

# Surgical management of clostridium difficile associated colitis with toxic megacolon in a transplant patient: Case Report and Review of Literature

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## Citation

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## Abstract

**PURPOSE:** The clinical presentation of Clostridium difficile colitis (CDC) can vary from a brief bout of diarrhea to fulminant disease with toxic megacolon and severe sepsis. The immunosuppressed are at an increased risk for CDC, often presenting in an atypical fashion and experiencing a more complicated course from C. difficile infection. **METHODS:** We describe a case of toxic megacolon secondary to CDC occurring in a renal transplant patient. Our preferred operative strategy and review of the literature is provided. **RESULTS:** This renal transplant patient with CDC progressed to toxic megacolon and was successfully managed with both intra-operative decompression and urgent subtotal colectomy. Typical risk factors present included immunosuppression and recent flouroquinolone exposure. **CONCLUSIONS:** Toxic megacolon is typically associated with Ulcerative Colitis and Crohn's Colitis, but bacterial colitides including pseudomembranous colitis are emerging as important and more frequent causes of toxic megacolon. CDC in the setting of immunosuppression makes the disease particularly hazardous and diagnosis of complications challenging.

## INTRODUCTION

The clinical presentation of Clostridium difficile colitis (CDC) can vary from mild abdominal cramping and a brief bout of diarrhea to fulminant disease with toxic megacolon and severe sepsis. The incidence of CDC has risen in recent years and emerging strains of C. difficile have become less responsive to standard therapies.

One population for whom this is a serious concern are those who undergo solid organ transplantation with therapeutic immunosuppression. Patients that are immunosuppressed are at an increased risk for CDC, often presenting in an atypical fashion and experiencing a more complicated course from C. difficile infection.

Diarrhea in the setting of solid organ transplantation has numerous infectious and non-infectious etiologies which may impede a timely diagnosis of CDC. Fulminant CDC is highly morbid and in the setting of immunosuppression can incur mortality up to 80% even with prompt diagnosis and appropriate treatment. A high index of suspicion for CDC is necessary when evaluating a solid organ transplant patient with diarrhea. We describe a case of toxic megacolon secondary to C. difficile colitis occurring in renal transplant

patient, which was successfully managed with urgent subtotal colectomy. Our preferred technique for operative strategy is also reviewed.

## CASE PRESENTATION

A 68-year-old woman was admitted with gastroenteritis. She had a cadaveric renal transplant seven years earlier for end-stage renal failure secondary to polycystic kidney disease. The prior months were significant for recurrent urinary tract infections treated as an outpatient with multiple courses of ciprofloxacin and nitrofurantoin. Initial stool tested positive for C. difficile toxin. The patient was treated with hydration and oral metronidazole. The immunosuppressive regimen included cyclosporine. Initial WBC count was 16,500 falling to 9,900 after 48 hours of therapy. The abdomen was mildly distended but soft and without peritoneal signs. Despite a fall in the WBC count, the diarrhea persisted and a CT scan of the abdomen was obtained revealing diffuse colonic thickening with scant ascites. [SEE FIGURE 1]

**Figure 1**

FIGURE 1: CT scan of the abdomen revealing diffuse colonic thickening with ascites.



Over the following 48 hours the WBC rose progressively to 18,700 and the patient developed peritoneal signs. Repeat imaging with plain abdominal radiograph demonstrated an 8.9cm transverse colon. [SEE FIGURE 2]

**Figure 2**

FIGURE 2: A plain abdominal radiograph demonstrating an 8.9cm transverse colon.



A subtotal colectomy with ileostomy was performed. Upon entering the abdomen, a dilated and friable colon was noted without evidence of perforation as well as a large amount of ascites. [SEE FIGURE 3]

**Figure 3**

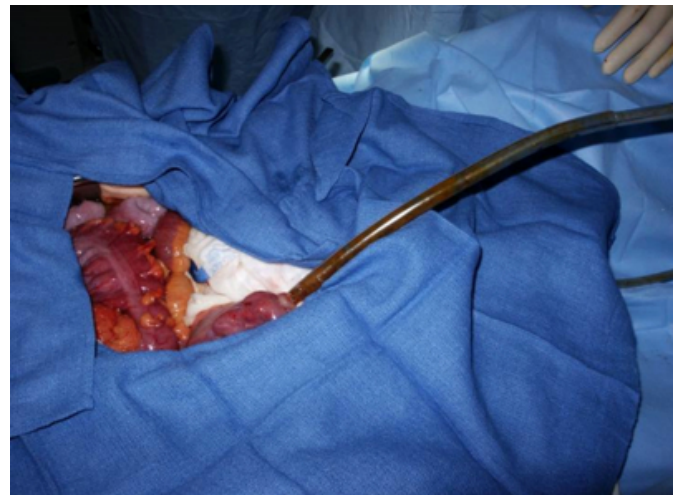
FIGURE 3: A dilated and friable colon was noted without evidence of perforation.



