ORIGINAL ARTICLE

Clostridium difficile Colitis: Reduced Time to Diagnosis in a Community-Based Outpatient Setting Between 1997 and 2004

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Abstract

Objective: We studied antibiotic use prior to the onset of *Clostridium difficile* colitis (CDC) and time interval between onset of gastrointestinal symptoms and diagnosis for two historical time periods with separate comparisons for inpatients and outpatients to determine whether time to diagnosis had decreased and whether previous metronidazole use is associated with CDC.

Method: We performed a retrospective chart review of adult patients (those 18 years or older) with positive findings on *Clostridium difficile* (CD) stool toxin tests performed at a Kaiser Permanente Southern California medical center. Independent assessments were compared for 1997–1998 and for 2004 time periods. These assessments used similar enrollment and exclusion criterion. Study populations were evaluated for previous antibiotic use and to determine time from clinical presentation of symptoms to diagnosis of CDC during each of the time periods, with assessments made separately for inpatients and outpatients.

Results: Findings showed a reduction in the average time from symptom presentation to diagnosis among outpatients with CDC from 17 days in the first time period (1997–1998) to ten days during the second time period (2004). No significant difference in the average time from symptom presentation to diagnosis of CDC was evident among inpatients (5.33 days for 1997–1998 and 6.00 days for 2004). Multiple antibiotic use prior to diagnosis of CDC was evident among both outpatients and inpatients in this study. Metronidazole had been used prior to the onset of CDC in approximately 15% of cases.

Conclusion: The time from symptom onset to a CDC diagnosis decreased by seven days between the 1997–1998 and 2004 time periods among outpatients in this health care setting. Previous metronidazole use appeared to be associated with some cases of CDC.

Introduction

Clostridium difficile–associated disease has been identified as an important cause of morbidity and mortality in the US.[1–3] Most studies have focused on inpatients and health care–associated infections, or nosocomial infections. There have been previous outpatient studies of *Clostridium difficile* colitis (CDC),[4–6] although recent outpatient studies have not included findings for inpatients. This study focused on previous antibiotic use and the time from onset of gastrointestinal (GI) symptoms to diagnosis, comparing time to diagnosis during two historical time periods among inpatients and outpatients. This study did not evaluate health care–associated infections, treatment for CDC, appropriateness of antibiotic usage before the onset of CDC, asymptomatic patients, or clinical recurrences of CDC.

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Methods

Independent retrospective assessments were performed using data from 1997–1998 and 2004 time periods. Study entry criteria required positive stool *Clostridium difficile* (CD) toxin test results and antibiotic use during the one-month period prior to diagnosis

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of CDC. The Southern California Kaiser Permanente (KP) regional laboratory performed CD stool toxin tests assessed in this study. The laboratory supplied a list of all KP patients who were screened for CD toxins; the list also included patients with negative results. The study evaluated previous antibiotic history and classified study groups on the basis of the setting in which and the time at which they received exposure to antibiotics before CDC symptoms, as well as the setting in which each study subject first experienced CDC. Data collected included patient age, patient sex, antibiotics prescribed prior to CDC diagnosis, inpatient or outpatient status, time between antibiotics and GI symptoms, time between symptoms and evaluation appointment, and time between symptoms and CDC diagnosis.

The major risk factor for CDC is any previous antibiotic use, including metronidazole.[7,8]

Study subjects were divided into four clinical groups that included patients exposed to antibiotics as inpatients during the one month prior to positive findings on a CD stool test and whose disease was diagnosed when they were inpatients (In/In), patients exposed to antibiotics as outpatients whose disease was diagnosed when they were outpatients (Out/Out), patients exposed to antibiotics as inpatients whose disease was diagnosed when they were outpatients (In/Out), and patients exposed to antibiotics as outpatients whose disease was diagnosed when they were inpatients (Out/In). Exclusion criteria included recent residence in a skilled nursing facility and treatment provided by a non-KP health care provider. The primary reason for these two exclusions was the difficulty in obtaining accurate and complete data under those conditions. The studies were performed as pharmacy-student projects toward a Loma Linda School of Public Health master of public health degree. A physician advisor (Charles Salemi) provided supervision for the projects.

Table 1. 1997–1998 study data for In/In and Out/Out groups

Group	No. of patients	Interval (days) from symptoms to diagnosis
In/In	39	5.33
Out/Out	26	17.24

t-test: $p < .0001$.

Table 2. 2004 study data for In/In and Out/Out groups

Groups	No. of patients	Interval (days) from symptoms to diagnosis
In/In	38	6
Out/Out	28	10

t-test: $p < .00001$.

Statistical Methods

Categoric variables' frequencies were tabulated. An unpaired *t*-test was performed for the continuous variable of the interval between the onset of symptoms and diagnosis by positive results on a CD stool toxin test. A statistically significant p value of <.05 was selected.

