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Risk Factors for Acquisition of *Clostridium difficile*-Associated Diarrhea Among Outpatients at a Cancer Hospital

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Abstract

Background—*Clostridium difficile*-associated diarrhea (CDAD) is an important infection in hospital settings. Its impact on outpatient care has not been well defined.

Objective—To examine risk factors of ambulatory cancer patients with CDAD.

Design—Case-control study.

Setting—Memorial Sloan Kettering Cancer Center, a tertiary-care hospital.

Methods—Cases of CDAD among oncology outpatients from January 1999 through December 2000 were identified via positive *C. difficile* toxin assay results on stool specimen sent from clinics or the emergency department. A 1:3 matched case-control study examined exposures associated with CDAD.

Results—Forty-eight episodes of CDAD were identified in cancer outpatients. The median age was 51 years; 44% were female. Forty-one (85%) had received antibiotics within 60 days of diagnosis, completing courses a median of 16.5 days prior to diagnosis. Case-patients received longer courses of first-generation cephalosporins (4.8 vs 3.2 days, $P = .03$) and fluoroquinolones (23.6 vs 8 days; $P < .01$) than did control-patients. Those receiving clindamycin were 3.9-fold more likely to develop CDAD ($P < .01$). For each additional day of clindamycin or third-generation cephalosporin exposure, patients were 1.29- and 1.26-fold more likely to develop CDAD ($P < .01$ and .04, respectively). The 38 CDAD patients hospitalized during the risk period (79.2%) spent more time as inpatients than control-patients (19.3 vs 9.7 days, $P < .001$).

Conclusions—Antibiotic use, especially with cephalosporins and clindamycin, and prolonged hospitalization contributed to development of CDAD. Outpatient CDAD appears to be most strongly to be related to inpatient exposures; reasons for delayed development of symptoms are unknown.

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INTRODUCTION

Clostridium difficile-associated diarrhea (CDAD) is an increasingly common complication of medical therapy. Risk factors for development of nosocomial CDAD in hospitalized patients have been well delineated during the past 20 years and include the use of broad-spectrum antibiotics,[1] chemotherapy,[2] and hospitalization with a carrier or case.[3,4] Previous studies on outpatient occurrence of CDAD focused primarily on antibiotic exposure.

As the treatment of sicker patients moves increasingly into the outpatient arena, the risk of various nosocomial infections in this setting must be defined. Patients who shuttle between the hospital and the ambulatory clinic may be at particular risk for contracting CDAD and exposing others. In this case-control study, we analyze the risk factors for CDAD in an outpatient oncology population to characterize the demographics, antecedent antibiotic exposure, and other therapy-related factors associated with CDAD in this setting.

METHODS

All adult and pediatric patients with a positive result on *C. difficile* toxin B culture neutralization assay (Techlab, Inc., Blacksburg, VA) for the 2-year period from January 1, 1999 to December 31, 2000 were identified via microbiology laboratory records. The assay has a reported sensitivity of 99.1% and specificity of 99.3%. The microbiology laboratory performs this assay only on diarrheal stool. Among these 387 patients, 73 (18.9%) with specimens collected in outpatient settings (clinic or emergency department) were identified. Those who had experienced episodes of CDAD within the 2 years before the study period (n = 13) were excluded on the basis that the episode was likely to represent a recurrence. Patients without cancer (n = 8) were excluded as they had no potential exposure to cancer therapies. Four additional patients were excluded because of inadequate records of antecedent exposures, CDAD treatment or outcome (Figure). A total of 48 oncology outpatients met the case definition of new-onset CDAD and were included in the study.

Three control-patients were matched to each case-patient. Control-patients were selected at random from a computer-generated list of patients who had been hospitalized and discharged during the study period without positive results on *C. difficile* assays, and were matched to the case-patients by gender, age, and type and stage of cancer. Control-patients were not excluded if they had diarrhea or a negative *C. difficile* assay result because they represent the appropriate base population from which the case-patients arose.

Charts were extracted for multiple demographic and clinical variables. The risk period for CDAD patients was defined as the 60 days preceding the positive *C. difficile* assay result. The comparable risk period assigned to control-patients was the 60-day period starting two weeks prior to hospital discharge. Specific duration and timing of hospitalizations and antibiotic therapy were recorded. Details of the antibiotics and the infections for which they were administered were also documented. Antibiotic therapy was classified as perioperative if it was given in the perioperative period as prophylaxis against surgical-site infections. Performance and timing of surgeries and gastrointestinal tract procedures, treatment

administered for CDAD, severity of disease (hospitalization and mortality due to CDAD), and outcome, when complete, were noted as well.

