Clostridium difficile–associated diarrhea in a tertiary care medical center

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This retrospective, case-control study aimed to identify variables associated with the incidence of *Clostridium difficile*–associated diarrhea (CDAD) in acute care facilities and to specifically identify the relationship of fluoroquinolones and acid suppressive agents in the development of CDAD. Seventy-one symptomatic patients positive for *C. difficile* toxin A or B hospitalized for at least 72 hours were compared with 142 control patients hospitalized for at least 72 hours who were not positive for *C. difficile* toxin A or B. Two controls were matched to one case patient for age within 5 years, unit of admission, and date of admission. The mean ages for cases and controls were 63.5 and 62.7 years, respectively. After adjusting for two confounding variables—hospital stay within 3 months and Charlson Comorbidity Index—conditional multiple logistic regression identified six risk factors for development of CDAD: gastrointestinal procedures within 60 days (odds ratio [OR] 9.1, $P < 0.013$), levofloxacin exposure (OR 8.2, $P < 0.033$), moxifloxacin exposure (OR 4.1, $P < 0.026$), imipenem exposure (OR 14.9, $P < 0.014$), laxative use (OR 20.2, $P < 0.0001$), and immunosuppressive use (OR 20.7, $P < 0.034$). The risk of CDAD after exposure to levofloxacin or moxifloxacin was not significantly different. Acid suppressive therapy was not a risk factor for CDAD development.

Outbreaks of *Clostridium difficile*–associated diarrhea (CDAD) have been reported in acute care as well as long-term care facilities (1, 2). Disruption of the normal gut flora allows colonization with *C. difficile* (3). *C. difficile* colonization in adult patients may increase by 10% to 30% during hospitalization, but not all patients will develop disease. Known risk factors associated with CDAD development include prior exposure to antimicrobials, gastrointestinal (GI) surgery, feeding tubes, chemotherapy, environmental exposure, advanced age, severity of comorbid conditions, and GI stimulants, stool softeners, and enemas (1, 2, 4, 5). Although the strongest evidence with antimicrobial exposure exists with clindamycin, penicillins, and cephalosporins (4–11), reports have implicated fluoroquinolone use as a potential risk factor in the development of CDAD (2, 11–20). Proton pump inhibitors (PPIs) are another pharmacologic class suggested as a risk factor in the development of CDAD (21, 22).

Hillcrest Medical Center is a licensed 557-bed tertiary care hospital located in northeast Oklahoma. This institution had

experienced an apparent increase in CDAD cases over a 2-year period (years 2001–2003) with no defined cause, although a correlation with a formulary change from levofloxacin to moxifloxacin had been postulated. In addition, intravenous PPI therapy became available during this time period. The primary objective of this study was to evaluate the relationship of CDAD with levofloxacin or moxifloxacin use in acutely ill patients. Secondary study objectives included evaluating the relationship between CDAD and PPI use in acutely ill patients and describing the treatment regimens and outcomes of CDAD patients.

METHODS

Study design

This study was conducted in the general medical wards and intensive care units (ICUs) at Hillcrest Medical Center. A retrospective chart review was conducted in patients with CDAD or at risk for CDAD in acute care areas who were admitted between August 1, 2001, and August 31, 2003. Levofloxacin was the formulary fluoroquinolone from August 2001 to June 2002, and moxifloxacin was utilized from July 2002 to the end of the study analysis. Patients were excluded from participation if they were discharged from the hospital in <72 hours, were <18 or >89 years of age, had a previous CDAD diagnosis, showed symptoms within rather than after 72 hours of hospitalization, were treated in nonacute care areas, or did not have a chart available from medical records. This study was approved by the institutional review boards of the University of Oklahoma Health Sciences Center and Hillcrest Medical Center. Medical charts included in the study were identified using microbiological data

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(identification of *C. difficile* toxin A/B during the study period; Wompole™ *C. Diff* QuikChek Complete™, Inverness Medical, Princeton, NJ) and admission data.