After mobilization of the right colon and division of the terminal ileum, a chest tube was then inserted via a purse-string to decompress the colon. [SEE FIGURE 4]

**Figure 4**

FIGURE 4: A chest tube inserted via a purse-string to decompress the colon.



The remainder of the procedure was carried out without spillage or gross contamination. Final pathologic evaluation revealed pseudomembrane formation consistent with pseudomembranous colitis. [SEE FIGURE 5]

**Figure 5**

FIGURE 5: Final pathologic evaluation revealed pseudomembrane formation consistent with pseudomembranous colitis.



**DISCUSSION**

Clostridium difficile is a gram-positive sporulated rod that grows in strict anaerobic conditions. (1) C. difficile was first described in 1935 as part of the normal flora of neonates. (2) Antibiotic associated pseudomembranous enterocolitis was first described in the 1950's and originally attributed to Staphylococcus aureus and Candida albicans. (2) In 1978, C. difficile was described as the predominant etiology of antibiotic associated diarrhea and colitis. (1-3) Risk factors for C. difficile-associated colitis (CDC) include recent antibiotic use (6-8 weeks in >90% of cases associated with antibiotics), antineoplastic agents, antifungal agents, antiviral agents, advanced age, immunosuppression, hemodialysis, cancer, ulcerative colitis, malnutrition, solid-organ transplantation, HIV infection and residence in hospital or long-term care facility. (3,4) CDC is defined by diarrhea and isolation of C. difficile toxin in the stool. (5) Recent antibiotic use is the most common risk factor and seen in the majority of CDC cases. Diarrhea occurs in 3-29% of hospitalized patients receiving antibiotics and C. difficile is the most common nosocomial infection causing antibiotic-associated colitis. (2,5) The most frequently implicated antibiotic was clindamycin but antibiotics of all classes have been reported with fluoroquinolones thought to be the predominant offending agent in recent years. (6,7) Toxin producing strains of C. difficile flourish after alteration of gut flora and are responsible for disease. Several toxins have been identified including toxin A, toxin B and binary toxin. (3) These toxins increase vascular permeability due to opening of tight junctions between cells which leads to the typical presentation of watery diarrhea. (8) It is unclear why

some infection progresses to fulminant colitis with complications such as severe sepsis or toxic megacolon. CDC has been reported to occur in 1-4% of general surgery patients. (4,5) The incidence of CDC among hospitalized patients has risen in recent years as have the associated complications and mortality. (1) Mortality associated with CDC has risen from 1999 to 2002 in the United States and from 2001 to 2005 in England and Wales. (4) In the United States, mortality related to CDC rose from 5.7 deaths per million population in 1999 to 23.7 deaths per million population in 2004. (4) The precise reason for this dramatic increase in both the incidence of CDC and the clinical severity of it are unclear but have been postulated to be the result of the emergence of more virulent strains of C. difficile. While greater than 100 C. difficile ribotypes have been identified, a few particular strains have been implicated in recent outbreaks. (9) Isolates of the B1/NAP1 strain, presence of binary toxin, and toxinotype III C. difficile are increasingly present and associated with recent hospital outbreaks. (6,10) Pseudomembranous colitis is more frequent with toxinotype III infection. (10) Toxins A and B are encoded by genes tcdA and tcdB, respectively. (11) A regulatory gene exists at tcdC and mutation of this gene is associated with pathogenicity and has also been found in increasing prevalence. (6,10,11) Concurrent with these newer strains and more virulent clinical patterns, more recurrence of disease and primary therapy failure has occurred in recent years. (7) Initial treatment consists of general resuscitative measures such as hydration, electrolyte repletion as well as stopping the offending antibiotic. This treatment alone may resolve the diarrhea in 48-72 hours in up to 20% of patients. (2) Oral vancomycin was originally first-line therapy but presently oral metronidazole therapy for 7-14 days is currently considered the first-line therapy for CDC. (2,7) Failure of this therapy would be defined by continued diarrhea, persistent isolation of C. difficile toxins in the stool or toxic appearance. Second line medical therapy includes the addition of oral vancomycin and if oral therapy cannot be tolerated then intravenous metronidazole has been used although it should be switched to oral therapy when feasible. (2) Progression to fulminant disease warrants surgical evaluation as discussed below. Other agents have been used with success (clindamycin, teicoplanin, fusidic acid, pooled human immunoglobulin) but are not currently a part of standard treatment regimens. Anion exchange resins such as cholestyramine may bind the secreted C. difficile toxins; however, clinical success is inconsistent and this therapy also binds oral vancomycin and is therefore not

