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The Impact of *Clostridium difficile* on a Surgical Service

A Prospective Study of 374 Patients

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Objective
To evaluate the epidemiology of *Clostridium difficile* colitis (CDC) in a subset of patients admitted specifically to a surgical service.

Summary Background Data
CDC is an increasingly prevalent nosocomial infection that can prolong hospitalization and adversely affect patient outcome. Although this disease has been investigated extensively in patients admitted to medical services, the incidence and risk factors for the development of this disease in patients admitted to a surgical service have not been studied.

Methods
Over a 5-month period, 374 patients admitted to the general, vascular, thoracic, and urologic surgery services were monitored for the development of symptomatic CDC (defined as >3 bowel movements per 24 hours and a positive cytotoxin assay or culture).

Results
Twenty-one patients developed CDC (incidence, 5.6%). Factors that independently predisposed to infection included admission from a skilled care facility, use of the antibiotic cefoxitin, and an operative procedure for bowel obstruction. Other factors associated with CDC included colectomy, treatment with any antibiotic, nasogastric tube suction, advanced age, and prior antibiotic treatment. Abdominal pain and fever were also more common in patients with CDC. Morbidity included prolonged hospitalization in all patients and urgent colectomy in one.

Conclusions
CDC frequently affects surgical patients, producing morbidity ranging from mild diarrhea to life-threatening illness. A variety of factors, many of which are associated with intestinal stasis, predispose to the development of CDC.

Clostridium difficile colitis (CDC) is a common hospital-acquired infection that produces discomfort, inconvenience, and occasionally severe illness in patients admitted with unrelated medical or surgical conditions. This morbidity is compounded by the cost associated with the frequent need for extended hospitalization or rehospitalization of infected patients. The spectrum of disease can vary from asymptomatic colonization to a fulminant, life-threatening infection.[1] In its mildest form, CDC presents as colitis without pseudomembrane formation and produces diarrhea and mild abdominal discomfort. More severe colitis is associated with profuse, debilitating diarrhea, abdominal pain, distention, fever, and elevated white blood count. Occasionally, patients with CDC develop fulminant toxic colitis, a condition that can be lethal despite aggressive medical or surgical treatment.[2,3]

A number of risk factors have been associated with the development of CDC, including increased age, transfer from a nursing home, renal failure, chemotherapy, and antibiotic treatment.[1,4,5] However, environmental contamination remains the primary cause of the frequent clustering that is typical of this disease.[6,7] Several interventions designed to reduce local contamination have been successful in diminishing the frequency and magnitude of outbreaks.[8,9]

Although an increased incidence of CDC has been demonstrated after surgical procedures,[10–12] a prospective study in which only surgical patients are evaluated has not been undertaken. Risk factors and the natural history of this disease process may differ in patients undergoing surgical procedures *versus* those receiving medical interventions.[12,13] Therefore, we designed a prospective study to evaluate the incidence, risk factors, and clinical course of CDC in patients admitted exclusively to a surgical service. We identified several risk factors that predisposed to the development of CDC in these patients. We also describe the clinical course of surgical patients who developed this infection.

METHODS

Over a 5-month period, 374 patients admitted to the general, vascular, thoracic, and urologic surgical services were prospectively evaluated for the development of symptomatic CDC. Inclusion in this study required that a patient remain in the hospital for >48 hours. Patients found to have CDC as the reason for admission were excluded from this study.

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Rectal cultures were obtained from each patient before (<9 days) or within 24 hours of admission and then at 2-day intervals until discharge. Rectal swabs were placed immediately in anaerobic transport medium (Anaerobe Systems, San Jose, CA) and stored at −4 C before transport to the clinical laboratory. Samples were then cultured in agar and broth selectively designed to isolate *C. difficile*.[14]

Specimens were obtained by a study nurse during weekdays and by resident physicians at night and on weekends. Each patient enrolled in this study was interviewed and examined by a nurse at the time of admission and coincident with the interval cultures. This evaluation included a thorough history and an abdominal examination. Patient demographics, pre- and postadmission clinical course, and pertinent laboratory results were recorded. Symptoms and signs recorded included the presence of diarrhea (>3 bowel movements per 24 hours), abdominal pain or distention, fever (>100.5 F occurring >48 hours after surgery), and elevated white blood count. Cytotoxin assays were routinely ordered on all patients who developed diarrhea.