For categorical variables, conditional logistic regression was used to determine whether they were associated with case-control status. Differences in continuous variables by case-control status were assessed using generalized estimating equations to take into account the matched sets of case-patients and control-patients. Multivariate analyses were performed using conditional logistic regression to obtain adjusted estimates of the odds ratios. Variables that showed a *P* value of less than .20 on univariate analysis were entered into the model. The effect of possible confounding factors was verified by introducing them into the final model and noting the change in the coefficients of the risk factors. Univariate and multivariate analyses were performed using conditional logistic regression. All tests were two-tailed, with a *P* value of less than .05 considered statistically significant. Data were processed and analyzed using SPSS (version 10.1; SPSS Inc., Chicago, IL) and SAS (version 8.0; SAS Institute, Inc., Cary, NC) software.

RESULTS

Characteristics of the patients

During the 2-year study, there were 387 incident episodes of CDAD, of which 73 were identified from specimens submitted from outpatient settings. Among these, 48 patients (66%) had underlying cancer and had not previously developed CDAD. The mean age of the group was 51.3 years and 44% were female. Six patients were younger than 18 years. The majority (81%) of the patients had solid tumors, with nearly half being treated for metastatic disease. Stool specimens for 10 patients were sent from the emergency department; specimens from the remaining 38 were submitted from outpatient clinics.

The median interval from hospital discharge to CDAD diagnosis among the 38 patients who had been hospitalized was 20.3 days (range 2 to 60 days). The median interval from completion of most recent antibiotic therapy to a positive assay result was 16.5 days (range, 0 to 49 days).

A subset of 7 patients with CDAD (15%) received no antibiotics during the risk period. Four of these patients had received cytotoxic chemotherapy within 10 days of the diagnosis of CDAD. Two had no documented predisposing factors for CDAD except hospitalization.

Outcome of outpatient CDAD

Nineteen (40%) of the patients required hospitalization for management of CDAD. All patients survived.

Case Control Study

CDAD patients and control-patients were well matched for gender, age, and type and stage of cancer (Table 1).

Hospital exposure

Hospitalized CDAD patients spent more total time as inpatients (19.3 days) than did control-patients (9.7 days; $P < .001$) during the risk period, often in multiple admissions (Table 2). Case-patients also had significantly longer admissions immediately preceding diagnosis of their CDAD (10 days) than did control-patients (6.7 days) during the equivalent risk period ($P = .02$).

By conditional logistic regression modeling, outpatients who had been hospitalized for 8 or more days within the risk period were 2.16-fold more likely to develop CDAD than those who spent 7 or fewer days in the hospital ($P = .04$), after adjusting for the effects of perioperative antibiotic use and exposure to both clindamycin and third-generation cephalosporins.

Antibiotic exposure

Equal proportions of CDAD patients and control-patients received antibiotics during the 60-day risk period (85% in each group). There were no significant differences in the mean number of antibiotics that case-patients and control-patients received (2.0 vs 1.9). CDAD patients experienced more antibiotic-days in the preceding 60 days (20.4 days) than did control-patients (12.7 days), but the difference did not reach statistical significance ($P = .13$). A greater proportion of CDAD patients (40%) than control-patients (33%) received outpatient antibiotics, but this difference was not statistically significant.

The exposure of patients to each class of antibiotics was evaluated (Tables 3 and 4). On univariate analysis, patients with CDAD had more days of use of first-generation cephalosporins (4.8 vs 3.2 days; $P = .03$) and fluoroquinolones (23.6 vs 8 days; $P < .01$) than did control-patients. The risk of developing CDAD for patients who had received clindamycin was 3.88 times that of patients without clindamycin exposure ($P < .01$).

Multivariate regression analysis revealed that for each additional day of clindamycin or third-generation cephalosporin exposure, patients were 1.29- and 1.26-fold more likely to develop CDAD ($P < .01$ and .04, respectively), after adjusting for the effects of admission duration and perioperative antibiotic use. There were no other significant differences in exposure to perioperative antibiotics or other classes of antibiotics or total number or duration of antibiotics during the risk period.

Therapies and Procedures

There were no significant differences between CDAD patients and control-patients in exposure to chemotherapy (43.8% vs 45.1%), radiation therapy (2.1% vs 9.7%), or surgeries or procedures involving the gastrointestinal tract (29.2% vs 21.5%).

DISCUSSION

Individuals recently discharged from the hospital remain at risk for a variety of nosocomial complications, despite their return home. One such complication is outpatient CDAD, which represented 19% of all CDAD episodes at our hospital during a 2-year period. CDAD in

outpatients with cancer caused substantial morbidity, including rehospitalization for almost half.

