Incidence of *Clostridium difficile* Infection in Inflammatory Bowel Disease

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Background & Aims: ***Clostridium difficile*-associated disease (CDAD) rates have been increasing. We sought to determine whether CDAD incidence has increased specifically in hospitalized patients with IBD. We also explored possible differences in the risk for and time to presentation of CDAD between IBD and non-IBD patients.** **Methods:** **We analyzed hospital admissions from 1998-2004 for demographics, length of stay, *C difficile* infections, and time from admission to a positive *C difficile* test. We calculated CDAD incidence for non-IBD, all IBD, CD, and UC admissions and used logistic regression to estimate the risk for CDAD.** **Results:** **CDAD incidence increased in each group and was higher in all IBD than non-IBD groups. During the observation period, CDAD rates approximately doubled in CD (9.5 to 22.3/1000 admissions) and tripled in UC (18.4 to 57.6/1000). Length of stay was similar among the groups. For all years combined, the adjusted odds ratios for CDAD in all IBD, CD, and UC admissions were 2.9 (95% confidence interval, 2.1-4.1), 2.1 (1.3-3.4), and 4.0 (2.4-6.6), respectively. The median times from admission to a positive *C difficile* test result for non-IBD, CD, and UC were 4.0, 0.8, and 0.5 days, respectively.** **Conclusions:** **CDAD incidence in IBD has increased and is higher than in the non-IBD population. IBD and UC patients in particular have a higher risk for CDAD. *C difficile* infections in IBD are confirmed predominantly within 48 hours of admission, suggesting most were acquired before hospitalization.**

Clostridium difficile-associated diarrhea (CDAD) has emerged as a major medical problem in the United States and throughout the world. Pseudomembranous colitis from *C difficile* infection can cause significant morbidity and death in hospitalized patients.[1] In the general hospital population, the incidence of CDAD continues to increase, with a doubling of cases between 1996-2003 on the basis of discharge diagnoses of short stay hospitals,[2] and an estimated 3 million cases of CDAD and colitis occur annually in the United States.[3] Recognized risk factors for infection include advanced age (>65 years old), recent (<2 months) broad-spectrum antibiotic therapy, long hospital stay, and presence of multiple comorbidities.[2,4,5] Risk factors for fulminant *C difficile* colitis include immunosuppression and systemic infection.[1,4] Studies show that *C difficile* infections are becoming more severe and resistant to antibiotics, conferring a mortality rate of 1%-2% in such cases.[5]

Patients with CD and UC are hospitalized commonly with worsening diarrhea, which in many instances is attributable to progression of the underlying IBD, but it might also be the result of infection with enteric organisms or opportunistic agents such as cytomegalovirus and *C difficile*.[6] Thus, prompt diagnosis and treatment of infection become paramount. Previous studies have reported that 5%-19% of patients admitted for relapsing IBD are positive for *C difficile*.[6,7] However, trends in the incidence of CDAD over multiple years in hospitalized CD and UC patients have not been examined in detail.

In this study, we sought to determine whether the incidence of CDAD in patients hospitalized for IBD has increased in recent years, as in the general medical population. We postulated that the incidence of CDAD might be higher in UC compared with CD because the latter condition in particular is treated often in the outpatient setting with antibiotics such as metronidazole, which is effective against *C difficile*. Moreover, on the basis of the observations that *C difficile* infection might cause diarrhea despite quiescent IBD or, alternatively, might precipitate a flare of UC or CD resulting in hospitalization, we also hypothesized that *C difficile* toxin positivity in these patients might occur on average within the first few days of admission, which suggests that the infection was acquired in the outpatient setting or perhaps during a previous hospitalization.

Materials and Methods

We performed a retrospective cohort study by using inpatient electronic medical records to determine the incidence of CDAD in hospitalized IBD patients. We obtained data from the Barnes-Jewish-Christian clinical data repository, a medical informatics industry-standard relational database containing information on diagnoses, International Classification of Diseases ninth revision admission and discharge codes, demographics, and laboratory test results for all admissions to Barnes-Jewish Hospital, a large tertiary care medical center, during a 7-year period from January 1, 1998-December 31, 2004. Demographic information available included age, gender, and race. Data extracted from this database were merged with results of positive *C difficile* laboratory tests linked by admission registration numbers.