We focused our evaluation on the patients who developed symptomatic CDC, defined as >3 bowel movements during a 24-hour period and a positive cytotoxin assay or culture for *C. difficile*. Pearson two-sided chi square, Fisher's exact test, and stepwise logistic regression were used for statistical comparisons. A p value <0.05 was regarded as significant.

RESULTS

Three hundred seventy-four patients (182 female, 192 male) on four surgical services were studied. The average age was 61 years (range, 18–101). The proportion of patients on each service was general surgery (54%), vascular surgery (27%), urology (14%), thoracic surgery (4%).

Twenty-one patients developed symptomatic CDC. Nineteen patients had both a positive cytotoxin assay and culture, one patient had a positive cytotoxin assay and a negative culture, and one patient had only a positive culture. In this latter patient, who had profuse diarrhea, a cytotoxin assay was inadvertently not obtained.

There was no clustering of cases or "outbreaks" of CDC during this study, nor was there an association between CDC and a particular ward, surgeon, or team. The monthly incidence of CDC did not statistically vary during the study.

Risk factors that predisposed to the development of CDC are shown in Table 1. The average age was significantly greater for patients who developed CDC (72 *vs.* 60 years, p = 0.0047). Other factors that predisposed to the development of CDC included admission from a nurs-

Table 1. VARIABLES THAT PREDISPOSE TO THE DEVELOPMENT OF CLOSTRIDIUM DIFFICILE COLITIS

Variable	Incidence of CDC (%)	p Value
Preadmission living situation		
Nursing home/rehabilitation center	20.0	0.013
Home	4.9	
Admitting diagnosis		
Acute small or large bowel obstruction	15.2	0.02
All other admissions	4.7	
Admitting service		
General (intestinal)	10.6	0.004
General (nonintestinal)	2.5	
Thoracic	0.0	
Urology	3.7	
Vascular	3.9	
Specific operative procedure		
Colectomy	21.0	0.0004
All other procedures	3.4	
Operation/bowel obstruction	29.0	0.005
All other procedures	4.7	
Nasogastric tube		
Yes	11.1	0.016
No	4.1	
Antibiotics		
Current admission		
Yes	6.7	0.0448
No	0.0	
Cefoxitin		
Yes	17.9	0.00001
No	2.4	
Last 6 mo		
Yes	9.1	0.0456
No	4.0	
Symptoms		
Abdominal pain		
Yes	33.0	0.011
No	13.0	
Temperature > 100.5 F		
Yes	52.0	0.037
No	31.0	

ing home or rehabilitation center, an admitting diagnosis of acute large or small bowel obstruction, intestinal surgery, an operative procedure for bowel obstruction, colectomy, nasogastric tube suction for >48 hours, treatment with antibiotics, exposure to the specific antibiotic cefoxitin, and treatment with antibiotics during the 6-month period before hospitalization. Not surprisingly, there was a statistically higher incidence of abdominal pain and fever in patients who developed CDC. Using stepwise logistic regression, three of these variables—admission from a nursing home or rehabilitation center, use of the antibiotic cefoxitin, and an operative procedure for bowel obstruction—each independently increased the risk of developing CDC.

Factors that did not predispose to the development of CDC are outlined in Table 2. Diagnostic procedures, such as sigmoidoscopy and colonoscopy, were not associated with the development of CDC, although the overall number of procedures was small. Of the medical therapies evaluated, stool softeners appeared to protect against the development of CDC, although this association was not statistically significant ($p = 0.066$). Several studies have demonstrated a female predisposition for the development of CDC; however, we found CDC to be equally likely to develop in both genders.

The duration of hospitalization for patients who developed CDC was 19.0 ± 12.6 days (range, 4–53) *versus* 9.9 ± 10.7 days (range, 2–136) for patients without CDC ($p = 0.0002$). However, in the 21 symptomatic patients, the average duration of hospitalization that preceded the development of symptoms was only 7.9 ± 5.2 days (range, 2–25), a period that was not statistically different than the total duration of hospitalization in patients without CDC ($p = 0.45$).

