

Toxic megacolon associated *Clostridium difficile* colitis

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Abstract

Toxic megacolon is a severe complication of *Clostridium difficile* (*C. difficile*) colitis. As the prevalence of *C. difficile* colitis increases and treatments become more refractory, clinicians will encounter more patients with *C. difficile* associated toxic megacolon in the future. Here, we review a case of toxic megacolon secondary to *C. difficile* colitis and review the current literature on diagnosis and management. We identify both clinical and radiologic criteria for diagnosis and discuss both medical and surgical options for management. Ultimately, we recommend using the Jalen criteria in conjunction with daily abdominal radiographs to help establish the diagnosis of toxic megacolon and to make appropriate treatment recommendations. Aggressive medical management using supportive measures and antibiotics should remain the mainstay of treatment. Surgical intervention should be considered if the patient does not clinically improve within 2-3 d of initial treatment.

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Key words: Toxic megacolon; *Clostridium difficile*; Colitis; Diarrhea; Surgery; Colon; Antibiotics; Metronidazole; Vancomycin

INTRODUCTION

Clostridium difficile (*C. difficile*) is a gram positive, anaerobic, spore forming bacterium spread by the fecal oral route^[1-4]. It produces toxins A and B, causing severe mucosal destruction and pseudomembrane formation^[1-5]. Clindamycin, cephalosporins and fluoroquinolones are the most common antibiotics associated with *C. difficile* infection^[3,6,7]. The prevalence of *C. difficile* colitis has been increasing^[8]. The percentage of complicated cases of *C. difficile* rose from 7.1% in 1991 to 18.2% in 2003, and the proportion of patients who died within 30 d after a severe *C. difficile* associated diarrheal episode rose from 4.7% in 1991 to 13.8% in 2003^[9]. Between 2003 and 2006, *C. difficile* infection became more severe and refractory to standard therapy. It also became more likely to relapse than in previous years^[4,6,10].

Toxic megacolon, first described by Marshak *et al*^[11] in 1950 is a known complication of *C. difficile* colitis. The incidence of toxic megacolon associated *C. difficile* colitis varies from 0.4%-3% of cases^[12,13]. Toxic megacolon is thought to develop from inflammatory changes that penetrate into the muscularis propria resulting in neural injury, altered motility and dilation^[13]. Risk factors for toxic megacolon include any severe inflammatory condition

such as inflammatory bowel disease, ischemic colitis and infectious colitis. Risk factors for development of toxic megacolon include concurrent malignancy, severe chronic obstructive pulmonary disease, organ transplantation, cardiopulmonary procedures, diabetes mellitus, immunosuppression and renal failure^[13-16]. Patients with toxic megacolon will often present with peritoneal signs, abdominal distension, diarrhea, oliguria, tachypnea, fever, hypotension, and marked leukocytosis. In atypical cases, diarrhea may be absent^[13,15,17-19].

The mortality rate of toxic megacolon secondary to *C. difficile* colitis is substantial and varies from 38% to 80%^[5,13]. Early recognition and aggressive treatment of toxic megacolon associated with *C. difficile* may lead to improved outcomes. Yet, standards for diagnosis and management of this potentially lethal condition are not clearly defined.

CASE REPORT

A 64-year-old woman presented to the hospital with 3 days of abdominal pain, nausea, vomiting and profuse watery diarrhea. She was recently discharged from the hospital for a urinary tract infection and acute renal failure. She had just completed a 14 d course of ciprofloxacin.

The past medical history was significant for hyperlipidemia, hypertension, and gouty arthritis. There were no prior surgeries except for a remote history of tonsillectomy. She used tobacco and on average she drank four cans of beer daily. She denied using intravenous drugs.

On admission to the hospital the blood pressure was 65/41 mmHg. Hypothermia was present. The temperature was 35.8°C. She was obese and appeared in mild distress. Her abdomen was mildly distended, with hypoactive bowel sounds. There was tenderness in the lower quadrants without rebound.

The WBC was 53.9 K/mcl with 84% neutrophils. The Hct was 36.1%. There was severe metabolic acidosis with an anion gap of 19, bicarbonate level of 12 mmol/L, lactic acid level of 3.6 mmol/L. The arterial blood gas demonstrated a pH of 7.11, CO₂ of 16, and O₂ of 150 on 2 liters of oxygen via nasal canula. The serum creatinine was 11.5 mg/dL. The K⁺ was 2.5 mmol/L, and Mg⁺⁺ of 0.6 mg/dL. The INR was 2.1.

The patient was resuscitated with IV fluids, and placed on dopamine and later norepinephrine. She was also given intravenous ciprofloxacin 500 mg every 12 h, oral vancomycin 250 mg every 6 h and IV metronidazole 500 mg every 6 h.

A CT of the abdomen and pelvis demonstrated circumferential wall thickening of the colon consistent with a pancolitis (Figure 1). The transverse colon was dilated to 5.8 cm.