All subjects aged 10 years and older and both medical and surgical admissions were included. We used discharge International Classification of Diseases ninth revision codes to identify patients hospitalized with the primary diagnoses of CD and UC. In the event that an admission was coded for both CD and

Abbreviations used in this paper: **aOR, adjusted odds ratio; CDAD, *Clostridium difficile*-associated disease; CI, confidence interval; LOS, length of stay.**

1542-3565/07/$32.00
doi:10.1016/j.cgh.2006.12.027

UC (n = 44), we reviewed medical records, including available history, radiography, and pathology, to clarify the diagnosis. Of these, 5 cases were indeterminate for either CD or UC and were excluded. We assigned each of the remaining 39 cases to either the CD or UC groups. Information on antibiotic and immunosuppressive medication use before admission was not available.

The primary analysis compared CDAD incidence between non-IBD and all IBD admissions. All IBD was further subanalyzed as CD and UC versus the non-IBD group. To determine the incidence of CDAD in all groups, we calculated the ratio of number of admissions with a positive *C difficile* test result to the total number of admissions for each group, both by year and by all years combined, reported as cases per 1000 admissions. In June 2002, the hospital stool laboratory test for *C difficile* converted from a traditional cell cytotoxic culture assay that is sensitive to toxin B only to a *C difficile* toxin A/B II Enzyme Immunoassay (Techlab, Inc, Blacksburg, VA), which detects toxins A and B. We assumed that a positive stool test for *C difficile* by either method indicated infection with this organism. Positive *C difficile* test results that might have occurred before admission were not available. However, for all admissions in the database, any testing performed in the emergency department before hospitalization was captured in our data. Time, in days, to a positive *C difficile* test result was calculated by subtracting the date of admission from the first date of test positivity. After the first positive *C difficile* test result, any additional positive tests for the same admission were not included in the analysis. In both the UC and CD groups, time to test positivity was not normally distributed; therefore, a Mann-Whitney *U* test was used to compare time to test positivity between IBD and non-IBD cases. We calculated total length of stay (LOS), in days, by subtracting the date of admission from the date of discharge. LOS was not normally distributed and therefore was compared among the groups by using a Mann-Whitney *U* test. In addition, we calculated the LOS at risk, which is defined as number of days of hospitalization until a *C difficile* infection is diagnosed and excludes all subsequent days of hospitalization after infection is detected. For admissions in which no CDAD occurred, LOS and LOS at risk are equivalent. We analyzed the data first by using LOS and then repeated the analysis by using LOS at risk, but results were similar for both. Only results with LOS at risk are reported hereafter.

Because recurrent *C difficile* infection might cause hospital readmission, we reviewed cases to ascertain whether the same subject was responsible for multiple admissions and repeat *C difficile* test positivity. We defined recurrent CDAD as readmission with a positive *C difficile* toxin within 60 days of a prior admission and reported results as percent of total CDAD cases for each group.

We used Pearson χ^2 testing and performed a univariate analysis to estimate the relative risks for *C difficile* infection among the groups. We then performed a multivariate analysis with logistic regression modeling to calculate odds ratios for *C difficile* infection, adjusting for other factors. For the multivariate analysis, we performed a nested case-control study in which 4 controls were chosen randomly for each *C difficile* positive case. We included all admission types. Matching of controls to cases, for example, by age or year of admission, was not performed to adjust for these variables of interest in the regression equation. We excluded all cases of repeat and recurrent *C difficile* positivity for any individual to maintain independence of events. For the logistic regression, the primary outcome of interest was a *C difficile* positive test result. The primary risk factor of interest was a diagnosis of IBD. UC and CD were assessed individually as risk factors in a separate analysis. We analyzed the following additional risk factors for CDAD as covariates in our regression equations: sex, defined as male or female; race, dichotomized as white or other; age, divided into 3 categories; Charlson score[8,9] of medical comorbidity, divided into 4 categories; year of admission; and LOS at risk, categorized into 6 time intervals. We tested individual Charlson comorbidities in a separate model along with other co-factors as defined above.

For multiple testing, a P value of $<.01$ was considered significant. The 95% confidence interval (95% CI) was provided where appropriate. We performed all analyses with statistical software packages SPSS version 13.1 (SPSS Inc, Chicago, IL) and EpiInfo version 3.3.2 (Centers for Disease Control and Prevention, Atlanta, GA). The study was approved by the Institutional Review Board at Washington University School of Medicine.

