with nosocomial diarrhea due to *Clostridium difficile*. Clin Infect Dis 2002;34:346.
3. Miller MA, Hyland M, Ofner-Agostini M, Gourdeau M, Ishak M. Canadian Hospital Epidemiology Committee. Canadian Nosocomial Infection Surveillance Program. Morbidity, mortality, and healthcare burden of nosocomial *Clostridium difficile*-associated diarrhea in Canadian hospitals. Infect Control Hosp Epidemiol 2002;23:137.
4. McFarland LV, Surawicz CM, Rubin M, Fekety R, Elmer GW, Greeberg RN. Recurrent *Clostridium difficile* disease: epidemiology and clinical characteristics. Infect Control Hosp Epidemiol 1999;20:43.
5. Wilcox MH, Cunniffee JG, Trundle C, Redpath C. Financial burden of hospital-acquired *Clostridium difficile* infection. J Hosp Infect 1996;34:23.
6. Olsen MM, Shanholtzer CJ, Lee JT, Gerding DN. Ten years of prospective *Clostridium difficile*-associated disease surveillance and treatment at the Minneapolis VA Medical Center, 1982-1991. Infect Control Hosp Epidemiol 1994;15:371.
7. Muto CA, Pokrywka M, Shutt K, Mendelsohn AB, Nouri K, Posey K, et al. A large outbreak of *Clostridium difficile*-associated disease with an unexpected proportion of deaths and colectomies at a teaching hospital following increased fluoroquinolone use. Infect Control Hosp Epidemiol 2005;26:273.
8. Loo VG, Poirier L, Miller MA, Oughton M, Libman MD, Michaud S, et al. A predominantly clonal multi-institutional outbreak of *Clostridium difficile*-associated diarrhea with high morbidity and mortality. N Eng J Med 2005;353:2442-9.
9. McDonald LC, Killgore GE, Thompson A, Owens RC Jr, Kazakova SV, Sambol SP, et al. An epidemic, toxic gene-variant strain of *Clostridium difficile*. N Eng J Med 2005;353:2433-41.
10. Gerding DN, Johnson S, Peterson LR, Mulligan ME, Silva J. *Clostridium difficile*-associated diarrhea and colitis. Infect Control Hosp Epidemiol 1995;16:459.
11. Sunenshine RH, McDonald LC. *Clostridium difficile*-associated disease: new challenges from an established pathogen. Cleveland Clinic J Med 2006;73:187-97.
12. Bignardi GE. Risk factors for *Clostridium difficile* infection. J Hosp Infect 1998;40:1-15.
13. Barbut F, Petit JC. Epidemiology of *Clostridium difficile*-associated infections. Clin Microbiol Infect 2001;7:405-10.
14. Lai K, Melvin ZS, Menard MJ, Kotilainen HR, Baker S, et al. *Clostridium difficile*-associated diarrhea: epidemiology, risk factors, and infection control. Infect Control Hosp Epidemiol 1997;18:628.
15. Yip C, Loeb M, Salama S, Moss L, Olde J. Quinolone use as a risk factor for nosocomial *Clostridium difficile*-associated diarrhea. Infect Control Hosp Epidemiol 2001;22:572.
16. Gaynes R, Rimland D, Killum E, Lowery HK, Johnson TM, Killgore G, et al. Outbreak of *Clostridium difficile* infection in a long-term care facility: association with gatifloxacin use. Clin Infect Dis 2004;38:640.

17. Muto CA, Blank MK, Marsh JW, Vergis EN, O'Leary MM, Shutt KA, et al. Control of an outbreak of infection with the hypervirulent *Clostridium difficile* BI strain in a university hospital using a comprehensive "bundle" approach. Clin Infect Dis 2007;45:1266-73.
18. Helfenstein U. Box-Jenkins modeling in medical research. Stat Methods Med Res 1996;5:3-22.
19. Durbin J, Watson GS. Testing for serial correlation in least-squares regression. Biometrica 1951;38:159-77.
20. Fowler S, Webber A, Cooper BS, Phimster A, Price K, Carter Y, et al. Successful use of feedback to improve antibiotic prescribing and reduce *Clostridium difficile* infection: a controlled interrupted time series. J Antimicrob Chemother 2007;59:990-5.
21. Valiquette L, Cossette B, Garant MP, Diab H, Pepin J. Impact of reduction in the use of high-risk antibiotics on the course of an epidemic of *Clostridium difficile*-associated disease caused by the hypervirulent NAP1/027 strain. Clin Infect Dis 2007;45:S112-21 3.
22. McCusker ME, Harris AD, Perencevich E, Roghmann MC. Fluoroquinolone use and *Clostridium difficile*-associated diarrhea. Emerg Infect Dis 2003;9:730.
23. Pepin J, Saheb N, Coulombe MA, Alary ME, Corriveau MP, Authier S, et al. Emergence of fluoroquinolones as the predominate risk factor for *Clostridium difficile*-associated diarrhea: a cohort study during an epidemic in Quebec. Clin Infect Dis 2005;41:1254-60.
24. Koopman JS, Longini IM Jr. The ecological effects of individual exposures and nonlinear disease dynamics in populations. Am J Pub Health 1994;84:836-42.
25. Blakely TA, Woodward AJ. Ecological effects in multi-level studies. J Epidemiol Community Health 2000;54:367-74.