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Clostridium difficile Infection: A Surgical Disease in Evolution

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Abstract
Introduction Several recent publications suggest an increase in the incidence of *Clostridium difficile* colitis. However, such studies commonly lack denominators over which to index this rise. There is also concern in the literature that disease virulence is increasing.
Methods Billing, admission, operative, and infection databases at a single tertiary care center identified patients admitted from 1990 to 2006 with a diagnosis of *C. difficile* infection. Grouped by era, case numbers were indexed against overall hospital, operative, and laboratory volumes. *C. difficile* colectomy cases were individually examined and analyzed.
Results The number of hospitalized patients diagnosed with *C. difficile* colitis increased in a linear fashion during the study period (1990, 14 cases; 2006, 927 cases). The colectomy per *C. difficile* case ratio did not change over the study period (era 1, 0.17%; era 2, 0.20%; era 3, 0.16%). Thirteen patients underwent colectomy with 54% surviving. The increase in patients admitted with a diagnosis of *C. difficile* was significantly associated with hospital volume ($p=0.04$), operative volume ($p<0.001$), and lab testing volume ($p=0.008$).
Conclusion The number of *C. difficile* patients admitted to our hospital is rising at an alarming rate. This reflects national trends and urgent action seems warranted to prevent a *C. difficile* epidemic.

Keywords *Clostridium difficile* · Colitis · Colectomy

Introduction

Clostridium difficile is a gram-positive, anaerobic, spore-forming bacillus which manifests a spectrum of disease, ranging from asymptomatic carrier to *C. difficile*-associated diarrhea to pseudomembranous colitis (PMC) to toxic megacolon with septic shock and death. Infection can begin with small innocula of difficult-to-eradicate spores, which germinate in the host colon. The first reported case of PMC was in 1893 in a 22-year-old woman following gastric polyp resection.[1] In 1943, penicillin was found to induce a lethal penicillin-resistant bacterial infection now presumed to be *C. difficile*.[2] Researchers attributed PMC to a "local toxin" in 1965[3] and described clindamycin-induced PMC in the mid 1970s.[4] Isolation of *C. difficile* toxin provided the biologic link between antibiotic use, unchecked toxin-producing Clostridial overgrowth, and the clinical phenotype known today as *C. difficile*-associated diarrhea.

PMC is a toxin-mediated colonic injury pattern usually caused by *C. difficile*. Two toxins, enterotoxin A and cytotoxin B, cause the severe colonic and systemic illnesses.[5] Typical symptoms include foul smelling diarrhea, fever, and abdominal pain which range from mild disease to fulminant colitis. The process usually occurs with anteced-

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ent antibiotic use, carries a significant (~20%) rate of recurrent diarrheal illness,[6] and progresses to toxic megacolon in up to 3% of cases.[7] In mild cases, the disease responds to supportive therapy including discontinuation of offending antibiotics, avoidance of narcotics and anti-diarrheal agents, and maintenance of fluid/electrolyte intake. More severe cases require hospitalization for intravenous hydration. A minority of patients (~3%) with *C. difficile*-associated diarrhea develop toxic megacolon. This is a grave disease requiring surgical intervention with a reported mortality rate of 25–40%.[7]

Over the last 3 years, investigators in the US, Canada, and the UK reported increased *C. difficile* rates associated with hypervirulent strains.[8,9] In the US, the estimated colonization rate of hospitalized adults with *C. difficile* is 383 cases per 100,000 hospital discharges.[10] Other reports estimate the incidence of *C. difficile* colonization to be 1% in patients with hospital stays <1 week and 50% if hospital stay exceeds 4 weeks.[11] Additional treatment charges in patients acquiring *C. difficile* infection average over 75,000 US dollars/patient.[12]

Despite study and observations of specific intervention (s) on *C. difficile* infection rates,[13–19] little attention has been paid to long-term trends in disease incidence until recently. Due to a perception of increased refractory *C. difficile* disease requiring colectomy, we investigated the incidence at a major tertiary referral hospital and hypothesized that the number of patients admitted with a diagnosis of *C. difficile* and the number of colectomies performed for fulminant *C. difficile* PMC increased over the last 16 years. Ricciardi et al. recently described such a trend using the Nationwide Inpatient Sample database.[10] One weakness of that study was the lack of denominating factors that may have influenced the observed trend of increasing disease incidence over time. This study evaluates the relationship of refractory *C. difficile* infections indexed by the number of at-risk patients, number of operative cases performed, and number of *C. difficile* assays.

