BRIEF REPORT

Diagnostic and Treatment Delays in Recurrent *Clostridium difficile*–Associated Disease

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BACKGROUND: Because *Clostridium difficile*–associated disease (CDAD) is primarily an inpatient issue, hospitalists are at the forefront of the timely diagnosis and treatment of patients with this disease.

DESIGN: The study was a retrospective cohort of all inpatients with CDAD at Brigham and Women's Hospital from 1997 to 2004 in order to determine the time to diagnosis and treatment in initial and recurrent episodes of disease.

RESULTS: The mean time to sampling, between 2.09 and 2.24 days, was not significantly different between initial and recurrent CDAD hospital episodes. The mean time to treatment (from symptoms and sampling) was shorter in recurrent episodes but was still 2.5 days.

CONCLUSIONS: Patients with recurrent disease were more likely to be treated earlier but not diagnosed earlier than those with initial disease. Because both groups had significant diagnostic and treatment delays, this is an area in which hospitalists can have a major impact on patient care. ***Journal of Hospital Medicine* 2008;3: 156–159.** © *2008 Society of Hospital Medicine.*

KEYWORDS: *Clostridium difficile,* patient isolation, recurrent disease, hospitalists.

Clostridium difficile–associated disease (CDAD) is a well-known complication of hospitalization and is the most frequently identified cause of nosocomial diarrhea that hospitalists encounter. Despite widespread epidemiologic attempts to control the disease, its prevalence and clinical severity appear to be increasing.[1] The resulting social and economic consequences are profound. The estimated 3 million inpatient cases of CDAD a year result in an average increase in the length of stay of 3.6 days at a cost in inpatient health care of more than $1 billion.[2]

Early diagnosis of index cases is crucial. A diagnostic delay can result in a treatment delay for the index case, as well as in a delay in implementing isolation procedures to prevent horizontal transmission. Acquisition of CDAD is time dependent and occurs in 20% to 30% of hospitalized patients at a rate of approximately 8% per week.[3,4] This transmission is primarily a result of environmental contamination with CDAD spores, found on 59% of the hands of hospital personnel caring for infected patients, in 49% of rooms of symptomatic patients, and in 29% of rooms of asymptomatic carriers.[5] Despite the need for early diagnosis, a study from the United Kingdom documented that the average time from the onset of diarrhea to sampling of CDAD patients is 4.7 days.[6] An additional challenge for early diagnosis is the delay in microbiological confirmation of CDAD in a suspected patient. Cytotoxic assays, which have become the standard diagnostic technique for CDAD, exhibit excellent sensitivity and specificity but have a

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lengthy processing time, between 2 and 4 days. Although antigen detection assays can be rapidly performed, many have inadequate sensitivity and specificity.[7]

These issues of diagnostic and treatment delays are compounded in patients with recurrent CDAD. As many as 15%-35% of patients with an initial CDAD infection will experience a recurrence, usually within 2 months. At least half these infections are a result of reinfection, not relapse.[8] This implies that early detection and strict isolation of infected patients is essential for reducing the exposure of at-risk patients to the disease. There is evidence that the burden of patients on the same ward simultaneously having CDAD increases a patient's risk of acquiring the disease.[9] It is currently unknown if recurrent CDAD cases are diagnosed or treated earlier than initial cases. If not, this is a potentially important patient population for hospitalists to target for aggressive containment strategies. This study sought to determine the mean time to sampling and treatment in patients with recurrent CDAD infection compared with those in patients who are initially infected.

Design

The study cohort consisted of all adult patients more than 18 years old with CDAD (by ICD9 code) who had been hospitalized at Brigham and Women's Hospital between 1997 and 2004. Retrospectively, patients were identified through the Partners Healthcare Research Patient Data Repository (RPDR). The RPDR is a centralized clinical data registry that gathers data from various hospital legacy systems and was used to determine the patient demographics and first date of treatment (with vancomycin or metronidazole). Medical and microbiologic records were reviewed to determine the dates of cytotoxic assay submission and symptom onset. Symptoms were defined as diarrhea, abdominal pain/cramping, or radiological/colonoscopic evidence of colitis. Recurrence was defined as any repeat inpatient CDAD diagnosis within 2 months (regardless of admission diagnosis). Baseline characteristics in the recurrence and no-recurrence populations were compared by the 2-sided Student *t* test or the chi-square test (for continuous and categorical variables, respectively). Mean time from symptom to sampling, from symptom to treatment, and from sampling to treatment were compared between initial and recurrent disease episodes by the 2-sided Student *t* test. All P values $< .05$ were considered significant. Institutional review board approval was obtained by Partners Healthcare.