Data

Table 1 shows the data from the two studies performed in 1997–1998. The initial study showed a 12-day interval from onset of symptoms to diagnosis of CDC when comparing inpatients to outpatients. This interval decreased to four days in the 2004 study (Table 2). The outpatient interval to diagnosis was 17 days in 1997–1998 and decreased to ten days in the 2004 study. The distribution of all of the cases of CDC is shown in Table 3. The only groups analyzed for this study were the In/In and Out/Out groups. The data comparing inpatients to outpatients were statistically significant at $p < .05$ using unpaired *t*-test analysis. The data (Table 4) shows that metronidazole was given in approximately 15% of the cases prior to the onset of CDC. The total and results of medical center CD stool toxin tests from 1999 through 2004 are shown in Table 5. There was an increase in the total number of stool CD toxin tests ordered, but the percentage of positive test results varied by a nonsignificant amount over the time interval.

Table 3. Total *Clostridium difficile* colitis cases

Group	No. of patients
In/In	77
Out/Out	54
In/Out	95
Out/In	50

Discussion

The major risk factor for CDC is any previous antibiotic use, including metronidazole.[7,8] Our study documents that metronidazole was used before the onset of CDC in >14% of cases. This was unusual because an effective treatment regimen for CDC includes the use of metronidazole. Metronidazole resistance to CD has not been documented during the study period.[9] Metronidazole can be used in conjunction with other antibiotics for treating selected infections or as a sole agent, and this difference could be a risk factor for CDC.

This study did not evaluate metronidazole prescription practices. For example, there have been changes in clinical indications for metronidazole use over the course of the study, particularly for empiric coverage

Table 4. Metronidazole use before the onset of *Clostridium difficile* colitis for two study periods

Study	Total no. of patients	No. of patients taking metronidazole	Percentage of patients taking metronidazole
1997–1998	44	7	16
2004	173	25	15

Table 5. Medical center *Clostridium difficile* stool toxin tests

Year	Total no. of tests	No. of tests with positive results	Percentage of tests with positive results
August 1995–December 1996	875	60	7
January 1997–December 1998	1864	197	11
1999	1340	120	9
2000	1518	150	10
2001	1781	220	12
2002	2490	366	15
2003	2939	410	14
2004	3119	395	13

for anaerobic organisms and for eradication of *Helicobacter pylori*. The clinically important issue is that health care providers might not consider the diagnostic possibility of CDC if metronidazole was previously used, especially as a sole antibiotic. The importance of this finding is to make providers aware that the prior use of metronidazole does not eliminate the possibility of CDC, a finding noted in other studies as well. We did not analyze other specific antibiotics in this study; reports in the published literature have examined other specific antibiotics and their association with CDC.

The results of the two studies showed that there was a significant decrease in the time interval to outpatient diagnosis of CDC, from approximately 17 days in 1997–1998 to 10 days in 2004. The inpatient interval did not significantly change between the two studies. The results of the 1997–1998 study were not presented or reported to the medical staff at our medical center. The improvement in CDC data may be attributable to increasing knowledge among health care providers of the clinical importance of CDC, increasing knowledge of the importance of previous antibiotic usage, and increased attention to patients' access to health care services.

The difference in the time to CDC diagnosis between inpatients and outpatients may be attributed in part to the different level of care provided in the hospital. Inpatient care is rendered in a highly standardized environment, especially with regard to prescribed medication, with rigorous documentation of medication use being the norm. Detailed documentation of vital signs and health status, including the presence of diarrhea, are kept in the medical record as part of nursing notes and progress notes. The nursing service plays a critical role in providing this clinical information. In addition, there is the practice of empiric use of metronidazole at the onset of severe diarrhea and when a stool CD toxin test is ordered. We did not include this variable in the analysis of the data but suggest that it be considered in future studies of CDC.

Other patient-related factors can affect the timing of diagnosis and treatment of CDC. Patients may not report self-medication with antibiotics to their primary health care providers. Patient delay in seeking care should also be considered, because the onset of CDC symptoms may be attributed to other factors such as food poisoning rather than the GI symptoms being associated with previously taken antibiotics. Health care provider issues that could increase the time to diagnosis might include obtaining an incomplete history regarding previous antibiotic use, omission of specific stool CDC toxin tests, and lack of familiarity with the diagnosis of CDC in the outpatient setting.

Patients may not report self-medication with antibiotics to their primary health care providers.

Timeliness of access to outpatient medical services improved in our medical center between 1997 and 2004, for two possible reasons: 1) Significant national attention has been directed at patient access and availability of health care services, and there are now national benchmark standards for this area of health care; and 2) KP dedicated significant additional resources to improve access to and availability of health care to their patients between 1997 and 2004.

Conclusion

The time to diagnosis of CDC decreased by seven days in the outpatient setting in a community-based medical center between the years of 1997 and 2004,

possibly partly because of efforts to increase patient access to and availability of health care. Also, previous metronidazole usage can be associated with CDC. ❖

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Never an Accident

Quality is never an accident;
it is always the result of high intention, sincere effort,
intelligent direction and skillful execution;
it represents the wise choice of many alternatives.

— *Anonymous*