Methods

The Institutional Review Board for Human Subjects at the University of Wisconsin-Madison approved this study. De-identified electronic and paper records of study patients with PMC who underwent operative intervention were examined. Billing, admission, and infection control databases at the University of Wisconsin Hospital (a 465-bed academic tertiary care center) were queried to identify all patients admitted to the hospital with a current or previous (and thus at risk for recurrent disease) diagnosis of *C. difficile* between January 1, 1990 and September 30, 2007. As available, hospital admissions data were analyzed for total hospital admission volume during the study period. Additionally, available data from laboratory and operating room databases were queried for total *C. difficile* tests performed and operative case volumes during the study period.

Patients assigned an ICD-9 diagnosis of *C. difficile* pseudomembranous colitis (008.45) were cross-referenced with patients undergoing colonic surgery (all study years) to identify those with possible fulminant, refractory *C. difficile*. Fulminant, refractory PMC was defined as PMC in a patient with hemodynamic instability. Review of the clinical chart confirmed all diagnoses with one or more of the following indicators: positive *C. difficile* toxin assay, positive colonoscopy, surgical pathology specimens, CAT scans, or autopsy. Due to small annual numbers, surgically treated patients were grouped into three time periods: 1990–1995, 1996–2000, and 2001–2006. The relationships between hospital admission volume, operative case volume, and *C. difficile* laboratory testing volume on the number of *C. difficile*-positive patients admitted and colectomy for fulminant *C. difficile* colitis were analyzed by pairwise linear regression analysis.

Results

Data regarding number of patients admitted to the hospital carrying a diagnosis of *C. difficile* infection and the number of colectomies performed for refractory fulminant *C. difficile* PMC were available for the entire period of study. Data regarding the total number of *C. difficile* tests performed were available from 2001 to 2006. Prior laboratory testing data were unavailable due to a change in lab database management during 2000. Total hospital admissions data were available between 1999 and 2006 and annual operative volume data were available since 1993.

A near-linear increase in patients admitted to the hospital carrying a diagnosis of *C. difficile* infection occurred over the study period. This reflects an increase from 14 such patients in 1990 to 927 patients in the first 9 months of 2006. If grouped by era, this increase is a straight line (Fig. 1, $r^2=0.999$).

Surgeons recommended colectomy for fulminant *C. difficile* colitis for 18 patients during the study period. Three patients declined operation and expired after institution of comfort care measures. Fifteen patients underwent operation identified by the following ICD-9 colectomy procedure codes: 45.79 (partial/subtotal), 45.72 (cecal), 45.75 (left colon), 45.71 (multiple segmental), 45.73 (right colon), 45.76 (sigmoid), 45.8 (total), and 45.74 (transverse colon). Two patients received non-colectomy operations (one transverse colostomy and one cecostomy) and were excluded from this analysis.

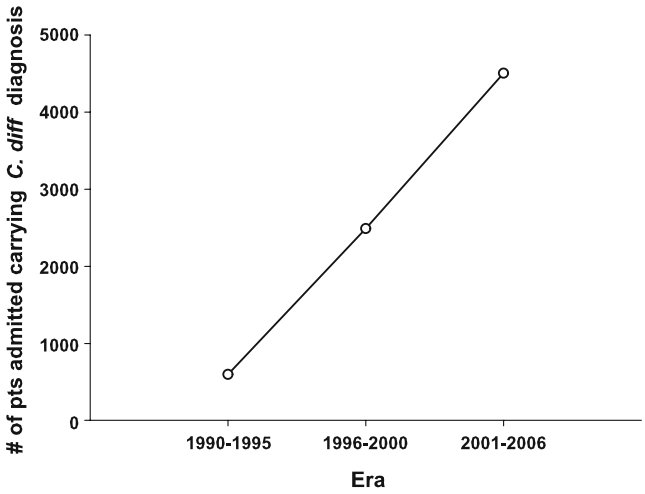

Figure 1 Number of *C. difficile*-positive patients admitted to hospital during the study period.