Previous outpatient studies have focused on specific antibiotic use and found that, similar to inpatient disease, outpatient CDAD occurs among individuals with exposures to certain antimicrobials. Levy et al., studying CDAD among a large cohort of patients enrolled in a health maintenance organization, found 87 cases among 358,359 ambulatory enrollees.[5] Evaluating only those patients with exposure to a single antibiotic, the authors determined that antecedent cefixime and cephalexin were risk factors for CDAD.

Hirschhorn et al evaluated antibiotics alone and in combination.[6] They identified nitrofurantoin, cefuroxime, cephalexin plus dicloxacillin, ampicillin-clavulanate plus cefaclor, and ampicillin/clavulanate plus cefuroxime as associated with increased risk for ambulatory CDAD. Riley et al. found that the spectrum of antecedent antibiotics associated with CDAD reflected the spectrum of antibiotics prescribed in the general practice setting.[7,8]

These studies, however, have not examined the contribution of recent hospitalization to the development of CDAD. In our series, hospitalization for at least 8 days in the previous 2 months was significantly associated with development of CDAD. The duration and intensity of antibiotic therapy during the 60-day study period was higher in CDAD patients than in control-patients, but this association did not reach statistical significance. This suggests that time in the hospital may amplify risk, regardless of amount of antibiotics received.

In our study, several classes of antibiotics were implicated; on multivariate analysis, a patient's likelihood of acquiring CDAD increased significantly with each additional day of therapy with clindamycin or a third-generation cephalosporin. Of note, we found that the median time from discontinuation of antibiotics to disease diagnosis was more than 2 weeks.

We also found that most cases of CDAD were diagnosed unexpectedly late: approximately 3 weeks after discharge or, in a few, substantially longer. We suspect that most patients left the hospital infected with *C. difficile,* but, for some reason, did not manifest symptoms until weeks later. This finding may provide important insight into the pathogenesis of the disease, which appears to require many factors beyond simple exposure and acquisition to cause illness.

Perioperative prophylactic antibiotics were not a risk factor for CDAD in this study. Although the selection of *C. difficile* in fecal flora[9] and the anecdotal occurrence of CDAD following even a single dose of antibiotics are well reported,[10,11,12] prophylactic antibiotics have not been shown to be a specific risk factor for developing CDAD.[13] The large proportion of patients in both groups receiving exclusively prophylactic antibiotics (44% and 45%) reflects the frequency of surgical intervention in our hospital.

This study has several limitations. First, the assignment of a control group for CDAD studies is imperfect. We drew controls from our base population, matching by age, gender, cancer type and stage, and hospitalization during the 2-year period of the study.

We considered a risk period for development of CDAD that was longer than the intervals used in most studies. Levy et al. and Hirshhorn et al., studying only antibiotics as a risk factor, designated a period of 42 days after prescription.[5,6] Our risk period was longer because we were evaluating many types of exposures as potential risk factors. The selection of a risk period and event date for control-patients was problematic because the control-patients had no comparable event. We chose an event date of 46 days after hospital discharge so that the antecedent 60-day risk period would comprise inpatient as well as outpatient exposures.

Subjects in our study were outpatients at the time of CDAD diagnosis, but most had been recently hospitalized and most antibiotic courses were administered at least in part in the inpatient setting. Some authors have classified CDAD that develops soon after hospital discharge to be effectively nosocomial CDAD.[6,14] Frequent hospital admissions and frequent outpatient follow-up are characteristics of the outpatient population at a cancer center—features not comparable to previous studies of large ambulatory health plan cohorts.

Person-to-person spread is a well-documented means of acquiring nosocomial CDAD. Because this was a retrospective study, we did not attempt to determine whether *C. difficile* isolates were shared among outpatients or related to those of inpatients. Such investigation might have elucidated the source of infection for the sole CDAD patient in our study without discernible risk factors. Physical proximity to other hospitalized patients with CDAD, a known risk factor for nosocomial CDAD,[15] was also not evaluated in this study.

In this retrospective case-control study, ambulatory cancer patients who developed CDAD had recent prolonged hospitalizations and exposure to certain antibiotics, particularly clindamycin and third-generation cephalosporins. They required hospitalization at a higher rate than was reported in previous studies of broad outpatient populations, possibly due to their underlying condition. Further studies are needed to identify the source of infecting *C. difficile* strains; molecular epidemiology techniques could determine whether spread within the hospital, an outpatient clinical setting, or the community plays a role in the development of ambulatory CDAD in this vulnerable population. Until the disease in outpatients is better defined, the diagnosis of CDAD must be considered in any patient hospitalized in the 2 months preceding the diagnosis, regardless of exposure to antibiotics or chemotherapy.