The patient did not improve despite treatment over the next 36 h. The WBC rose to 62.4 K/mcl. There was no other source of infection. Blood, urine and stool cultures were negative. The cytotoxicity assay for *C. difficile* on stool samples was also negative.

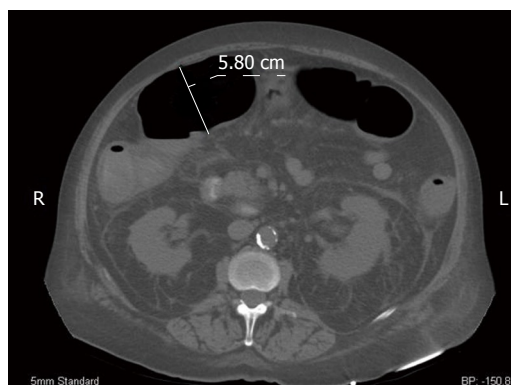


Figure 1 Computerized tomography axial image of our patient. We measured the patient's transverse colon at 5.80 cm. Additionally, perinephric fluid is markedly evident bilaterally.



Figure 2 Colonoscopic image taken of the descending colon consistent with pseudomembranous colitis.

The surgery service was consulted for presumed toxic megacolon. A rigid sigmoidoscope was advanced to 25 cm from the anal verge. The mucosa appeared pink without pseudomembranes. The gastroenterology service next performed a colonoscopy, which demonstrated edematous mucosa with raised yellowish plaques consistent with pseudomembranous colitis in the sigmoid and descending colon. No biopsies were taken (Figure 2).

Medical treatment was continued and surgery was not offered at this time. Vancomycin 500 mg enemas every 12 h were added to the regimen. On subsequent stool samples the cytotoxicity assay for *C. difficile* was positive.

The patient's blood pressure began to improve on the third day and IV pressors were discontinued. The patient was discharged after 23 d.

DISCUSSION

Concerning this case, we were presented with three questions: (1) What are the criteria for the diagnosis of toxic megacolon? (2) Is endoscopy necessary to confirm the diagnosis of *C. difficile* related toxic megacolon? and (3) When should surgery be performed for *C. difficile* related toxic megacolon? In order to answer these questions, we performed a systematic literature review. We searched the

Web of Science, PubMed, MEDLINE, the Cochrane Library and Google Scholar for articles written between January 1990 and June 2009 using a combination of keywords and MeSH terminology “*Clostridium difficile*” and “toxic megacolon.” We limited our search to English language articles. We initially identified 55 articles. All articles were reviewed for content to determine relevance to the discussion. 17 articles were excluded because of lack of relevance to the topic. The citations of identified articles were also examined for additional publications. The total number of articles that were selected for our review was 37.

The diagnosis of toxic megacolon requires radiological evidence of colonic dilatation primarily involving the ascending or transverse colon. The degree of dilation is somewhat controversial - some using > 5 cm as a cut-off, while others require colonic dilation of > 6 cm to make the diagnosis^[6,13,20-23].

CT is helpful in confirming the diagnosis of a toxic megacolon. CT findings commonly seen in patients with toxic megacolon are: pericolonic fat stranding, colonic wall thickening, absence or distortion of haustral folds, and ascites^[13,15,24]. Other CT findings include the ‘target’ sign, which indicates mucosal hyperemia and submucosal edema and the ‘accordion’ sign, which is due to marked thickening of the haustral folds^[24]. In a study by Hall *et al*^[5], which reviewed 36 patients who had documented toxic megacolon at surgery, CT was accurate in 94% of cases.

In addition to colonic dilation, several clinical criteria must be fulfilled. The most accepted clinical criteria for toxic megacolon are derived from Jalan *et al*^[19]. To establish the diagnosis of toxic megacolon three of the following four criteria should be present: fever > 101.5 F; HR > 120 beats/min; WBC > 10 500/mm³; and anemia with hemoglobin or hematocrit level less than 60% of normal. In addition, the patient must have any one of the following four clinical findings: dehydration, electrolyte disturbance, hypotension or changes in mental status.

Endoscopy is seldom used to confirm the diagnosis of *C. difficile* related toxic megacolon since the diagnosis can be made by a combination of immunotoxin assay, clinical findings and imaging. An endoscopy may be dangerous, especially in a setting of fulminant colitis due to the increased risk of perforation^[6,25]. A study by Johal *et al*^[26], however encouraged the use of flexible sigmoidoscopy as a tool for the diagnosis of *C. difficile* toxic colitis when stool assays are negative. In their study 52% of patients who tested negative for *C. difficile* toxin assay had pseudomembranous colitis on flexible sigmoidoscopy.

Endoscopy is recommended for the diagnosis of *C. difficile* toxic colitis under the following conditions: (1) when there is a high level of clinical suspicion for *C. difficile* despite repeated negative laboratory assays; (2) when a prompt diagnosis is needed before laboratory results can be obtained; (3) when *C. difficile* infection fails to respond to antibiotic therapy or (4) for atypical presentations of *C. difficile* colitis such as in patients who present with ileus, acute abdomen, or leukocytosis without diarrhea^[3,15,21].