Results

For the 7 years studied, 357,242 admissions met inclusion criteria and were available for analysis. Demographic characteristics of the groups and a summary of *C difficile* testing results are shown in Table 1. Compared with the non-IBD population, admissions for both CD and UC were of younger age and had a higher proportion of white race. The UC group had a higher percentage of men compared with the non-IBD group. Although the mean LOS at risk was similar among the groups, a small difference of less than 1 day was detected between the all IBD and non-IBD groups, and this difference was statistically significant. Median LOS at risk was higher in the IBD groups. The median times from admission to a positive *C difficile* test result for CD, UC, and non-IBD patients were 0.8, 0.5, and 4.0 days, respectively, and this difference was statistically significant. For all IBD admissions, 63% of *C difficile* infections were positive within 48 hours of admission. In the non-IBD group, only 37% of CDAD diagnoses occurred within 48 hours of admission. Recurrent CDAD occurred in only 4 (0.1%) admissions for UC and CD during the study period. In contrast, recurrent *C difficile* infection was noted in 8.7% of cases in the non-IBD population.

For all years combined, the incidences of CDAD in the non-IBD, all IBD, CD, and UC groups are shown in Figure 1. In univariate analysis, the relative risks for *C difficile* infection compared with non-IBD admissions were 1.9 (95% CI, 1.5-2.4), 1.3 (0.9-1.8), and 3.2 (2.4-4.3) for all IBD, CD, and UC, respectively. Compared with CD, the relative risk for CDAD in UC was 2.5 (1.6-4.0). Combining all groups and years, the overall rate of CDAD in our cohort was 12.4/1000 admissions. The incidences of CDAD by year for all 4 groups are shown in Figure 2. Comparing 1998 and 2004 data, CDAD incidence approximately doubled in the non-IBD group (8.5 to 15.9/1000 admissions) and CD group (9.5 to 22.3/1000 admissions) and tripled in UC group (18.4 to 57.6/1000 admissions; χ^2 test for trend = 3.8; $P = .05$).

The results of our multivariate logistic regression analysis to estimate the risk of *C difficile* infection are shown in Table 2. After elimination of repeat cases and controls and exclusion as a result of missing data, 16,759 events were available for analysis in our nested case-control study. IBD was an independent

Table 1. Characteristics of Study Groups, Barnes-Jewish Hospital, 1998–2004

	Non-IBD (n = 353,845)	All IBD (n = 3397)	CD (n = 2331)	UC (n = 1066)
Age, y				
Mean (range)	54 (10–109)	46[a] (10–99)	45[a] (10–99)	48[a] (15–92)
Male gender, %	41	42[a]	40[b]	47[b]
White race, %	62	84[a]	83[a]	87[a]
LOS at risk (days)				
Mean ± standard deviation	5.7 ± 8.7	5.8 ± 5.8[a]	5.6 ± 5.5[a]	6.4 ± 6.3[a]
Median	3.4	4.3	4.1	4.9
C difficile stool test results				
No. positive (%)	4363 (1.2)	79 (2.3)	37 (1.6)	42 (3.9)
Mean positive per year (range)	623 (412–863)	11.3 (2–24)	5.3 (2–15)	6.0 (0–11)
No. with relapse (%)	379 (8.7)	4 (.05)	3 (.08)	1 (.02)
Median time to positive test (*days*)	4.0	0.8[a]	0.9[a]	0.5[a]

NOTE. Paired comparisons (χ^2, Mann–Whitney *U*) made with non-IBD as reference.
[a]$P < .001$.
[b]$P < .02$.

risk factor for CDAD after adjustment for age, sex, race, Charlson score, year of admission, and LOS at risk, with a nearly 3-fold increased risk for *C difficile* infection compared with the non-IBD group. Both CD and UC demonstrated increased risk for CDAD in a separate multivariate analysis, but the adjusted odds ratio (aOR) was substantially higher in UC. A modest increased risk was observed with male sex and white race. Increasing age and comorbidity score increased the risk of *C difficile* infection in a dose-dependent fashion. With regard to individual Charlson comorbidities, the following were found to be significantly and independently associated with *C difficile* infection: congestive heart failure, chronic obstructive pulmonary disease, mild liver disease, diabetes, chronic renal failure, leukemia/lymphoma, human immunodeficiency virus, and metastatic cancer.