Thirteen patients underwent total or subtotal colectomy for refractory fulminant PMC during the study period. The mean age of colectomy patients was 56.4±19.9 years and 54% were male. The incidence (by era) increased in parallel with the increase in number of patients admitted carrying a *C. difficile* diagnosis (Fig. 2, r^2=0.993). Interestingly, the ratio of colectomies to *C. difficile*-positive patients did not change over time: 1990–1995=1 colectomy/598 patients (0.17%); 1996–2000=5 colectomies/2,486 patients (0.20%); 2001–2006=7 colectomies/4,504 patients (0.16%), for an average incidence of one colectomy per 583 patients admitted to the hospital with a diagnosis of *C. difficile* (Table 1, 0.17%). Medical comorbidities of these patients are shown in Table 2.

Antecedent antibiotic use (13/13) and exogenous immunosuppression (7/13) preceded development of fulminant disease in patients requiring surgery. Chronic renal insufficiency or end stage renal disease was common (5/13, 38%). Nearly all patients (11/13, 85%) received acid suppression with H_2 blockade or proton pump inhibitors. Most patients also had a recent (within 30 days) history of surgery (8/13, 62%).

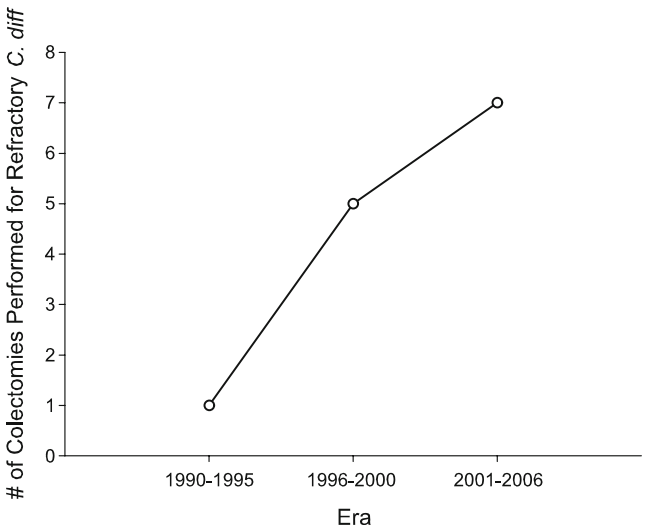

Figure 2 Number of colectomies for *C. difficile* colitis during the study period.

Table 1 Ratio of *C. difficile*-positive Admissions/Colectomy for Refractory C. *difficile*

Era	# *C. difficile* (+) admissions	# Colectomies	Colectomy/ test ratio
1990–1995	598	1	0.17
1996–2000	2,486	5	0.20
2001–2006	4,504	7	0.16
Overall	7,588	13	0.17

Diagnostic features included *C. difficile* toxin positivity in 92% (12/13) and leukocytosis in 85% (11/13, Table 3). Clinicians noted peritonitis in 46% (6/13) of patients. Most (8/13, 62%) had developed acute renal failure and were vasopressor dependent (9/13, 69%) prior to operation (Table 3). Time from patients' first diagnosis of symptomatic *C. difficile* infection to operation varied from 1–138 days (mean 23 days, median 5 days). The time from acute diagnosis (whether initial or recurrent) of *C. difficile* colitis to operation averaged 3 days (range 1–8). Seven patients (54%) had received prior antibiotic treatment specifically for *C. difficile* colitis. Colonoscopy revealed pseudo-membranes in 54% (7/13) of patients and CT scan was diagnostic of colitis in 62% (8/13) of patients.

