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Authors

Bowman, Jessica A

Utter, Garth H

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Evolving Strategies to Manage *Clostridium difficile* Colitis

Jessica A. Bowman, MD, **Garth H. Utter, MD MSc**

Department of Surgery (Cox, Utter) and the Department of Surgery Outcomes Research Group (Utter), University of California, Davis, Medical Center, Sacramento, California.

Abstract

Clostridium difficile infection remains a common nosocomial illness with a significant impact on health care delivery. As molecular phenotyping of this organism has changed our understanding of its transmission and virulence, so too have diagnostic methods and treatment strategies evolved in recent years. The burden of this infection falls predominantly on elderly patients with comorbidities who have recently received antibiotics. Oral or enteral vancomycin is now preferred for first-line antimicrobial treatment across the disease spectrum, including mild-moderate initial cases. Fidaxomicin (a novel macrolide antibiotic), bezlotoxumab (a monoclonal antibody against toxin TcdB), and fecal microbiota transplantation expand the therapeutic armamentarium, particularly for recurrent infection. Operative treatment should be reserved for patients with fulminant infection, and early identification of patients who would benefit from an operation remains a challenge. Less invasive surgical options—such as laparoscopic diverting ileostomy with colonic irrigation—may improve survival and other outcomes relative to total abdominal colectomy and represent an attractive alternative particularly for frail patients.

INTRODUCTION

Optimal management of *Clostridium difficile* infection (CDI)—including surgical treatment—is undergoing gradual but important evolution. Once a disease for which, when fulminant, the only widely accepted operation was total abdominal colectomy, now management might include new antibiotics, immunotherapeutic agents, fecal microbiota transplant, and ileostomy with colonic irrigation. In this article, we review recently elucidated aspects of the pathophysiology of *Clostridium difficile*, current treatment options, and the role of surgical care.

Epidemiology

CDI remains a persistent and major burden of nosocomial disease. A 2011 survey by the Centers for Disease Control and Prevention estimated 453,000 incident cases/year in the

Corresponding author: Garth H. Utter, MD MSc, Department of Surgery, University of California, Davis, Medical Center, 2335 Stockton Blvd., Rm. 5027, Sacramento, CA 95817. Tel: 916-734-1768; Fax: 916-734-7755; ghutter@ucdavis.edu.

U.S. [1]. Individuals 65 years or older had an eight-fold higher rate of CDI than those younger than 65, and 30-day mortality among patients with health-care associated CDI was 9% [1]. A single episode of CDI costs between $9,000–12,000, and—although only one species of bacteria causes CDI—the aggregate annual cost is approximately $500–800 million [2], ranking fourth among all nosocomial infections, behind only surgical site infections, ventilator-associated pneumonia, and central line-associated bloodstream infections [3].

Pathophysiology

C. difficile is a gram positive, spore-forming, anaerobic bacillus that produces two exotoxins, TcdA and TcdB. A patient becomes colonized by ingesting *C. difficile* spores or vegetative cells. While the vegetative cells typically cannot withstand the stomach's acid, the resilient spores pass unharmed through the stomach and germinate in the small intestine in the presence of bile. If the host is immunosuppressed or the gastrointestinal microbiota is sparse due to antibiotics, *C. difficile* bacteria can colonize the colonic mucosa. Colonization typically lasts for at least a week before potentially transitioning to infection, and longer duration of asymptomatic colonization is associated with lower risk of developing CDI [4]. True infection occurs in only a small proportion of all colonized patients; it manifests when the exotoxins interact with colonocyte Rho guanosine triphosphatases, causing disruption of tight junctions, increased vascular permeability, and cell death. The products of cell death and the host-inflammatory response produce the pathognomonic pseudomembrane: cellular debris, neutrophils, fibrin, and mucin [5]. Bowel necrosis or perforation are probably mediated secondarily by non-occlusive mesenteric ischemia from hypovolemia, vasopressors, colonic distention, and abdominal compartment syndrome [6].

Among the most commonly isolated strains NAP1, NAP4, and NAP11 [1, 7] ("NAP" signifying "North American pulsed-field gel electrophoresis"), NAP1 (also known as BI/NAP1/027) is especially virulent, resistant to fluoroquinolones, and associated with increased toxin production and three-fold higher mortality compared to other strains [8]. While patients with NAP1 infection are more likely to be elderly and have more comorbidities, their outcomes are worse independent of these factors [7].

Risk Factors

The primary and most modifiable risk factor for *C. difficile* infection remains recent antibiotic use. Clindamycin, ampicillin, amoxicillin, cephalosporins, and fluoroquinolones are most commonly associated with CDI, but virtually every antibiotic has been associated. Not only antibiotic choice, but the number and duration of antibiotics also increase the risk of CDI. Thus, implementing antibiotic stewardship programs has been shown to significantly decrease CDI [9].