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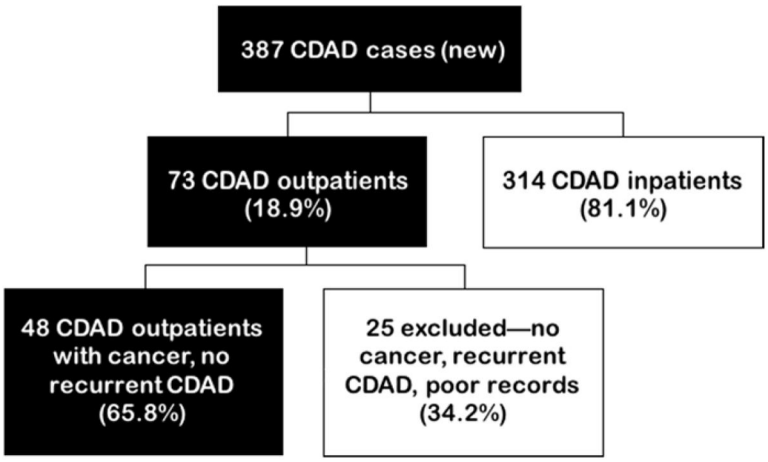

Figure 1.
Derivation of population of outpatients with *Clostridium difficile*-associated diarrhea (CDAD).

Table 1

Characteristics of Patients with *Clostridium difficile*-Associated Diarrhea and Control-Patients

Characteristic	CDAD Patients (n=48)	Control-Patients (n=144)
Mean age, y (± SD)	51.3 (23.3)	50.7 (22.9)
Median age, y	56	55
Female	21 (44%)	63 (44%)
Male	27 (56%)	81(56%)
Type of cancer		
Hematologic	9 (19%)	27 (19%)
Solid	39 (81%)	117 (81%)
Stage of cancer		
I	5 (10.4%)	15 (10.4%)
II	2 (4.2%)	6 (4.2%)
III	8 (16.7%)	24 (16.7%)
IV	22 (45.8%)	66 (45.8%)
Not staged	11 (23.0%)	33 (23.0%)

CDAD = *C. difficile*-associated diarrhea; SD = standard deviation

Table 2

Exposures of Patients with *Clostridium difficile*-Associated Diarrhea and Control-Patients

Characteristic	CDAD Patients	Control-Patients	*P*
No. of patients hospitalized during the risk period	38 (79.2%)	144 (100%)	*
Mean duration of last hospitalization, d (± SD)			
All patients	7.1 (8.0)	6.7 (7.4)	NS
Hospitalized only[a]	10.0 (7.8)	6.7 (7.4)	.02
Total hospital days during risk period, d (± SD)			
All patients	14.9 (14.3)	9.7 (9.7)	.02
Hospitalized only[a]	19.3 (13.4)	9.7 (9.7)	< .001
Mean no. of antibiotics received (± SD)			
All patients	2.0 (1.5)	1.9 (1.5)	NS
Patients with antibiotic exposure[b]	2.4 (1.4)	2.2 (1.4)	NS
Median no. of antibiotics received			
All patients	2.0	1.5	NS
Patients with antibiotic exposure[b]	2.0	2.0	NS

CDAD = *C. difficile*-associated diarrhea; SD = standard deviation; NS = not significant.

*Hospitalization status was a selection criterion for control-patients.

[a]Excludes patients who were not hospitalized during the risk period.

[b]Excludes patients who received no antibiotics or an unknown quantity of antibiotics.

Table 3

Antibiotic Usage During Risk Period Among Antibiotic-Treated Patients with *Clostridium difficile*-Associated Diarrhea and Matched Control-Patients

Mean Antibiotic-Days*	CDAD Patients	Control-Patients	*P*
First-generation cephalosporin	4.8	3.2	.03
Second-generation cephalosporin	1.4	4.2	NS
Third-generation cephalosporin	6.3	3.6	NS
Fourth-generation cephalosporin	16.8	5.2	NS
Clindamycin	10.3	3.5	NS
Fluoroquinolone	23.6	8.0	< .01
Penicillin	8.1	9.9	NS
Macrolide	8.5	6.8	NS
Aminoglycoside	5.6	5.0	NS
Metronidazole	5.0	4.4	NS
Vancomycin	8.7	6.4	NS
Other[a]	4.0	12.6	NS
Total	20.4	12.7	NS

CDAD = *C. difficile*-associated diarrhea; NS = not significant.

*Excludes patients who did not receive antibiotics.

[a]Included carbapenems, monobactams, chloramphenicol, tetracyclines, and trimethoprim-sulfamethoxazole.