A retrospective case-control study design was used. Cases included patients with acute onset of loose bowel movements persisting for ≥ 2 days who tested positive for *C. difficile* toxin A and/or toxin B. The date of positive toxin test was defined as the date of diagnosis. For each case patient with CDAD, two control patients were matched for age (within 5 years), unit of admission, and month of admission. Controls had to have a minimum length of stay of 3 days. Data from a single case of CDAD for each patient were included in the study analysis. Data collected included patient age, gender, race, the presence of comorbidities, alcohol abuse or current use of cigarettes as identified in the social history, patient location at time of CDAD diagnosis, and diagnosis at admission. The following variables were documented and assessed as risk factors associated with exposure before the development of CDAD: recent hospital admission within the previous 90 days, admission to the ICU, length of hospital stay prior to CDAD diagnosis, total hospital length of stay, GI procedure or surgery within 60 days of illness or during admission, previous antimicrobial use (e.g., fluoroquinolones, vancomycin, clindamycin, penicillins, cephalosporins, metronidazole), duration of antimicrobial treatment, other medications (chemotherapy, immunosuppressives, PPIs, histamine-2 receptor antagonists [H2RAs]), administration of enteral or parenteral nutrition, and presence of a nasogastric or nasotracheal tube. Data were recorded until the patient was discharged from the hospital, transferred to a long-term care facility, or died.

Statistical analysis

Statistical analysis was performed using SAS software, version 9.1 (SAS Institute, Cary, NC) (23). Univariate analysis was performed separately for each of the variables. Variables with a *P* value of ≤ 0.2 in the univariate analysis were included in a conditional multiple logistic regression model, as were the indicator variables for prior exposure to moxifloxacin and levofloxacin since these were the primary variables of interest. A manual backward selection process was used. Risk factors were checked for confounding and colinearity. Confounders were included in multivariate models if covariate inclusion changed the coefficient of any statistically significant variable in the logistic regression model by 10% or greater. The odds ratios for prior exposure to moxifloxacin and levofloxacin were evaluated using a *Z* test comparing parameter estimates. All tests were two tailed, and a *P* value of ≤ 0.05 was considered significant in the multivariate model.

RESULTS

Based on microbiological data, 302 patients were identified as positive for *C. difficile* toxin A or B during the study period. Of these patients, 46 were excluded for prior *C. difficile* infection, 26 patients were symptomatic within 72 hours of hospitalization, 102 patients were admitted to the rehabilitation or long-term care units, 27 patients did not meet the age requirements, and 30 patients were unable to be matched to the

two required control patients. Data were collected and analyzed for 71 case and 142 control patients.

Only three patient characteristics were significantly different between the case and control groups: recent hospitalization, GI procedure in the last 60 days, and GI procedure in the hospital (Table 1). The most commonly performed GI procedures for both groups included colonoscopy, exploratory laparotomy, esophagogastroduodenoscopy, and percutaneous endoscopic gastrostomy tube placement. The use of several types of medication was associated with CDAD, but PPIs and H2RAs were not among them (Table 2).

In the logistic regression model controlling for hospital stay within the previous 3 months and Charlson Comorbidity Index, six variables were found to increase the risk of CDAD (Table 3). The risk of developing CDAD after moxifloxacin or levofloxacin exposure was not significantly different. The case patients who received levofloxacin therapy received it primarily on an outpatient basis where a majority of patients who received moxifloxacin were treated on an inpatient basis. Treatment of the CDAD episode for case patients included metronidazole therapy in 89% and withdrawal of the suspected causative agent in 11%. As shown in Table 4, patients who developed CDAD had longer lengths of stay for both the ICU and total hospitalization. Mortality was similar in the case and control patients.

DISCUSSION

Our study suggests that there is an increased risk of CDAD after exposure to moxifloxacin or levofloxacin in patients who develop symptoms and test positive for *C. difficile* toxin A or B after 72 hours of admission to the hospital. No statistically

Table 1. Characteristics of subjects with *Clostridium difficile*-associated diarrhea and controls

Variable	Cases (n = 71)	Controls (n = 142)	<i>P</i> value
Female	54%	56%	0.558
Age (years $\pm$ SD)	63.5 $\pm$ 15	62.7 $\pm$ 15.6	0.213
ICU admission	32%	32%	0.895
Recent hospitalization	38%	17%	0.0006
Admitted from nursing home	13%	9%	0.322
Admitted from outside hospital	26%	20%	0.341
Charlson Comorbidity Index $\pm$ SD	2.38 $\pm$ 1.9	2.28 $\pm$ 2.02	0.712
GI procedure in last 60 days	30%	4%	<0.0001
GI procedure in hospital	39%	16%	0.0006
Enteral nutrition	26%	20%	0.261
Parenteral nutrition	16%	13%	0.407
Nasogastric tube	26%	22%	0.334
Nasotracheal tube	1%	0%	0.991

SD indicates standard deviation; ICU, intensive care unit; GI, gastrointestinal.

