

## ***Clostridium difficile* enteritis: A report of two cases and systematic literature review**

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### INTRODUCTION

*Clostridium difficile* (*C. difficile*) is a common nosocomial infection caused by a gram-negative spore forming organism that most commonly leads to pseudomembranous colitis<sup>[1,2]</sup>. The incidence of *C. difficile* infection has been increasing rapidly since the early 2000s<sup>[2,3]</sup>. The rate of *C. difficile* infection nearly tripled between 1996 and 2005<sup>[2]</sup>. The number of severe cases of *C. difficile* infection is also rising; the number of fatal cases in England rose from approximately 500 in 1999 to nearly 3400 in 2006<sup>[2]</sup>. The increasing severity of disease may be due to a rise in an epidemic strain, NAP1/BI/027, which produces toxin A and B in significantly greater quantity compared to the normally occurring strain. *C. difficile* resides in the colon and risk factors for infection, such as antibiotic use, are generally those that alter normal colonic flora. However, we present two cases of patients diagnosed and treated with *C. difficile* enteritis. Due to the rare nature of this disease we reviewed the literature on the subject and present data to suggest increasing recognition of this manifestation of *C. difficile*.

### CASE REPORT

#### Case 1

The first patient is a 54-year-old Caucasian male with ulcerative colitis who underwent a total proctocolectomy with end ileostomy in 1997. He developed a parastomal

### Abstract

*Clostridium difficile* (*C. difficile*) is the most common cause of healthcare associated infectious diarrhea. In the last decade, the incidence of *C. difficile* infection has increased dramatically. The virulence of *C. difficile* has also increased recently with toxigenic strains developing. *C. difficile* is generally a disease of the colon and presents with abdominal pain and diarrhea due to colitis. However, *C. difficile* enteritis has been reported rarely. The initial reports suggested mortality rates as high as 66%. The incidence of *C. difficile* enteritis appears to be increasing in parallel to the increase in colonic infections. We present two cases of patients who had otherwise uneventful abdominal surgery but subsequently developed *C. difficile* enteritis. Our literature review demonstrates 81 prior cases of *C. difficile* enteritis described in case reports. The mortality of the disease remains high at approximately 25%. Early recognition and intervention may reduce the high mortality associated with this disease process.

hernia that was becoming increasingly symptomatic. Following a discussion with the patient regarding the risks and benefits of parastomal hernia repair, he underwent an exploratory laparotomy with enterolysis, parastomal hernia repair and re-siting of the ileostomy. The hernia defect was repaired primarily with a biologic mesh underlay (Alloderm, Lifecell®). He received one preoperative dose of cefoxitin; consistent with preoperative antibiotic guidelines. The operation was uneventful. His postoperative course was uncomplicated; on postoperative day 4 he was tolerating a regular diet and had normal ileostomy output. He was subsequently discharged home.

Twenty-four hours later, he returned to the hospital emergency department with complaints of abdominal pain and feculent vomiting. Vital signs on arrival were notable for a temperature of 38.5 °C, heart rate of 130 beats per minute and blood pressure of 150/90 mmHg. On physical exam his abdomen was diffusely tender to palpation without peritoneal signs. The ileostomy was viable and there was gas and a small amount of fluid noted in the ostomy bag. A nasogastric tube was placed and returned 1600 mL of feculent effluent.

Laboratory examination revealed a white blood cell count of 5400 cells/mm<sup>3</sup>, hemoglobin of 16 g/dL, and 192 000 platelets/mm<sup>3</sup> and a serum lactate of 2.1 mg/dL. An abdominal and pelvic computed tomography (CT) scan obtained in the emergency department revealed mildly dilated, fluid filled small bowel without a transition point. There was a small amount of free fluid and air which was consistent with the history of recent laparotomy. Blood cultures were obtained in the emergency department.

He was transferred to the intensive care unit for fluid resuscitation and started on broad-spectrum antibiotics. Serial abdominal exams were performed over the course of the next several hours, and he began to stabilize clinically. Notably, his tachycardia began to resolve and his urine output increased. Additionally, during this time, his ileostomy began to produce copious amounts of fluid and gas requiring frequent ostomy bag changes. The following day, his blood cultures returned positive for *Enterococcus* and his stool studies from his stoma output were positive for *C. difficile*.