Because antibiotic use disturbs the intestinal microbiota, allowing *C. difficile* proliferation, investigators have evaluated the use of prophylactic probiotics to maintain non-pathogenic flora and thus prevent CDI. A 2015 meta-analysis examining the addition of probiotics to an antibiotic regimen (i.e., primary prevention) found that four probiotic formulations were associated with a decreased risk of CDI: *Saccharomyces boulardii* [RR 0.50 (95% C.I. 0.29–

0.85)], *Lactobacillus casei* [RR 0.07 (95% C.I. 0.01–0.55)], a mixture of *Lactobacillus acidophilus* and *Bifidobacterium bifidum* [RR 0.21 (95% C.I. 0.21–0.80)], and a mixture of *L. acidophilus*, *L. casei*, and *Lactobacillus rhamnosus* [RR 0.21 (95% C.I. 0.11–0.40)] [10]. However, these and other meta-analyses reflect studies that involved extremely high CDI rates among the control groups, so the applicability of the findings is questionable [4].

A strong risk factor for CDI is hospitalization, or contact with the healthcare system [6]. Being admitted to a hospital room with a prior CDI-positive occupant has been independently associated with developing CDI [HR 2.4 (95% C.I. 1.2–4.5)], but only accounted for 11% of CDI cases [11]. Most transmission probably instead involves transient contamination of the hands of healthcare personnel with *C. difficile* spores, carried between patients, some of whom are asymptomatic carriers [4, 12].

Factors that diminish the immune response such as advanced age, immunosuppressive medications, antineoplastic medications, and chronic disease also increase the risk of CDI. Proton pump inhibitors (PPIs) have been associated with an increased risk of CDI [13], but more recent evidence argues against this association being causal [4, 14].

Recurrent CDI (rCDI)—defined as symptoms with a positive test result following an assay-confirmed episode of CDI within the previous 2–8 weeks—becomes more likely after each bout of infection, occurring in 10–25% of patients after an initial CDI and 20–35% after a first recurrence [15, 16]. Risk factors for recurrence include antibiotic use, PPI use, age 65 years or older, infection with NAP1 strain, and low antibody titers [17].

SYMPTOMS

Diagnosis is occasionally challenging, as patients can present with a wide array of symptoms, from mild diarrhea to, paradoxically, ileus and toxic megacolon. In its mildest form, CDI commonly presents with watery diarrhea and crampy abdominal pain that must be distinguished from other forms of nosocomial diarrhea. As the infection progresses and patients mount an inflammatory response, they become febrile and develop increasing abdominal tenderness. Laboratory evaluation often reveals marked leukocytosis. Without adequate intervention, systemic illness and septic shock can occur as toxins accumulate; patients may develop ileus, toxic megacolon, bowel necrosis, perforation, and abdominal compartment syndrome.

DIAGNOSIS

Standard laboratory tests include enzyme immunoassays for bacterial toxins and nucleic acid amplification tests (NAAT). Stool tests should be run on unformed stool only, but in patients with ileus, NAAT of a perianal swab may be sufficient [18]. Due to its high sensitivity, NAAT is a superior screening test, but because it does not assess toxin production, colonized patients may test positive, too [19]. Thus, exclusive reliance on NAAT in the absence of toxin assays or strong clinical suspicion may lead to overdiagnosis [20]. After treatment and resolution of symptoms, repeat testing should not be done, as results can remain positive for 30 days [19, 21]. Stool culture is a valuable tool for epidemiologic surveillance, though it is not routinely performed in the clinical setting [21].

Abdominal CT scan is helpful to rule out toxic megacolon, overt ischemia, or perforation, but most typically identifies colonic edema (“thumbprinting”). CT scan and intraoperative extent of disease may be discordant in over 30% of patients [22]. Sigmoidoscopy or colonoscopy is useful to directly visualize the mucosa for pseudomembranes [18]. While identifying such changes is diagnostic, lack of pseudomembranes does not rule out CDI (24% false negative rate) [6]. When laparotomy precedes confirmation of a diagnosis of CDI, intraoperative examination of the colonic mucosa, either by sigmoidoscopy or colotomy, can be helpful because the serosal aspect may appear relatively healthy.