Table 2. Medication exposure of subjects with *Clostridium difficile*-associated diarrhea and controls

Medication	Variable	Cases (n = 71)	Controls (n = 142)	P value
Antibiotics	Outpatient	20%	6%	0.004
	Inpatient	93%	82%	0.024
Levofloxacin	Outpatient	6%	0%	0.0001
	Inpatient	10%	12%	0.468
	Duration (days ± SD)	7.8 ± 2.4	5.7 ± 4.1	
Moxifloxacin	Outpatient	1%	<1%	0.624
	Inpatient	43%	19%	0.005
	Duration (days ± SD)	6.6 ± 5.0	6.9 ± 5.5	
Imipenem/cilastatin	Inpatient	15%	3%	0.047
	Duration (days ± SD)	5.7 ± 3.4	6.3 ± 4.2	
Proton pump inhibitor	Outpatient	11%	9%	0.627
	Inpatient	56%	52%	0.532
	Duration (days ± SD)	11.2 ± 13.5	7.9 ± 5.4	
Histamine 2 receptor antagonist	Outpatient	4%	5%	0.823
	Inpatient	38%	32%	0.435
	Duration (days ± SD)	9.2 ± 7.9	7.1 ± 6.3	
Chemotherapy	Outpatient	0%	<1%	0.992
	Inpatient	6%	3%	0.297
	Duration (days ± SD)	3 ± 2	5.8 ± 3.8	
Steroid	Outpatient	9%	4%	0.171
	Inpatient	47%	30%	0.016
	Duration (days ± SD)	2.2 ± 3.8	6.3 ± 6.7	
Immunosuppression	Outpatient	6%	1%	0.096
	Inpatient	6%	1%	0.096
	Duration (days ± SD)	7 ± 4.2	9.5 ± 4.9	
Laxative	Inpatient	50%	15%	<0.0001

SD indicates standard deviation.

Table 3. Logistic regression model for variables that increase the risk of *Clostridium difficile*-associated diarrhea*

	Odds ratio (P value)	95% confidence interval
GI procedures within 60 days	9.1 (<0.013)	1.591–52.022
Levofloxacin	8.2 (<0.033) [†]	1.176–56.783
Moxifloxacin	4.1 (<0.026) [†]	1.180–14.067
Imipenem/cilastatin	14.9 (<0.014)	1.724–129.655
Laxative use	20.2 (<0.0001)	4.291–92.105
Immunosuppressive use	20.7 (<0.034)	1.258–340.038

*After controlling for recent hospitalizations within 3 months and Charlson Comorbidity Index.

[†]P > 0.05 (Z test of odds ratio).

Table 4. Outcome, length of stay, and patient disposition of cases with *Clostridium difficile*-associated diarrhea and controls

Variable	Cases (n = 71)	Controls (n = 142)
Clinical outcomes		
Discharge prior to completion of treatment	40%	Not applicable
Presumed success	37%	Not applicable
Microbiological outcomes		
Eradicated	9%	Not applicable
Presumed eradication	88%	Not applicable
Persistence	3%	Not applicable
ICU length of stay (days ± SD)	7.7 ± 18.1	2.3 ± 4.7
Hospital length of stay (days ± SD)	20.2 ± 20.8	9.6 ± 6.1
Discharged to home	51%	62%
Discharged to nursing home	37%	25%
Expired	12%	13%

ICU indicates intensive care unit; SD, standard deviation.