recommended. (12) Antimotility agents such as loperamide such be avoided if CDC has not been excluded due to the risk of precipitating toxic megacolon. (9) Isolation practices are important and recognition that alcohol-based hand sanitizers are not adequate and hand washing is still required. (10) A life-threatening complication of CDC is toxic megacolon. Toxic megacolon is a life-threatening emergency and a rare complication of pseudomembranous colitis and other forms of colitides. Toxic megacolon is characterized by acute dilatation of all or part of the colon to a diameter greater than 6cm associated with acute colitis with systemic toxicity. (13,14) Systemic toxicity can be defined as the SIRS response (severe inflammatory response syndrome) with fever, leukocytosis, tachypnea and tachycardia. (15) Progression of disease also presents with end-organ failure and hypotension. Other causes of acute colonic distention such as colonic pseudo-obstruction can be distinguished by the lack of an inflammatory trigger and systemic response. Severe colitis causing systemic illness can also be caused by salmonella, shigella, campylobacter, cytomegalovirus or cryptosporidium infection, ulcerative colitis (UC) or Crohn's disease. (16)

The most common etiology of toxic megacolon is inflammatory bowel disease. (14,16) Lifetime incidence of toxic megacolon in a patient with ulcerative colitis is 1-2.5%. (16) Toxic megacolon occurs in 0.4%-3% of patients with CDC and has an associated mortality rate of 38-80%. (16) Infection is the most common complication after organ transplantation. (17) Solid organ transplant recipients often have several risk factors for CDC and also have multiple potential causes of diarrhea. CDC is a growing concern among transplant patients. Stelzmueller reviewed 2,474 solid organ transplants from 1996 to 2005 with 89% of documented CDC occurring between 2000 to 2005. (8) While reports vary, lung transplantation seems to be associated with poorer outcomes from CDC. (29) Based on these data, the overall rate of progression with CDC to toxic megacolon seems to be greater with immunosuppression and solid organ transplantation. Given the rising prevalence of *C. difficile* infection with the emergence of more virulent strains and the potential devastating consequences of this infection in the setting of immunosuppression, prompt diagnosis and treatment of CDC is essential. Diarrhea is a well-known side effect of immunosuppressive therapy, in particular mycophenolate mofetil; however, infectious etiologies should be investigated. Immunosuppressive regimens can lead to increased rates of gastrointestinal (GI)

infection by bacteria, viral, fungal or parasitic causes. Viral GI infection with cytomegalovirus and herpes simplex virus are quite common among transplant patients. (18) Bacterial GI infection among transplant patients is frequently associated with *Yersinia enterocolitica* and *C. difficile*. (18) It is estimated that the overall incidence of CDC among transplant patients is 8%, with higher rates among combined kidney-pancreas recipients, females, antibiotic use, intra-abdominal graft placement and treatment of rejection with monoclonal antibodies. (18,19) Diarrhea after renal transplant occurred in 12.6%, with 41.5% being infectious and 34% attributed to drug side effect. (20) It is unclear how CDC affects long-term solid organ graft function; however, it is associated with more infectious complications overall. Among a cohort of liver transplant recipients, CDC was associated with more vascular, biliary and infectious complications. (19) Early post-transplant is the highest risk period as a result of maximal immunosuppression and perioperative antibiotic use. (8) During this period, any diarrhea should be screened for CDC and oral metronidazole therapy as the initial therapy. Anti-motility agents, anticholinergics and narcotics should be minimized as a possible exacerbating factor. (14) Hydration, bowel rest, electrolyte repletion and discontinuation of any offending antibiotic is optimal. Particular attention must be given toward tacrolimus (TAC) therapy as diarrhea may cause TAC levels to rise precipitously. (17) The reason for this rise has been attributed to increased intestinal permeability, reduced hepatic metabolism or hemoconcentration. (17) Daily TAC monitoring and early dose reduction is therefore recommended to minimize nephrotoxic or neurotoxic side effects as well as preventing excessive immunosuppression which may lead to more opportunistic infection. (17,21,22) If diarrhea continues, persistent isolation of *C. difficile* toxins in the stool or systemic toxicity develops, addition of oral vancomycin therapy is recommended and decrease in immunosuppression as feasible. Careful screening for toxic megacolon should entail frequent abdominal exams and radiographs as needed. Colonic distention greater than 6cm in the setting of systemic toxicity and concurrent CDC should prompt immediate consideration of surgical therapy.