In the treatment of *C. difficile* related toxic megacolon, aggressive medical therapy may help prevent surgical intervention in up to 50% of cases^[13]. In a retrospective review by Imbriaco *et al*^[27] 12 of the 18 patients (67%) with toxic megacolon due to *C. difficile* improved with medical therapy without the need for surgery.

The medical management of toxic megacolon includes oral vancomycin, IV metronidazole, bowel rest, bowel decompression, and replacement of fluids and electrolytes^[13,18,21]. Some authors note that adequate intracolonic concentrations of vancomycin may not be achieved with oral vancomycin because of poor intestinal motility. Therefore, vancomycin enemas have been recommended; however enemas may fail to treat right-sided disease of the colon. Other alternatives include direct instillation of vancomycin by colonoscopy, colostomy or ileostomy^[28].

The dilated colon may be decompressed with nasogastric suction and frequent repositioning of the patient^[13]. Some authors recommend prone positioning for 10 to 15 min every 2 to 3 h allowing the passage of flatus. Panos *et al*^[22] presented two cases where bowel decompression was successfully achieved with the knee-chest position.

Colonic decompression can also be achieved with a colonoscopy. Shetler *et al*^[29] reviewed seven patients with toxic megacolon due to *C. difficile* who underwent decompressive colonoscopy and intracolonic perfusion of vancomycin. The authors found that 57% of the patients had complete resolution of toxic megacolon. Their reported data suggested that decompressive colonoscopy may be safe and effective in the medical treatment of toxic megacolon although the number of patients in this study was small. Other authors suggest that endoscopic decompression may worsen disease^[21]. Colonoscopy may cause further dilation of the colon leading to impaired blood supply to the colon wall, increasing the risk of perforation and translocation of bacteria^[13,21].

Management of toxic megacolon also includes withholding medications that slow intestinal motility. These medications include anticholinergics, antidepressants, antidiarrheals, and narcotics^[6,13,30].

Surgical intervention may be necessary in up to 80% of patients with toxic megacolon due to *C. difficile* colitis^[22]. Indications for surgery include: perforation, progressive dilation of the colon, lack of clinical improvement over the first 48-72 h and uncontrolled bleeding^[9,13,21,26,31,32]. Auch *et al*^[31] evaluated 70 patients who had surgery for toxic megacolon due to *C. difficile* colitis and found that the most common indication for surgery was progressive colonic dilation. Clinical deterioration (36%) and uncontrolled bleeding (4%) were other reasons the authors noted.

The mortality rate for a colectomy has varies widely across studies. Byrne *et al*^[14] retrospectively reviewed 73 patients who underwent colectomy for toxic megacolon due to *C. difficile* colitis between 1994 and 2005. The hospital mortality rate was 34% with a single intraoperative death. This study along with others have found that preoperative vasopressor requirement, endotracheal

intubation, and altered mental status were significant predictors of mortality after colectomy^[5,9]. Miller *et al*^[33] retrospectively reviewed 49 patients who underwent colectomy for fulminant *C. difficile* colitis. The study found that the 30 d mortality rate was 57%, with an in-hospital mortality rate of 49%. The 5 year survival rate for those who lived past 30 d from a colectomy was 38%.

The surgical procedure of choice for toxic megacolon is total colectomy with preservation of rectum and diverting ileostomy^[6,7,13,31]. Outcomes are worse if a partial colectomy is performed, perhaps owing to residual diseased bowel left in place^[5,4,29,34]. Grundfest-Broniatowski *et al*^[35] reviewed 21 studies between 1976 and 1994. They reported a 24% mortality rate for subtotal colectomy compared to 40% for sigmoid resection alone. In a study by Koss *et al*^[25], total colectomy resulted in a lower mortality rate (11%) compared to those with a left hemicolectomy (100%).

It must be emphasized that clear standardized indications for surgery in patients with toxic megacolon due to *C. difficile* colitis do not currently exist. In several articles reviewed, surgery was performed only in patients who had signs of systemic toxicity such as shock requiring vasopressors, multisystem organ failure or peritonitis^[4,14,16,31,36]. It is interesting to speculate that mortality rates might be improved if patients were operated on earlier in the course of their illness, before signs of organ failure set in. Lamontagne^[37] advised surgery for patients with WBC > 50 K/mcl and lactate levels > 5 mmol/L as these patients were likely to die within 30 d of ICU admission without surgery.

In conclusion, toxic megacolon is a complication of *C. difficile* colitis. The diagnosis is made when colonic dilation is at least > 5 cm. CT is helpful in establishing the presence of toxic megacolon by demonstrating wall thickening and distortion of haustra. The criteria described by Jalan *et al*^[38] should be used in making the diagnosis. Patients should have aggressive medical management and daily abdominal X-rays. Patients with an ileus should be given rectal vancomycin as well - even though there is a lack of evidence-based studies to confirm its efficacy. Surgery should be considered if there is progressive colonic dilation or if clinical improvement is not noted within 2 to 3 d.

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