significant difference in risk of CDAD development was identified between moxifloxacin exposure and levofloxacin exposure. The hypothesis that moxifloxacin could increase CDAD rates as compared to levofloxacin is due to its greater propensity to affect anaerobic organisms (24). Several case reports and reviews have identified this potential risk (25). Our findings are similar to a recent case-control study of outpatients that found comparable risks of hospitalization for CDAD with gatifloxacin, moxifloxacin, and levofloxacin (26). Two studies have also postulated an increase in CDAD related to a change in formulary fluoroquinolone, although only one of these studies was able to control the outbreak by switching back to the original fluoroquinolone (2, 27). A large retrospective case-control study completed within the Veterans Administration (VA) documented that the increased CDAD rates observed were not associated with fluoroquinolone formulary change to gatifloxacin but with seasonal variation in CDAD rates (28). Another case-control study in the VA system confirmed that an increase in CDAD rates was not associated with the addition of gatifloxacin to the formulary (29). A prospective study of nosocomial CDAD in several Canadian institutions found an increased risk with ciprofloxacin, levofloxacin, and gatifloxacin in a multivariate model (30). Continuing research in this area suggests that fluoroquinolones in general are risk factors for CDAD development (11, 31–33).

The effect of acid suppressive therapy on rates of CDAD has recently been debated (34). In our study, no association was identified between PPIs or H2RAs and increased risk of CDAD. An explanation for this in our study may be the low number of patients using these agents in the outpatient setting and the possibility that increased risk may be related to prolonged use. Several other studies have found no link between acid suppressive therapy and CDAD, including a VA study (28), a recent case-control trial of community-dwelling

outpatients (35), a study of hospitalized patients (32), and a prospective study in several institutions in Canada (30). In contrast, a large community-based case-control trial found that the use of acid suppressants, especially PPIs, as well as nonsteroidal anti-inflammatory agents was associated with an increased risk for development of CDAD (36), and a retrospective case-control study in Kansas identified an increased risk of CDAD with exposure to PPI therapy (37). In all, the data remain inconclusive but confirm that PPIs should be screened for inappropriate use and discontinued in those situations to avoid potential adverse sequelae (38).

An interesting finding in our study was the increased risk of CDAD after GI procedures completed within the previous 60 days. The ability to associate the development of CDAD with the procedure itself versus the agents used prior to the procedures (i.e., electrolyte preparation solutions or topical antimicrobial agents) is limited by the lack of outpatient information. A proportion of patients in this study also underwent inpatient GI procedures, raising the question of whether these patients had inflammatory bowel disease that was previously undiagnosed and not captured due to study design. In prior studies, there appears to be a link with preexisting intestinal conditions or procedures and CDAD development (28, 39). The increased risk of CDAD with laxative exposure is not a new finding (4).

The increased risk of CDAD with imipenem/cilastatin found in our study is supported by evidence from other trials in patients with immunosuppression. A significant increase in CDAD occurred with imipenem/cilastatin compared with clinafloxacin for empiric treatment of febrile neutropenia (40). A similar finding of increased CDAD in neutropenic patients was found with imipenem and vancomycin compared with cefoperazone-sulbactam and vancomycin therapy for suspected or documented infections (41). Compared with ceftazidime, use of imipenem in febrile neutropenic patients was associated with greater gastrointestinal toxicity, including CDAD and nausea and vomiting (42). A recent case-control study of CDAD in hospitalized patients also identified that imipenem/cilastatin was associated with increased rates of CDAD (43).

The identification of those patients most at risk for CDAD is paramount in the prevention and treatment of this disease. Scoring models for CDAD have been developed to identify those patients who may be at risk (44, 45). The Waterlow score, used for identifying the risk of developing pressure ulcers, has also been linked to the risk of CDAD (44). Also utilized is the clinical risk scoring model, which has four variables (age, hemodialysis, surgical admission status, and ICU length of stay) and identifies those patients at risk for CDAD (45). These scoring models, when used appropriately, may help guide physicians when prescribing broad-spectrum antimicrobial therapy, ordering GI procedures, and implementing preventative CDAD procedures.