TABLE 1
Demographics of Patients with and without Recurrent Disease

Characteristic	Patients without recurrent disease (n = 1158)	Patients with recurrent disease (n = 151)	*P* value
Sex (% male)	45%	45%	.98
Age (mean)	68.3 years	69.9 years	.72
Race (% white)	80%	80%	.97
Language (English)	94%	92%	.83

RESULTS

Between 1997 and 2004 there were 1309 patients with an ICD9 code for CDAD, 151 of whom (12%) had a recurrence. Of these, 125 had 1 recurrence, 23 had 2 recurrences, and 3 had 3 recurrences. There were no significant differences between the groups in basic demographics (Table 1). The mean time to sampling was not significantly different between initial and recurrent CDAD hospital episodes (Table 2). However, the mean time to treatment (from symptoms and sampling) was shorter in recurrent episodes (Table 2). From 1997 to 2004 there was no significant reduction in time to sampling, but there was a significant reduction in time to treatment, from 3.89 days (1997-2000) to 2.30 days (2001-2004), $P = .0012$.

DISCUSSION

Clostridium difficile–associated disease (CDAD) has become a significant nosocomial infection in medical institutions, and recurrent CDAD is emerging as a disease of concern for hospitalists. Diagnostic delays represent a major epidemiologic problem, resulting in both delay of treatment delay of the index case and delay in implementing isolation procedures to prevent horizontal transmission. In this study, patients with recurrent disease did not have stool collected any earlier than did patients with their initial episode of CDAD, and these diagnostic delays did not change in successive eras. Recurrent disease patients did receive treatment earlier than did patients with initial episodes. Although this empiric treatment strategy is encouraging and likely reflects heightened awareness of the disease over time, the 2.5-day span from symptoms to treatment is still a clinically significant delay.

TABLE 2
Mean (Range) Time to Sampling and Time to Treatment in Initial and Recurrent Episodes of Disease

	First episode (n = 1309)	Recurrence (n = 180)*	*P* value
Symptoms to sampling	2.24 days (1-17 days)	2.09 days (1-16 days)	0.700
Symptoms to treatment	3.64 days (1-18 days)	2.52 days (1-19 days)	0.024
Sampling to treatment	3.76 days (1-19 days)	2.57 days (1-19 days)	0.006

*125 Patients with 1 recurrence (125 episodes) + 23 patients with 2 recurrences (46 episodes) + 3 patients with 3 recurrences (9 episodes) = 151 patients with 180 recurrent episodes.

Also of concern is the range of time from symptoms to treatment, as long as 19 days in the recurrent treatment group. Although most patients were treated within 1-2 days, this variability represents the burden of infectious patients with the potential for infecting others. Targeting recurrent CDAD populations for early diagnosis, treatment, and isolation would almost certainly reduce the morbidity associated with horizontal transmission rates.[9]

This study had several limitations. Our data found a lower incidence of recurrent CDAD than previously published in the literature. This can be accounted for by the identification of cases by ICD9 code, which previously has been documented to underestimate true disease.[10,11] We also were not able to capture recurrent episodes in outpatients or episodes that occurred after the 2004 cohort, which underestimated the true frequency of recurrence. At worst, this underestimation could bias the results toward the null hypothesis. An additional limitation of the study was the assumption that time to treatment was accurately reflected by time to prescription of either vancomycin or flagyl. Some patients may have been "treated" by suspending treatment with the offending antibiotic along with watchful waiting, which is a reasonable strategy for patients with mild disease and is endorsed by the American College of Gastroenterology and the Society for Healthcare Epidemiology of America.[12,13] This would overestimate time to treatment for those individuals and would make time to treatment appear longer, but would not affect time to sampling. In addition, the symptoms collected from chart review were assumed to be a result of the patient's CDAD, but there is a chance that these symptoms such as diarrhea, abdominal pain, and cramping may have been a result of a different diagnosis. These data were also limited to a cohort from a single institution and may not reflect the patient characteristics or practice patterns at other institutions.

In conclusion, CDAD is a major contributor to morbidity from nosocomial infections, and recurrent CDAD patients are a likely source of horizontal disease transmission. This study documented that there are significant diagnostic and treatment delays, even in populations with recurrent disease. It is especially important that hospitalists take measures to improve the early diagnosis, treatment, and isolation of these patients in order to improve these deficiencies in care.

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