Risk Stratification

CDI is categorized by severity—mild, moderate, severe, or fulminant—as well as initial versus recurrent episode, and more informative stratification early in the disease process would help select treatment. To guide antibiotic therapy, Hensgens et al. prospectively examined 395 patients with CDI at nine centers and identified risk factors for severe CDI (death, prolonged ICU admission, or colectomy) [23]. The most predictive characteristics included age 85 years or older [OR 5.0 (95% C.I. 1.4–17.6)], CDI diagnosis in the ICU [OR 7.0 (95% C.I. 2.0–24.4)], diarrhea at presentation [OR 3.3 (95% C.I. 1.6–6.8)], and hypotension [OR 3.3 (95% C.I. 1.5–6.9)]. Their pilot external validation found a low sensitivity but high specificity, 43% and 92%, respectively. Na et al. prospectively studied 600 patients at three centers to identify risk factors for severe CDI (megacolon, ICU admission, operation, or death) and develop a clinical prediction rule to guide antibiotic therapy [24]. The significant predictors were age 65 years or older [OR 2.4 (95% C.I. 1.1–5.4)], leukocytosis 20,000 cells/mm^3 or greater [OR 4.2 (95% C.I. 2.1–8.6)], and creatinine 2 mg/dL or greater [OR 8.2 (95% C.I. 2.5–26.3)]. The prediction tool had a sensitivity of 53% and specificity of 77%. Subsequent external validation of both models found poor discrimination in a patient population with a mix of endemic and outbreak CDIs. Hensgens’ model performed better when restricted to patients with endemic CDIs (area under the curve 0.78) [25].

Although some surgeons have advocated a scoring system to identify patients who would benefit from operation [26], these criteria have not yet been validated.

TREATMENT

Upon suspicion of *C. difficile* infection, patients should be placed in isolation with barrier precautions, preferably in a private room with a dedicated commode. Alcohol-based hand sanitizer is ineffective against *C. difficile* spores, so everyone interacting with the patient must perform mechanical hand washing with soap and water [18]. Patient rooms should be cleaned with chlorine-based products or other sporicidal agents, though this is probably most important during outbreaks [4].

Non-operative Treatment

Any non-essential antibiotics should be stopped. Patients should be supported with fluid and electrolyte replacement, as needed. Anti-diarrheal and anti-peristaltic medications should be avoided.

Antibiotic therapy is guided by infection severity and initial versus recurrent disease, as reflected by recently updated guidelines of the Infectious Disease Society of America that considered the role of the newer macrolide fidaxomicin [4]. For mild to moderate initial cases, vancomycin (125 mg orally four times per day for 10 days), or fidaxomicin (200 mg orally twice daily for 10 days) are preferred. If unavailable, metronidazole (500 mg orally three times per day for 10 days) can be used. Intravenous vancomycin is ineffective. For severe initial cases, vancomycin or fidaxomicin should be used (at the previously listed doses); metronidazole is not recommended. One recent pair of randomized trials found vancomycin superior to metronidazole across all disease severity (cure 81% versus 73%, respectively; p=0.02) [27]. Another trial showed no significant difference in cure or recurrence with metronidazole versus vancomycin for mild cases but higher rates of cure [RR 1.27 (95% C.I. 1.05–1.53)] and cure without recurrence [RR 1.44 (95% C.I. 1.08–1.92)] with vancomycin in severe cases [28]. Fulminant cases should be treated with multimodal therapy including high doses of oral vancomycin (500 mg four times per day) and intravenous metronidazole (500 mg three times daily). If patients have an ileus or are distended, vancomycin retention enemas (500 mg in 100 ml saline every six hours) should be administered [4].

First recurrences can be treated with vancomycin if the initial episode was treated with metronidazole, or vancomycin taper or fidaxomicin if the initial episode was treated with vancomycin. Subsequent recurrences can be treated with vancomycin taper, vancomycin followed by rifaximin (400 mg three times daily for 20 days), fidaxomicin, or fecal microbiota transplant (FMT).

Older guidelines reserved fidaxomicin for patients with a high risk of recurrence [18]. Relative to vancomycin, fidaxomicin appears to decrease CDI recurrence during a 4-week period after initial treatment. Potential explanations include less harm to the normal intestinal microbiota, bactericidal effect (vancomycin is bacteriostatic), and longer duration of action [29, 30]. When used for severe CDI or a first recurrence, fidaxomicin has been shown to be cost-effective compared to vancomycin [31].

Wilcox et al. conducted two randomized trials examining the addition of actotoxumab and bezlotoxumab, monoclonal antibodies to TcdA and TcdB, respectively, to standard antibiotic therapy [32]. Bezlotoxumab administered as a single 10 mg/kg infusion caused a modest decrease in recurrence compared to placebo or actotoxumab alone (from 27% to 17%). The addition of actotoxumab did not significantly lower the recurrence rate further [32]. Patients with rCDI have decreased serum antibodies to *C. difficile* toxin, while asymptomatic carriers have substantial anti-toxin antibodies. Such findings provide a rationale for development of a toxoid vaccine to help prevent CDI [6].