Due to the design of this study, several major limitations must be addressed. This review was conducted at a single institution. Our study focused on patients who may have acquired CDAD after hospitalization in an effort to capture inpatient exposures to medications or other risk factors, which limits the

ability to generalize these results to other patient populations. Due to the retrospective nature of the study, the agents selected for treatment for the initial suspected infection or CDAD could not be controlled. In addition, the complete duration of therapy of the various antimicrobial, immunosuppressive, laxative, and acid-reducing agents could not be specified with the current design, as only the inpatient duration could be captured. While patients with CDAD receive isolation control including hand-washing, gowning, and gloving as standard procedures in this institution, these variables are not routinely documented in the chart once isolation procedures are ordered. Another limitation to the study is the small number of patients who received moxifloxacin and levofloxacin during the study period, thus limiting the power of the study. This reduction in power may have resulted in the inability to find a significant difference between fluoroquinolone exposures. The number of potential patients was greatly reduced by excluding patients who were symptomatic within the initial 72 hours of hospitalization or who had previous CDAD and the inability to match case patients with controls meeting the specified criteria. The strains of *C. difficile* were not sent for epidemiologic typing to identify outbreak isolates, nor was antibiotic susceptibility testing completed for any of the isolates. This study is also limited because there could have been some changes in practice or differences in risk of CDAD due to other factors (seasonal or random differences in outbreaks) that could not be controlled.

In conclusion, in patients with CDAD identified after at least 72 hours of hospitalization, an increased risk is present after exposure to levofloxacin, moxifloxacin, imipenem/cilastatin, laxative use, immunosuppressive use, and GI procedures within the previous 60 days. The risk of CDAD exposure was not significantly different between moxifloxacin or levofloxacin exposure. Exposure to PPIs or H2RAs did not increase the risk of CDAD development.

- Gerding DN, Johnson S, Peterson LR, Mulligan ME, Silva J Jr. *Clostridium difficile*-associated diarrhea and colitis. *Infect Control Hosp Epidemiol* 1995;16(8):459-477.
- Gaynes R, Rimland D, Killum E, Lowery HK, Johnson TM 2nd, Killgore G, Tenover FC. Outbreak of *Clostridium difficile* infection in a long-term care facility: association with gatifloxacin use. *Clin Infect Dis* 2004;38(5):640-645.
- Groschel DHM. *Clostridium difficile* infection. *Crit Rev Clin Lab Sci* 1996;33(3):203-245.
- McFarland LV, Surawicz CM, Stamm WE. Risk factors for *Clostridium difficile* carriage and *C. difficile*-associated diarrhea in a cohort of hospitalized patients. *J Infect Dis* 1990;162(3):678-684.
- Owens RC Jr, Donskey CJ, Gaynes RP, Loo VG, Muto CA. Antimicrobial-associated risk factors for *Clostridium difficile* infection. *Clin Infect Dis* 2008;46(Suppl 1):S19-S31.
- Gerding DN, Olson MM, Peterson LR, Teasley DG, Gebhard RL, Schwartz ML, Lee JT Jr. *Clostridium difficile*-associated diarrhea and colitis in adults. A prospective case-controlled epidemiologic study. *Arch Intern Med* 1986;146(1):95-100.
- Tedesco FJ, Barton RW, Alpers DH. Clindamycin-associated colitis. A prospective study. *Ann Intern Med* 1974;81(4):429-433.
- Pear SM, Williamson TH, Bettin KM, Gerding DN, Galgiani JN. Decrease in nosocomial *Clostridium difficile*-associated diarrhea by restricting clindamycin use. *Ann Intern Med* 1994;120(4):272-277.
- Bartlett JG. Antibiotic-associated colitis. *Dis Mon* 1984;30(15):1-54.