Peritoneal signs are consistent with toxic megacolon but may be masked in the setting of immunosuppression. Computed tomography (CT) of the abdomen, when clinical suspicion for complicated CDC exists, is highly accurate. (1) Characteristic CT findings include colonic dilatation with distorted colonic contour or an ahaustral pattern, ascites,

colonic wall thickening, “accordion sign” (trapped contrast material and thickened haustral folds lining up in parallel fashion) or “target sign” (three concentric rings of alternating high, low and high density). (16,23) Occasionally colonic air-fluid levels are seen. Severe disease is indicated by perforation or portal thrombosis. (23) The ascending and transverse colon are most commonly involved. (16) Colonoscopy can be used to rule out *C. difficile* or another infectious colitis but in the setting of toxic megacolon should be approached with extreme care due to risk of perforation and minimal if any insufflation used and limited to sigmoidoscopy. In contrast to colonic pseudo-obstruction, endoscopic decompression is not indicated for toxic megacolon and may worsen the disease with risk of perforation. (14)

There is no role for decompressive colonoscopy as primary treatment for CDC complicated with toxic megacolon in a transplant patient. Decompressive colonoscopy has been rarely used with success for the treatment of toxic megacolon; however, in this setting the treatment of choice is total abdominal colectomy with ileostomy. (5,16) However, many surgeons favor the less morbid subtotal colectomy, mucus fistula and ileostomy. Segmental resection has been associated with higher mortality. (16) Interestingly, there is no difference in mortality between segmental colitis or pancolitis. (14) This may suggest that the sequelae of the disease are attributable to predisposing factors and the host response as well as the local inflammation of the colon. While mortality with toxic megacolon and CDC-associated pseudomembranous colitis has been reported from 30-80%, the mortality in the setting of immunosuppression and transplantation has varied with reports from 0-100%. (1,5,8,16,24,25) Alternatives to surgical treatment in a patient with clear indications who is deemed to sick for an operation (the criteria for this are only vaguely defined in the literature but may include multiple pressor requirement and severe sepsis) are rectal tube decompression, cautious endoscopic decompression, and the above mentioned medical therapy possibly with the addition of intravenous steroids and/or intravenous pooled immunoglobulin. (14) Other novel therapies have been tried such as insertion of chest tube into the colon via the terminal ileum to allow decompression. In the senior author’s opinion, division of the terminal ileum and decompression with a chest tube before any colonic mobilization is extremely useful in decreasing the incidence of perforation. Only after this decompression should careful mobilization of

the colon occur with minimal colonic handling. In the setting of a sealed perforation, the risk of creating a free perforation and its associated dramatic rise in morbidity and mortality should prompt consideration of a diversion (“blow-hole colostomy”) as recommended by Turnbull. (26,27) A sealed perforation may be diagnosed preoperatively by CT or be suggested by the intra-operation finding of densely adherent omentum to a friable colon. (27) Blow-hole colostomy and ileostomy for the treatment of toxic megacolon involves creation of a loop ileostomy and loop colostomy which is typically the transverse colon. (27) Besides contained perforation, other recommended circumstances for this procedure in the setting of toxic megacolon include dense adhesions (making mobilization and colectomy particularly hazardous), massive distention with a high splenic flexure (for similar reasons), pregnancy (where the enlarged uterus and dilated ovarian vessels also pose difficulties) and malignant metastatic obstruction. (27) This procedure is thought of as a bridge to definitive therapy and has been contraindicated in the setting of free perforation, abscess or hemorrhage. (27) It seems feasible to combine this procedure with adjunctive therapy such as percutaneous CT-guided drainage or even angioembolization, making these former contraindications relative.

Several questions remain unanswered. Why does only a fraction of CDC progress to fulminant colitis with toxic megacolon, even in those who are immunosuppressed? Should transplant patients be screened for *C. difficile* carriage and be treated even if asymptomatic and how should this practice apply to other “high risk” populations? How widely should postoperative *C. difficile* prophylaxis be implemented? This practice has been used with a dramatic short-term decline in CDC in the immediate post-transplantation period after kidney and kidney-pancreas transplants. (5) The significance of the changing genotypes of *C. difficile* as yet remains unclear but there is a recent trend of rising incidence and severity of CDC. This may be related to these genetic factors as well as increased use of broad spectrum antibiotics and numerous other variables.

In conclusion, toxic megacolon is typically associated with UC and Crohn’s colitis, but bacterial colitides including pseudomembranous colitis are emerging as important and more frequent causes of toxic megacolon. The spectrum of disease associated with *C. difficile* infection can range from mild diarrhea to fulminant colitis with toxic megacolon. With a rise in both the incidence of CDC and disease

severity, a high index of suspicion is required for any patient with risk factors for *C. difficile* disease. Solid organ transplant patients have numerous etiologies for diarrhea as well as specific risk factors for CDC. CDC in the setting of immunosuppression makes the disease particularly hazardous and diagnosis of complications challenging. Appropriate and timely treatment of CDC and its complications are of paramount importance for the transplant patient.

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