There was a trend toward increasing risk for CDAD with increasing year of admission (χ^2 test for trend = 170, $P < .001$), although not every year was associated with a statistically significant aOR. Year 2002 demonstrated the highest risk, and this corresponded to the year of highest absolute incidence for all groups apart from the UC group, in which the incidence increased in each of 2 subsequent years. There was also an observed pattern of increasing aOR for CDAD with increasing LOS at risk.

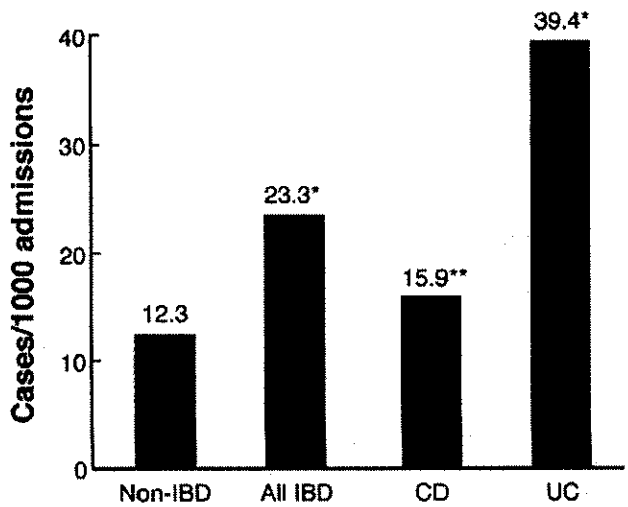

Figure 1. Incidence of CDAD at Barnes-Jewish Hospital based on 7 years of data combined. There was a significantly higher incidence of *C difficile* infection in all the IBD and UC groups. *$P < .001$ for all IBD and UC compared with non-IBD; **$P = .12$ for CD compared with non-IBD.

Discussion

Our results showed that the incidence of CDAD in IBD has increased during the 7 years for which data were available. As seen in Figure 2, the observed increase in CDAD incidence demonstrated in CD mirrors that of the non-IBD population. In contrast, the incidence of CDAD in UC in absolute terms was higher than that of the other 2 groups for each year except 1999 and also exhibited a faster rate of increase during the study period. This result is reflected in the estimates of risk for CDAD, which indicate that for all years combined, CDAD is significantly more common in UC than in CD and non-IBD patients. In addition, our results demonstrate an increase in risk with increasing year of admission on multivariate analysis.

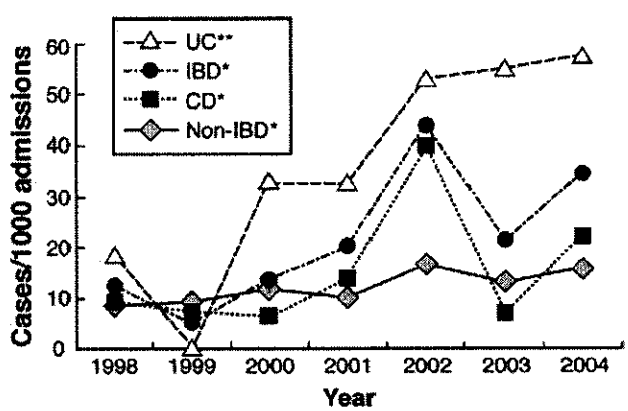

Figure 2. Annual incidence of CDAD at Barnes-Jewish Hospital from 1998–2004. Incidence of *C difficile* infections increased most appreciably in the non-IBD and all IBD groups. The UC group appears primarily to account for the increase observed in the IBD population as a whole. *$P < .001$ and **$P = .08$ comparing first and last 3 years of data.

Table 2. Multivariate Analysis of Risk Factors for a *C difficile* Positive Stool Test Result

Factor	Units	aOR[a]	95% CI
Sex	Male	1.1	1.0–1.2
Race	White	1.3	1.2–1.4
Age	Years		
<45		Reference	
45–64		1.5	1.3–1.7
≥65		2.1	1.8–2.3
Comorbidity index	Charlson score		
0		Reference	
1		1.4	1.3–1.6
2–3		2.0	1.8–2.2
≥4		2.6	2.1–3.3
Year of admission			
1998		Reference	
1999		1.1	0.9–1.3
2000		1.4	1.1–1.6
2001		1.1	0.9–1.3
2002		1.7	1.5–2.1
2003		1.4	1.2–1.7
2004		1.6	1.3–1.9
LOS at risk	Days		
<2.0		Reference	
2.0–3.9		0.3	0.2–0.4
4.0–6.9		0.4	0.3–0.5
7.0–13.9		0.9	0.7–1.0
14.0–27.9		1.8	1.5–2.1
≥28.0		2.4	1.9–3.0
IBD		2.8	2.0–4.0
CD		2.1	1.3–3.4
UC		4.0	2.4–6.6

[a]For each risk factor, $P < .01$ except years of admission 1999, 2001, and LOS at risk 7.0–13.9, $P < .3$.