Decisions regarding the treatment of CDC were made by the involved clinicians, who were made aware of the results of the cytotoxin assays only. Treatment of CDC was frequently instituted empirically, often before the results of the cytotoxin assay became available. Of the 21

Table 2. RISK FACTORS THAT DO NOT PREDISPOSE TO THE DEVELOPMENT OF CLOSTRIDIUM DIFFICILE COLITIS (CDC)

Variable	p Value
Gender	
Female *vs.* male	0.424
Admission	
Emergency *vs.* elective	0.162
Surgeon	0.291
Surgical team	0.506
Procedure	
Endoscopy	0.682
Colonoscopy	0.396
Upper GI series	0.818
Lower GI series	0.121
Abdominal CT (with contrast)	0.857
Sigmoidoscopy	0.100
Medicines	
Antacids	0.717
H2 blockers	0.148
Laxatives	0.501
Steroids	0.281
Stool softener	0.066
Antibiotics	
1 *vs.* 2 or more	0.414
Prior history of CDC	0.513
Hospitalization within last year	0.246
Operation *vs.* none	0.174
Hospital ward	0.216

symptomatic patients, 18 were treated with oral metronidazole, 1 with oral vancomycin, and 2 with metronidazole and vancomycin.

The clinical course of patients who developed CDC varied from mild diarrhea to fulminant colitis. Of the 21 symptomatic patients, 10 had diarrhea without systemic illness, 10 had diarrhea accompanied by fever, abdominal pain, or distention, and 1 patient developed toxic colitis requiring surgical exploration. This latter patient had initially undergone an elective right colectomy for removal of a sessile polyp, which was followed by an uneventful postoperative hospital course of 6 days. He was readmitted 8 days after the original procedure in a toxic state with fever, abdominal pain, and diarrhea. Abdominal exploration revealed inflamed small and large bowel. The affected bowel was resected and a new anastomosis created. Samples from the large and small bowel and from the patient's stool were positive for CDC. After a protracted course and treatment with oral vancomycin and metronidazole, this patient fully recovered.

DISCUSSION

A series of outbreaks of CDC at our hospital prompted concern over the potential morbidity produced by this nosocomial infection. Before the initiation of this study, several measures designed to reduce environmental contamination were introduced throughout the hospital. As evidenced by the lack of clustering of cases during this study, these measures were successful in reducing the influence of environmental contamination on the development of infection. The incidence of CDC remained relatively constant over the course of this study, and there was no association of CDC with any ward or surgeon.

The incidence of symptomatic *C. difficile* infection in hospitalized patients has been reported to range from 2.3% to 7.8%.[1,12,15] We found the incidence of symptomatic CDC in this cohort of surgical patients to be of similar proportion (5.6%). Several risk factors for CDC were identified. As noted in previous studies, increased age or transfer from a rehabilitation facility or nursing home predisposed to the development of CDC. CDC developed only in the patients taking antibiotics; however, neither the number of antibiotics prescribed nor the duration of therapy predisposed to disease.[16] Prior reports have identified clindamycin, ampicillin, and the cephalosporins as having the greatest potential for producing CDC.[4,17] However, despite the frequent use of cefazolin, ampicillin, and clindamycin in these patients, cefoxitin was the only antibiotic that was associated with infection. The relation between cefoxitin and CDC is not surprising. Cefoxitin is used to eliminate overgrowth of other bacteria in the routine culture of CDC.[5] Also, prior studies have shown that there is significant growth of *C. difficile* in stool cultures from patients treated with parenteral cefoxitin.[18] This finding is particularly relevant to gastrointestinal surgeons, who, because of the selectivity of cefoxitin for the flora of the large intestine (ironically, for the same reason that it is useful in isolating *C. difficile*), use this antibiotic frequently for prophylaxis for surgical procedures.

Of the surgical interventions evaluated in this study, intestinal operations were associated with the greatest incidence of infection. CDC developed frequently after colectomy and surgery for acute large or small bowel obstruction. Two previous studies suggested an association between colectomy and CDC. Kappas et al.,[11] in a retrospective study of 28 patients with histologically proven pseudomembranous colitis, found that 22 of these cases occurred after major surgery, and 11 of these procedures were colectomies. The prophylactic antibiotic prescribed for these patients varied, although lincomycin was frequently used and cefoxitin was prescribed in none. In a second study of 241 patients undergoing gastrointestinal procedures, there also appeared to a predilection for the development of CDC in patients undergoing colectomy.[19] Metronidazole and kanamycin were the most frequently used preoperative antibiotics for these patients. Despite a strong tendency for patients undergoing colectomy to develop CDC, this predilection was not independent of other risk factors identified, such as treatment with cefoxitin or surgery for bowel obstruction.