10. Golledge CL, Carson CF, O'Neill GL, Bowman RA, Riley TV. Ciprofloxacin and *Clostridium difficile*-associated diarrhoea. *J Antimicrob Chemother* 1992;30(2):141–147.
11. 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(9):572–575.
12. Bauwens JE, McFarland LV, Melcher SA. Recurrent *Clostridium difficile* disease following ciprofloxacin use. *Ann Pharmacother* 1997;31(9):1090.
13. McFarland LV, Bauwens JE, Melcher SA, Surawicz CM, Greenberg RN, Elmer GW. Ciprofloxacin-associated *Clostridium difficile* disease. *Lancet* 1995;346(8980):977–978.
14. Cain DB, O'Connor ME. Pseudomembranous colitis associated with ciprofloxacin. *Lancet* 1990;336(8720):946.
15. Dan M, Samra Z. *Clostridium difficile* colitis associated with ofloxacin therapy. *Am J Med* 1989;87(4):479.
16. Ozawa TT, Valadez T. *Clostridium difficile* infection associated with levofloxacin treatment. *Tenn Med* 2002;95(3):113–115.
17. Ortiz-de-Saracho J, Pantoja L, Romero MJ, López R. Moxifloxacin-induced *Clostridium difficile* diarrhea. *Ann Pharmacother* 2003;37(3):452–453.
18. Carroll DN. Moxifloxacin-induced *Clostridium difficile*-associated diarrhea. *Pharmacotherapy* 2003;23(11):1517–1519.
19. Muto CA, Pokrywka M, Shutt K, Mendelsohn AB, Nouri K, Posey K, Roberts T, Croyle K, Krystofiak S, Patel-Brown S, Pasculle AW, Paterson DL, Saul M, Harrison LH. 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(3):273–280.
20. McCusker ME, Harris AD, Perencevich E, Roghmann MC. Fluoroquinolone use and *Clostridium difficile*-associated diarrhea. *Emerg Infect Dis* 2003;9(6):730–733.
21. Dial S, Alrasadi K, Manoukian C, Huang A, Menzies D. Risk of *Clostridium difficile* diarrhea among hospital inpatients prescribed proton pump inhibitors: cohort and case-control studies. *CMAJ* 2004;171(1):33–38.
22. Cunningham R, Dale B, Undy B, Gaunt N. Proton pump inhibitors as a risk factor for *Clostridium difficile* diarrhoea. *J Hosp Infect* 2003;54(3):243–245.
23. SAS Institute Inc. *SAS/STAT Users Guide, Version 9.1*. Cary, NC: SAS Institute Inc., 2002–2003.
24. Adams DA, Riggs MM, Donskey CJ. Effect of fluoroquinolone treatment on growth of and toxin production by epidemic and nonepidemic *Clostridium difficile* strains in the cecal contents of mice. *Antimicrob Agents Chemother* 2007;51(8):2674–2678.
25. Gallagher JC, Du JK, Rose C. Severe pseudomembranous colitis after moxifloxacin use: a case series. *Ann Pharmacother* 2009;43(1):123–128.
26. Dhalla IA, Mamdani MM, Simor AE, Kopp A, Rochon PA, Juurlink DN. Are broad-spectrum fluoroquinolones more likely to cause *Clostridium difficile*-associated disease? *Antimicrob Agents Chemother* 2006;50(9):3216–3219.
27. Biller P, Shank B, Lind L, Brennan M, Tkatch L, Killgore G, Thompson A, McDonald LC. Moxifloxacin therapy as a risk factor for *Clostridium difficile*-associated disease during an outbreak: attempts to control a new epidemic strain. *Infect Control Hosp Epidemiol* 2007;28(2):198–201.
28. McFarland LV, Clarridge JE, Beneda HW, Raugi GJ. Fluoroquinolone use and risk factors for *Clostridium difficile*-associated disease within a Veterans Administration health care system. *Clin Infect Dis* 2007;45(9):1141–1151.
29. Walbrown MA, Aspinall SL, Bayliss NK, Stone RA, Cunningham F, Squier CL, Good CB. Evaluation of *Clostridium difficile*-associated diarrhea with a drug formulary change in preferred fluoroquinolones. *J Manag Care Pharm* 2008;14(1):34–40.
30. Loo VG, Poirier L, Miller MA, Oughton M, Libman MD, Michaud S, Bourgault AM, Nguyen T, Frenette C, Kelly M, Vibien A, Brassard P, Fenn S, Dewar K, Hudson TJ, Horn R, René P, Monczak Y, Dascal A. A predominantly clonal multi-institutional outbreak of *Clostridium difficile*-associated diarrhea with high morbidity and mortality. *N Engl J Med* 2005;353(23):2442–2449.