All colectomy patients initially survived operative intervention but 6/13 (46%) died post-operatively. No significant difference in survival over the three time periods was observed although a trend towards increased survival following colectomy was noted over time: 1990–1995=1/1 (100% survival); 1996–2000=1/5 (20% survival); 2001–2006=7/8 (88% survival). Yearly total hospital admissions increased 9% (21,039 to 22,860) from 1999 to 2006. Yearly total operative volume increased 58% (14,230 to 22,520)

Table 2 Demographics and Comorbidities of Colectomy Patients

Demographics and comorbidities	
Age	56.4±19.9
Gender	54% male
HTN	31%
CAD	38%
COPD	23%
Immunosuppressed	54%
CRI/ESRD	38%
Acid suppressed	85%
Recent operation	62%

HTN, hypertension; *CAD*, coronary artery disease; *COPD*, chronic obstructive pulmonary disease; *CRI*, chronic renal insufficiency; *ESRD*, end stage renal disease

Table 3 Diagnostic and Clinical Features of Patients Undergoing Colectomy for *C. difficile* Colitis

Pt.	Toxin+	Scope+	CT+	Pre-op WBC	Peritonitis	Pressors	ARF	Perforated	Survival
1	+	+	−	51.2	−	+	+	−	−
2	+	+	+	32.1	−	+	+	−	−
3	+	+	−	15.2	+	+	+	−	−
4	+	+	−	5.4	−	−	−	−	+
5	−	+	−	56.6	−	−	−	−	+
6	+	−	+	0.4	+	+	−	−	+
7	+	−	+	44.8	+	+	+	−	+
8	+	+	+	38.7	+	−	+	−	+
9	+	−	+	10	−	+	+	−	+
10	−	−	+	41.7	−	−	−	−	+
11	+	+	−	31.2	−	+	−	−	−
12	+	−	+	45.3	+	+	+	−	−
13	+	−	+	13.7	+	+	+	−	−
Total	85%	54%	62%	29.7±18.7	46%	69%	62%	0%	54%

from 1993 to 2006. Laboratory testing for *C. difficile* increased 59% (1,720 to 2,741) from 2001 to 2006.

Because admission, laboratory, and operative databases were incomplete during the study period, a valid multivariant linear regression analysis was impossible. However, pairwise correlation analysis was performed using available data. Overall, the data was highly co-linear. The number of patients admitted with a *C. difficile* diagnosis was the only factor significantly associated with the increase in colectomies performed (Table 4, $p=0.03$). However; as Table 4 also shows, the increase in number of positive patients was associated with the following factors: number of tests performed ($p=0.008$), hospital admissions ($p=0.04$), and operative volume ($p<0.001$).

Discussion

Between 1990 and September 2006, the number of patients developing or admitted to our hospital with a diagnosis of *C. difficile* increased dramatically. These data support our hypothesis, and other recently published reports, that the incidence of this disease is rising very rapidly. Correspondingly, the increase in *C. difficile* incidence results in more emergent colectomies for refractory *C. difficile* PMC. Our experience argues against increasing disease virulence since the ratio of operative interventions to positive toxin tests remained stable during the study period.

Table 4 Factors Influencing Number of C. *difficile* (+) Patients Admitted and Colectomy Rates

Variable	Vs. # of C. *difficile* (+) pts. admitted	Vs. colectomies
# of + *C. difficile* (+) pts. Admitted	−	0.03*
Total hospital admissions	0.04*	0.13
Operative volume	<0.001*	0.43
No. of *C. difficile* tests performed	0.008*	0.24

There appear to be multiple reasons for this increase in *C. difficile* and its complications. Overall hospital, surgical, and laboratory test volume were examined to explore possible associations with the increase of this diagnosis. The association between admission and operative volumes and *C. difficile* is somewhat intuitive in that as more patients are tested and treated, any given common disease process will be seen more frequently. Total operative volume might *distinctly* influence the incidence of this disease since antibiotic guidelines to reduce surgical site infections have led to more patients receiving "prophylactic" antibiotics prior to most surgical procedures. There is evidence that even a single dose of perioperative antibiotics can alter colonic flora and convert approximately 20% of patients from *C. difficile* negative to positive by culture and toxin although symptomatic disease may not occur.[20] Consistent with other studies, all patients requiring colectomy for refractory *C. difficile* received antecedent antibiotics and a majority of patients were immunosuppressed.