The appreciable increase in the CDAD rates in all groups between 2001–2002 might be partly explained by the fact that the enzyme immunoassay test for *C difficile* was adopted in 2001.

A number of reasons for the increasing incidence of CDAD in the general hospitalized patient are postulated. For example, increased awareness and testing for *C difficile* infection might contribute to the increasing rates of CDAD observed. Also, lower specificity testing with enzyme-linked immunosorbent assays might increase the false-positive yield compared with traditional cytotoxic culture testing. Use of gastric acid lowering medications has been implicated in community-acquired infections as well.[10] Lastly, McDonald et al[11] have recently reported the emergence of an epidemic strain of *C difficile* that confers greater virulence and mortality and can cause outbreaks of CDAD in hospitalized patients.

In the current study we have found that IBD patients have a higher incidence and risk of CDAD compared with the non-IBD population. IBD patients might possess unique features that result in a higher probability of diagnosis or add to their risk of CDAD. Compared with the non-IBD population, patients with IBD are more likely to be admitted with symptoms of diarrhea and thus might be subjected to greater amounts of testing for *C difficile*, particularly within the first few days of admission, as a part of the diagnostic evaluation for diarrhea. Furthermore, IBD theoretically predisposes patients to CDAD because IBD is characterized by a derangement of the inflammatory response in the gastrointestinal tract. Studies have shown that CDAD symptoms are caused by a robust mucosal inflammatory response (mediated by interleukin-8, macrophage inflammatory protein-2, substance P, tumor necrosis factor-α, and others), not from bacteremia with *C difficile*.[4] Use of immunosuppressive agents, which prior studies have shown are associated with fulminant *C difficile* colitis,[1] might also confer a risk toward CDAD in IBD. In immunocompromised patients, such as those with IBD, disease could occur without exposure to *C difficile* in the hospital setting. Finally, it is possible that the IBD population is infected by a different strain of *C difficile* than in the non-IBD population, although in the current study, strain data were not available because culture of *C difficile* is not routine.

In both univariate and multivariate testing, IBD patients were shown to have an increased risk for *C difficile* infection diagnosed during the hospital course. The increased risk with advancing age and higher comorbidity seen here agrees with previous studies. After adjusting for factors for which we had data, our study showed that UC patients have a significantly higher risk of CDAD compared with both the CD and non-IBD groups. A lower rate of CDAD in CD patients compared with UC might be explained by outpatient metronidazole use in CD, although preadmission antibiotic usage information was not available in our study. The increased risk of CDAD in IBD shown here appears attributable primarily to a higher risk observed in UC in particular. It is unclear whether the CD patients have a lower risk of CDAD compared with UC as a result of greater use of metronidazole, or whether UC patients possess additional characteristics that contribute to an increased risk beyond that of CD and the general population. The role of immunomodulators and biologics in this patient group, for example, should be explored in future investigations.

The doubling rate of CDAD during a period of 7 years agrees with the rates reported during similar time periods in prior studies.[12,13] However, the absolute incidence varies compared with other studies. The incidence of CDAD in hospitalized patients in North America has been reported to be between 3.4–8.4 cases/1000 admissions.[14] Our hospital data showing an overall rate of 12.4 cases/1000 admissions reflect a higher incidence of CDAD than previously reported. The difference observed could be explained by differences in the populations studied. For example, the current study focused on a single, tertiary care center in which CDAD rates are likely greater than those reported from non-tertiary care hospitals. Moreover, CDAD rates are reported to vary widely even among tertiary care centers in the United States.[15] Large variations in the incidences of CDAD reported might also be attributable to the differences in the characteristics of the study sites examined or lack of agreement on the surveillance definitions used for CDAD. Most important perhaps is that other studies, which tend to concentrate on nosocomial *C difficile* infection, exclude cases within 48 hours of admission. Such cases were incorporated into the analysis of all groups in our study, given the hypothesized increased likelihood of an early diagnosis of *C difficile* in hospitalized IBD patients.