Treatment for *C. difficile* was initiated with oral metronidazole but was subsequently changed to a combination of intravenous metronidazole and vancomycin enemas as the patient was not tolerating oral intake well. On hospital day 2, the antibiotic regimen used to treat the bacteremia was tailored to intravenous vancomycin alone based on sensitivity information. The patient improved with his antibiotic treatment and was transitioned to oral vancomycin for treatment of *C. difficile*. He was treated for a total of 14 d and he had complete resolution of his symptoms.

### Case 2

The second case is a 48-year-old male patient with a history of diverticulitis who presented with left lower

quadrant abdominal pain. His vital signs were normal on admission. A CT scan revealed inflammation of the sigmoid colon without evidence of a discrete fluid collection. The patient was initially started on intravenous antibiotics. However, approximately 24 h following admission, the patient developed worsening abdominal pain. His abdominal examination demonstrated worsening tenderness, with diffuse rebound and guarding. After discussion of operative risks he was taken to the operating room for exploration.

The sigmoid colon demonstrated only a focal area of perforation with moderate inflammation. A sigmoidectomy was performed with healthy proximal tissue and normal rectum. A primary anastomosis was performed using an EEA stapling device. A diverting ileostomy was performed to protect the anastomosis. The patient received 24 h of antibiotic treatment prior to operation which included three doses each of ciprofloxacin and metronidazole. Postoperatively, the patient developed an ileus which resolved on postoperative day 6. He was tolerating a diet following this. On postoperative day 8, the patient experienced significantly increased output from his ileostomy (greater than 2 L). A *C. Difficile* toxin sent from the ileostomy returned positive. The patient was started on intravenous metronidazole and improved. He was transitioned to oral medications upon discharge to complete a 14 d course.

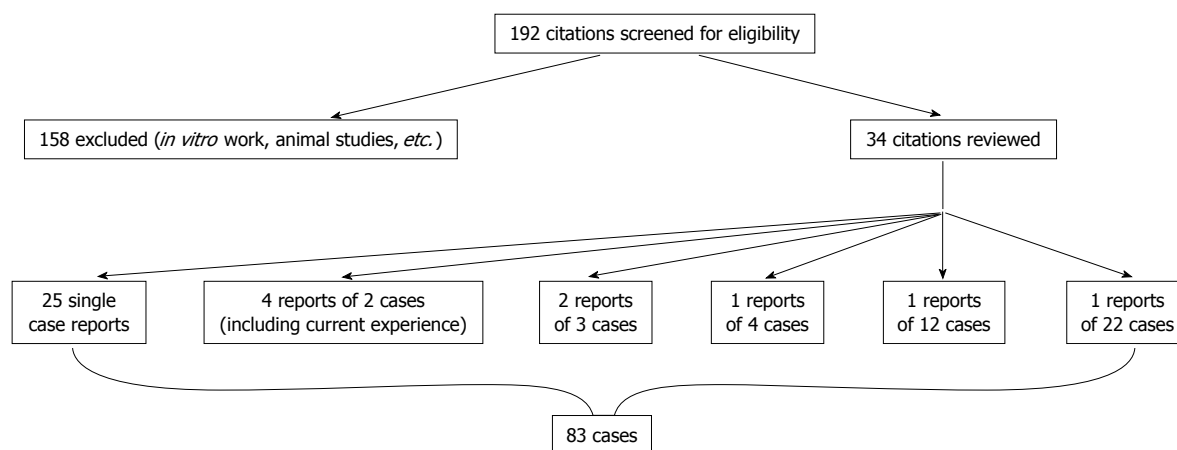
### Literature review

A systematic literature review was conducted by searching PubMed for the terms “enteritis” and “*Clostridium difficile*”. One hundred and ninety-two citations were screened. One-hundred and fifty-eight were excluded based on review of title or abstract. Thirty-four citations were reviewed and the references of individual reports were hand searched to identify any missed reports. Data was extracted from individual case reports. All patients were symptomatic and tested positive for *C. difficile*. There were 34 reports identified from this search (Figure 1). We did not perform a meta-analysis due to the heterogeneity of the data and lack of randomized trials.