We also found an increased incidence of CDC in patients with acute large or small bowel obstruction. This propensity was even greater if surgery to relieve the obstruction was required ($p = 0.005$). It has been suggested that functional intestinal obstruction predisposes to the development of CDC. Patients treated with antiperistaltic medicines, narcotics, or both for symptoms of CDC can have an exacerbation of their symptoms, and cathartics may be protective for CDC.[20] It is, therefore, not surprising that mechanical obstruction might also predispose to this disease. Intestinal stasis associated with either colectomy or bowel obstruction might allow for overgrowth of *C. difficile*. The hypothesis that intestinal stasis predisposes to CDC is further supported by the observation that nasogastric tubes, which are used to treat anatomic and functional obstruction, are associated with an increased incidence of CDC (although the presence of a nasogastric tube was not an independent risk factor). An association between CDC and nasogastric suction has been made previously, but support for this association was derived from a case-controlled study of only 10 patients.[10] Finally, the trend toward fewer episodes of CDC among patients taking stool softeners might also be explained by a reduction in colonic stasis provided by this treatment.

Abdominal pain was more common in patients with CDC; nevertheless, only 33% of the patients with CDC complained of abdominal pain. More than 50% of the

patients with CDC had a temperature >100.5 F at a point >48 hours after surgery. However, 31% of patients without CDC also had a similar late temperature elevation. Because abdominal pain and fever are frequent findings in postoperative patients, especially after laparotomy, these signs and symptoms, although statistically more probable in patients with CDC, were not specific for the diagnosis.

The spectrum of illness associated with CDC ranged from mild diarrhea without systemic signs to fulminant colitis. The majority of symptomatic patients in this study developed a limited form of disease. Nevertheless, CDC provided discomfort, prolonged the duration of hospitalization, and undoubtedly resulted in additional expense for all affected patients. Moreover, symptoms related to this disease process were often difficult to differentiate from those that might result from a complication of the surgical procedure. Although in this study only one patient developed a toxic colitis necessitating surgical exploration and bowel resection, we recently reported several deaths at this institution after similar clinical illness.[3] The length of stay for patients who developed CDC was significantly greater than the average hospital stay for all other patients. Although a portion of this prolonged hospital stay was probably related to the treatment of CDC, it is impossible to distinguish whether the underlying illnesses of these patients might have also contributed to their prolonged hospitalization.

Mild self-limited diarrhea is a common symptom in postoperative patients, and many patients who developed diarrhea during this study were treated empirically at the onset of their symptoms with oral metronidazole or vancomycin (before the results of the cytotoxin assay became available). This approach resulted in inappropriate treatment of many patients who were eventually found not to have CDC. It recently has been recommended that for patients who develop mild diarrhea, antibiotics should be changed or their use terminated.[21] Such an approach would avoid culture or inappropriate treatment of the many patients who either do not have CDC or have only a mild form of this disease. Although this policy could reduce cost and avoid unnecessary treatment of many patients, it risks permitting progression of a mild, untreated case of CDC to a more severe and even life-threatening form of the disease. This issue may be of greater concern in postsurgical patients because intestinal stasis, which predisposes to CDC, is common. Consequently, we recommend that a cytotoxin titer should be sent on all patients with postoperative diarrhea, but that treatment should be withheld until a positive cytotoxin assay is obtained. Only if systemic signs and symptoms suggest that a more severe form of CDC has already developed should treatment be empirically initiated.

CONCLUSIONS

We found that CDC is common in surgical patients, particularly those undergoing intestinal surgery. Although several risk factors for CDC were identified, the three that were independent predictors of CDC were admission from a nursing home or rehabilitation center, use of the antibiotic cefoxitin, and an operative procedure for bowel obstruction. In the majority of patients, the course of illness is not severe and the infection responds well to oral metronidazole or vancomycin. However, as demonstrated by the one patient in this study who required laparotomy, significant morbidity can occasionally occur as a consequence of this disease. We defined several factors that predispose to the development of CDC. We believe that surgical patients who develop CDC should be aggressively treated, particularly if there is associated intestinal stasis.

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