We found that the time from hospital admission to *C difficile* positivity occurred significantly earlier in patients with IBD than in those without IBD. There was a statistically significant difference among the groups with regard to mean LOS at risk;

however, in clinical terms, this small difference of less than 1 day would not be expected to profoundly impact the risk of CDAD. In the non-IBD population, median time to *C difficile* positivity was day 4 of hospitalization, which corresponds to previous studies indicating that risk of CDAD increases with increasing LOS.[16] In contrast, *C difficile* positivity in both CD and UC occurred predominantly within the first 24 hours of hospitalization, which is generally regarded as insufficient time for a nosocomial infection to arise. In these cases *C difficile* infections probably represent a cause for admission. This has been observed clinically when CD and UC patients admitted for diarrhea are found to be *C difficile* positive and improve with antibiotic therapy. We cannot exclude the possibility that some *C difficile* infections within 24 hours in IBD patients were acquired during recent admissions to other hospitals, although we would expect that this might occur to a similar extent in the non-IBD population as well. Furthermore, a recent study[17] reported that 76% of *C difficile* infections in IBD patients were detected in the outpatient setting, which lends support to our conclusion that a large proportion of IBD patients acquire infection before hospitalization, or that many of these infections result in hospitalization.

Strengths of our study include its large size and the multiple years of data available. The low rate of recurrent CDAD in the CD and UC groups eliminates the possibility that a small number of recurrent cases could account for the increased incidence in IBD. Limitations of our study include lack of data on antibiotic and immunosuppressive medication use before admission. Although CD patients are more likely to receive metronidazole as part of their therapeutic regimen, the number of CD patients who had received this or another antibiotic before admission is unknown. Analysis of antibiotic usage in these groups would be helpful in future studies to determine whether antimicrobials account for the observed higher incidence of CDAD in IBD. Some cases diagnosed as UC might actually represent indeterminate colitis or Crohn's colitis. Reassignment of diagnoses among subjects in the UC group could alter the observed difference in CDAD incidence between CD and UC. Another limitation stems from the fact that only positive *C difficile* test results were recorded in the database used in this study. Compared with the non-IBD patient, CD and UC patients are more likely to be hospitalized for diarrhea and thus are more likely to be tested for CDAD, which introduces the possibility of detection bias. Because we lacked data on the total number of *C difficile* tests, both positive and negative, ordered per year, we cannot exclude the possibility that increasing testing for CDAD in general contributed to the observed increase in *C difficile* infection rate.

Conclusions drawn from this study might be further limited because, in general, interpreting the results of *C difficile* testing can be confusing, particularly in the IBD patient. It is conceivable, for example, that some positive test results for *C difficile* do not in fact represent CDAD. Arguing against this is the fact that testing for *C difficile* is usually reserved for those patients with clinically significant diarrhea and is not performed on solid stool. Nevertheless, false-positive testing for *C difficile* might partially explain increasing CDAD rates. Repeated testing for *C difficile* during the same admission could result in a larger number of false-positive results, but as shown in this study, test positivity in IBD patients occurs early in the hospital course and thus would obviate repeat testing. Finally, because clinical disease might be absent despite positive *C difficile* assay and culture results, it is difficult to ascribe diarrhea to this organism in hospitalized patients with multifactorial causes for diarrhea and in IBD patients who might manifest diarrhea as a sign of worsening underlying disease.

In summary, we have shown in this study of hospitalized patients that the incidence of *C difficile* infection in IBD has increased and is higher than that in the non-IBD population. IBD patients appear to be at higher risk for CDAD than non-IBD patients. Infection occurs earlier during the hospital course and might be primarily community-acquired. The risk of *C difficile* infection in UC is significantly higher than in the non-IBD population, and the incidence appears to be increasing at a faster rate. On the basis of these results, clinicians should maintain a high index of suspicion for CDAD in IBD and in UC in particular. A greater emphasis on possible *C difficile* infection in the outpatient setting might be warranted. Additional studies are necessary to further explain the findings of this study. The role of antibiotics, those that predispose to and protect against CDAD, should be investigated because this factor could account for the differences observed here. A comparison of CDAD rates between IBD and non-IBD patients hospitalized primarily for diarrhea might add additional insight into the apparent increased risk of CDAD in IBD. Last, a similar study of incidence of *C difficile* infection in CD and UC outpatients might complement or oppose the findings of this study.

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Supported by a grant from the Centers for Disease Control and Prevention (#UR8/CCU715087-06/1).