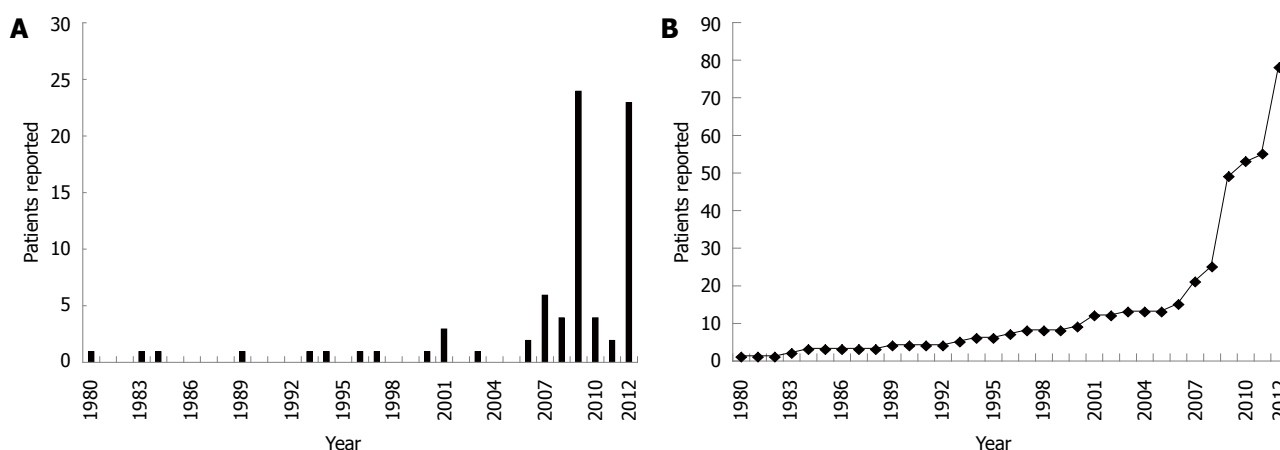
There were 81 cases of *C. difficile* enteritis found in the literature<sup>[4-37]</sup>, with the addition of our cases, the total number of cases is now 83. Figure 2 illustrates that the number of cases has increased considerably in the last decade. There were 9 cases reported between the years 1980 and 2000. Since then there have been 73 cases reported. The mortality from the first 9 cases reported was 67% (6/9). The overall mortality of the 83 cases published is 23%. The average age of patients is 54 ± 2.44 years. Male patients constituted 53% of the cohort. Antibiotic use in the prior 4 wk was 71% and the incidence of inflammatory bowel disease was 41%. Twenty-one of 83 patients died resulting in a mortality rate of 23%.

### DISCUSSION

*C. difficile* is the most common cause of health care-associated infectious diarrhea<sup>[3]</sup>. As first described, *C. difficile*



**Figure 1** CONSORT diagram indicating the results of the systematic literature review. The results of the systematic review demonstrated 34 citations that met criteria for inclusion. There were a total of 83 patient-cases of *Clostridium difficile* enteritis identified.



**Figure 2** Number of cases has increased considerably in the last decade. A: The number of cases (patients) reported in the literature each year between 1980-2012; B: The cumulative number of cases over the same time period.

colitis was thought to be associated with the exclusive use of clindamycin administration<sup>[2]</sup>. Ironically, the bacteria that was difficult to grow (thus the *difficile*) is now increasing with dramatic incidence<sup>[2,38]</sup>. The increase in incidence is due, in part, to the highly virulent NAP1/BI/027 strain of *C. difficile*. In the United States, the frequency of *C. difficile* infection has doubled in the past 10 years<sup>[38]</sup>. The understanding of *C. difficile* and its pathophysiology has increased substantially over the past few decades. Severe *C. difficile* infection is being reported more frequently in patients not previously thought to be at high risk, including children<sup>[38,39]</sup>. It is possible that *C. difficile* enteritis is less dependent on alterations in colonic flora to develop. *C. difficile* enteritis has previously been considered a rare disease. However, as highlighted in our review, the incidence of this also appears to be increasing.

Predisposing factors to *C. difficile* infection include prior antibiotic use; which is thought to alter the colonic flora, allowing *C. difficile* to proliferate. Many case reports, including ours, would suggest that previous antibiotic use is also associated with *C. difficile* enteritis. Laval-

lée *et al*<sup>[19]</sup> report that ten of twelve patients with ileal *C. difficile* had recent antibiotic administration (one did not have recent antibiotic use and one was not documented). Similarly, Lundeen *et al*<sup>[20]</sup> present 6 cases of *C. difficile* enteritis in which all 6 cases had recent antibiotic exposure. However, Tsiouris *et al*<sup>[30]</sup> report 22 cases in which the association with prior antibiotic use is less strong. Of the 22 patients in this series, only 22.7% demonstrated recent use of antibiotics. Based on our review, the association is still high, as 71% of patients had received antibiotics within 4 wk of presentation with *C. difficile* enteritis.