Post-surgical (as well as non-surgical) inpatients remain at risk of contracting the disease simply by their hospital-bound status since *C. difficile* is readily transmissible by fomites, prolonged antibiotics are frequently administered, and environmental eradication and control techniques remain imperfect.[21–23] Perhaps even more intuitive is the association between increased testing and increased number of positive patients, suggesting that the more one looks for *C. difficile*, the more one finds it. Likely this contributes to

a cycle of "self-fulfilling prophecy" as increased testing yields more positives and more positives lead clinicians to consider the diagnosis and test for it more frequently. This phenomenon remains unclear, however, as data from other institutions both support[24] and refute[25] this line of reasoning.

Fulminant, refractory *C. difficile* is a potentially lethal disease. Byrn et al. recently published a single center experience to identify risk factors predictive of mortality in patients undergoing colectomy for *C. difficile colitis*.[26] Our mortality of 46% exceeded the 34% reported by Byrn et al. but there are several potential reasons for this. First, our colectomy rate of 0.17% was lower than the rates reported in studies by Ricciardi (0.28% colectomy rate) or Byrn et al. (1.3% colectomy rate). The decision to operate probably differs between the various sites since hemodynamic instability usually preceded the decision to operate at our institution. Despite a lower resection rate, only the sickest patients were subjected to surgery with a resulting higher mortality rate. Institutions that operate earlier may experience lower mortality due to more frequent operations on less ill patients that may have responded to aggressive medical therapy, i.e., they operated on less ill individuals resulting in an overall reduction in mortality but at the expense of unnecessary colectomies. Since clinical judgment guides the decision to operate without defined guidelines of "medical failure" for "refractory *C. difficile* colitis", it is difficult to state which approach is preferable. Secondly, there appear to be differences between our patient populations with respect to significant pre-existing pulmonary (Byrn et al., 8%; this study 23%) and renal (Byrn et al., 7%; this study 38%) disease system comorbidities. Overall, the trend demonstrated in our study agrees with several recent publications on this topic.

We found no evidence of the hypervirulent strain of *C. difficile* recently reported by other centers since our constant colectomy rate over time suggests that, while the incidence of disease may be rising, the virulence of "normal" bacterial strains remains unchanged over time. Even so, the increasing burden of this disease almost certainly increases overall morbidity, workload, and charges/costs. While not currently included in the list of hospital acquired infections that Medicare will cease reimbursement for beginning October 1, 2008, this is a disease that is largely hospital acquired and a current draft proposal of factors influencing reimbursement considers *C. difficile* a non-reimbursable complication.

No attempt was made to examine trends in antibiotic or antisepsis use and/or protocols during the study period. Many others have studied the effects of antibiotic type and usage patterns on *C. difficile* disease; it seems clear that the "antibiotic variable" influences this disease.[8,16,18–20,27–29] During the final period of study (2001–2006), our hospital instituted several generalized protocols to define, restrict, and monitor antibiotic usage resulting in an overall hospital-wide trend of decreased antibiotic use (personal communication with Barry Fox MD, hospital infection control officer). We cannot address more specific observations on possible relationships between antibiotics and *C. difficile* at our hospital during this study period.

One weakness of this study is that we used admission ICD-9 codes to identify patients admitted with a diagnosis of *C. difficile*. Patients carry this diagnosis over time so some patients counted in the study may have been admitted for reasons unrelated to a prior infection. Also, a patient admitted more than once during the study period would have been counted at each admission since they remained at risk at each admission. If so, our data may overestimate the true incidence of *C. difficile* infections in *individual* patients at our institution. Alternatively, a diagnosis of *C. difficile* may be an indicator of a sicker patient population requiring frequent readmissions and overall increased medical care.

Conclusions

Regardless of current study limitation, there exists a rapidly growing number and/or frequency of patients carrying a diagnosis of *C. difficile* being admitted to the hospital, needing medical attention, and utilizing ever-scarce health-care resources. Using the Nationwide Inpatient Sample Database, Ricciardi et al. recently showed a similar *national* upward trend in the incidence and prevalence of this disease. The trend we confirmed is alarming and likely occurring at many other hospitals. Aggressive study of this disease is urgently needed to prevent a *C. difficile* surgical epidemic.

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