31. Kazakova SV, Ware K, Baughman B, Bilukha O, Paradis A, Sears S, Thompson A, Jensen B, Wiggs L, Bessette J, Martin J, Clukey J, Gensheimer K, Killgore G, McDonald LC. A hospital outbreak of diarrhea due to an emerging epidemic strain of *Clostridium difficile*. *Arch Intern Med* 2006;166(22):2518–2524.
32. Pépin J, Saheb N, Coulombe MA, Alary ME, Corriveau MP, Authier S, Leblanc M, Rivard G, Bettez M, Primeau V, Nguyen M, Jacob CE, Lanthier L. Emergence of fluoroquinolones as the predominant risk factor for *Clostridium difficile*-associated diarrhea: a cohort study during an epidemic in Quebec. *Clin Infect Dis* 2005;41(9):1254–1260.
33. Deshpande A, Pant C, Jain A, Fraser TG, Rolston DD. Do fluoroquinolones predispose patients to *Clostridium difficile* associated disease? A review of the evidence. *Curr Med Res Opin* 2008;24(2):329–333.
34. Cunningham R, Dial S. Is over-use of proton pump inhibitors fuelling the current epidemic of *Clostridium difficile*-associated diarrhoea? *J Hosp Infect* 2008;70(1):1–6.
35. Lowe DO, Mamdani MM, Kopp A, Low DE, Juurlink DN. Proton pump inhibitors and hospitalization for *Clostridium difficile*-associated disease: a population-based study. *Clin Infect Dis* 2006;43(10):1272–1276.
36. Dial S, Delaney JA, Barkun AN, Suissa S. Use of gastric acid-suppressive agents and the risk of community-acquired *Clostridium difficile*-associated disease. *JAMA* 2005;294(23):2989–2995.
37. Aseeri M, Schroeder T, Kramer J, Zackula R. Gastric acid suppression by proton pump inhibitors as a risk factor for *Clostridium difficile*-associated diarrhea in hospitalized patients. *Am J Gastroenterol* 2008;103(9):2308–2313.
38. Dalton BR, Lye-Maccannell T, Henderson EA, Maccannell DR, Louie TJ. Proton pump inhibitors increase significantly the risk of *Clostridium difficile* infection in a low-endemicity, non-outbreak hospital setting. *Aliment Pharmacol Ther* 2009;29(6):626–634.
39. Pierce PF Jr, Wilson R, Silva J Jr, Garagusi VE, Rifkin GD, Fekety R, Nunez-Montiel O, Dowell VR Jr, Hughes JM. Antibiotic-associated pseudomembranous colitis: an epidemiologic investigation of a cluster of cases. *J Infect Dis* 1982;145(2):269–274.
40. Winston DJ, Lazarus HM, Beveridge RA, Hathorn JW, Gucalp R, Ramphal R, Chow AW, Ho WG, Horn R, Feld R, Louie TJ, Territo MC, Blumer JL, Tack KJ. Randomized, double-blind, multicenter trial comparing clinafloxacin with imipenem as empirical monotherapy for febrile granulocytopenic patients. *Clin Infect Dis* 2001;32(3):381–390.
41. Bodey G, Abi-Said D, Rolston K, Raad I, Whimbey E. Imipenem or cefoperazone-sulbactam combined with vancomycin for therapy of presumed or proven infection in neutropenic cancer patients. *Eur J Clin Microbiol Infect Dis* 1996;15(8):625–634.
42. Freifeld AG, Walsh T, Marshall D, Gress J, Steinberg SM, Hathorn J, Rubin M, Jarosinski P, Gill V, Young RC, et al. Monotherapy for fever and neutropenia in cancer patients: a randomized comparison of ceftazidime versus imipenem. *J Clin Oncol* 1995;13(1):165–176.
43. Baxter R, Ray GT, Fireman BH. Case-control study of antibiotic use and subsequent *Clostridium difficile*-associated diarrhea in hospitalized patients. *Infect Control Hosp Epidemiol* 2008;29(1):44–50.
44. Tanner J, Khan D, Anthony D, Paton J. Waterlow score to predict patients at risk of developing *Clostridium difficile*-associated disease. *J Hosp Infect* 2009;71(3):239–244.
45. Garey KW, Dao-Tran TK, Jiang ZD, Price MP, Gentry LO, Dupont HL. A clinical risk index for *Clostridium difficile* infection in hospitalised patients receiving broad-spectrum antibiotics. *J Hosp Infect* 2008;70(2):142–147.