It is believed that gastric acid is a key mechanism of defense against ingested pathogens<sup>[1]</sup>. *C. difficile* has been identified as a pathogen in animals and has been identified in some food products<sup>[40]</sup>. Therefore, it is possible that transmission from ingested meats may occur<sup>[40]</sup>. Proton pump inhibitor (PPI) and H2-blockers are frequently used for gastric acid suppression. Acid suppressive therapy has been demonstrated to significantly increase the risk for *C. difficile* infection<sup>[1,41]</sup>. The patient in Case 1 was

treated preoperatively with a PPI for gastroesophageal reflux disease. Case 2 was not on outpatient therapy, but did receive a PPI postoperatively. This association is not entirely clear, however, as Lundeen *et al*<sup>[20]</sup> reported six cases, in which only one patient was on acid reducing therapy.

The pathophysiology of *C. difficile* enteritis is not well understood. Patients with an ileostomy may develop a metaplasia of the terminal end, creating an environment more similar to the colonic environment<sup>[42]</sup>. Additionally, changes in the intestinal flora have been noted after ileostomy<sup>[43]</sup>. Testore *et al*<sup>[44]</sup> isolated *C. difficile* from jejunum in asymptomatic human autopsy specimens. This supports the theory that small bowel may act as a reservoir. Kralovich *et al*<sup>[15]</sup> demonstrated *in vivo* that a patient with a jejunal-ileal bypass developed *C. difficile* infection in the defunctionalized limb. In addition to alterations in the host, changes in the pathogen may also be responsible for the development of *C. difficile* enteritis. Small bowel mucosa requires a higher concentrations of toxin for infection to occur<sup>[45]</sup>. In this case, the toxigenic NAP1/BI/027 strain may be more capable of causing small bowel infection. This is hypothetical at this point, but the increased recognition of *C. difficile* enteritis is compatible with the timing of the rise in NAP1/BI/027. This strain has been confirmed as the causative agent in one case of *C. difficile* enteritis<sup>[19]</sup>. We did not specifically test for NAP1/BI/027 strain and, therefore, cannot determine if this was a predisposing factor in our patients.

The diagnosis of *C. difficile* enteritis requires a high index of suspicion. As many patients may not initially be suspected of *C. difficile* infection, CT scan evidence may be useful. Wee *et al*<sup>[33]</sup> reviewed CT scan findings in four patients with *C. difficile* enteritis. They suggest that ascites and fluid-filled small bowel in the presence of mild mesenteric stranding could be considered consistent with *C. difficile* enteritis. Our patient in Case 1 demonstrated fluid filled loops of small bowel and a moderate amount of ascites. This was initially thought to be due to his recent surgery. However, these findings are consistent with the reported CT findings of small bowel *C. difficile*.

Treatment for *C. difficile* enteritis is generally similar to that for colonic infections. Oral metronidazole is considered standard first line therapy. However, Follmar *et al*<sup>[8]</sup> report the use of vancomycin for metronidazole resistant *C. difficile*. Severe *C. difficile* infection may be better treated with vancomycin<sup>[46,47]</sup>. In our patient, due to his ileus and his severe clinical status, we elected to use intravenous metronidazole and vancomycin enemas for his initial treatment.

It should be noted that our review is focused on case reports. There is no prospective data on the incidence of *C. difficile* enteritis. Therefore, it is not possible to know whether the apparent increase in cases is a true increase in incidence or if there is simply more reporting of the disease. However, even in the context of simply more reporting, the mortality remains high and increased rec-

ognition will still remain a priority.

The mortality of *C. difficile* enteritis has historically been considered very high as the initial 9 reports demonstrated a mortality of 66%. However, as the experience has steadily accumulated, the mortality rate appears to be decreasing. Our report of a mortality rate of 25.3% is lower than earlier reports, but remains substantial. This clinical entity is still rare and requires a high index of suspicion to initiate treatment early. As the use of antibiotics, immunosuppressive agents, and the age of the patient population will all continue to increase it is likely that *C. difficile* infections, including *C. difficile* enteritis will only continue to increase. Awareness of this process and efforts to determine the optimal treatment will continue to be necessary.

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