Following infection, restoration of colonic microbiota takes upwards of 12 weeks, and this delay may make patients susceptible to rCDI. Although probiotics have not been clearly efficacious for secondary prevention [10], FMT appears more promising to expedite recolonization of normal flora, especially in patients with rCDI. Possible routes for FMT include nasogastric or nasojejunal, colonoscopy, enemas, and more recently, oral capsules [18, 33]. Case series of nasoduodenal FMT indicate a cure of 82% after just one treatment. If

patients had a recurrence after initial FMT, cure was achieved with either antibiotics alone or repeat FMT [34]. Oral capsules have been shown to be non-inferior to colonoscopic FMT, and patients reported a better experience with oral capsules compared to colonoscopy [35]. A meta-analysis demonstrated that, in the short term, FMT cures 80% of patients with rCDI [36]. In small studies, there has not been a difference in cure rate or number of FMT treatments needed for cure between fresh versus frozen fecal material [37]. In a follow-up survey evaluating long-term cure rates, 82% of respondents were disease-free at 22 months [38].

Challenges to widespread use of FMT include the identification of quality donors and a robust, standardized screening process. The U.S. Food and Drug Administration considers FMT a biologic therapeutic agent and recommends using donors who are known to the patient. However, many clinical trials use banked stool from donors unknown to the patient [39]. FMT has the potential to transmit disease from donor to recipient, and long-term outcomes are unclear. Some disease processes such as inflammatory bowel disease or irritable bowel syndrome, may be ameliorated by FMT, but it may exacerbate others. In one series, over half of FMT recipients reported weight gain [38]. Furthermore, the essential components of FMT—specific bacterial species versus fecal matter—remain unknown. For example, fecal filtrate transfer (FFT), in which the stool has been sterile-filtered so that no bacteria remain, has demonstrated efficacy in pilot studies [40]. While initial results are compelling, a national FMT registry has been established to monitor long-term outcomes and adverse events and help guide future recommendations [39]. In the meantime, some have started applying FMT to cases of severe, medically refractory CDI [41], potentially expanding its indications beyond rCDI.

Operative Treatment

Early surgical consultation is important for patients who present with severe or fulminant disease or who have disease progression despite medical therapy. While limiting time from diagnosis to operation is associated with decreased mortality, the optimal indications for and timing of operation remain unclear. The standard surgical option for severe/fulminant CDI, total abdominal colectomy with end ileostomy, has significant morbidity and mortality, so physicians feel compelled to give patients ample time to respond to maximal medical therapy [6]. In a retrospective review using the National Surgical Quality Improvement Program (NSQIP) database, patients undergoing total abdominal colectomy for CDI had over 30% 30-day mortality [42]. Increased risk of death was associated with age 80 years or older (OR 5.5), preoperative mechanical ventilation (OR 3.1), chronic steroid use (OR 2.9), preexisting cardiopulmonary disease (OR 2.0), and acute renal failure (OR 1.7). The risk of death using their calculator was consistently higher than using the standard NSQIP surgical risk calculator.

Traditionally, total abdominal colectomy has been recommended for management of toxic megacolon, whether from CDI or other causes, and small cohort studies support the notions that total colectomy is superior to non-operative management [43] and partial colectomy [44] for fulminant CDI generally. However, one recent analysis found no differences in mortality or complications between partial and total colectomy for severe complicated

infections [45]. Furthermore, because CDI is usually confined to the mucosa, some now advocate that—in the absence of toxic megacolon, necrosis, or perforation—diverting loop ileostomy and colonic lavage is a less morbid and potentially more effective approach [6, 26, 46]. This procedure involves diagnostic laparoscopy to ensure no transmural necrosis, laparoscopic loop ileostomy, and intraoperative irrigation with 8 liters of warmed polyethylene glycol, followed by postoperative antegrade enemas with vancomycin (500 mg in 500 ml crystalloid for 10 days) and intravenous metronidazole. In a review of one center's experience, laparoscopic diversion was successfully completed in over 80% of cases, with the remainder of patients requiring laparotomy [26]. Thirty-day mortality was 19% in the diverting ileostomy cohort, compared to 50% in an historic colectomy cohort. Subsequently, 79% of patients in the diverting ileostomy cohort underwent ileostomy reversal compared to 19% in the colectomy group. A retrospective multicenter review found the adjusted mortality with diverting ileostomy to be lower than with colectomy (17% versus 40%) [46], but another analysis of NSQIP patients suggested decreased complications but no different mortality with loop ileostomy [47]. Critics note the risk of bias with historical controls, including more relaxed indications for operation during the use of diverting ileostomy [48]. A recent report of a patient who developed recurrent, fulminant CDI with subsequent death following ileostomy takedown after diverting ileostomy for CDI [49] highlights the need for additional, more rigorous study of this approach.

An even less invasive approach is gastrointestinal lavage (GIL). After confirmation of nasojejunal feeding tube placement and a rectal tube to monitor output, lavage is performed with 8 liters of polyethylene glycol over a 48-hour period. A retrospective review comparing GIL to standard total abdominal colectomy at a single institution showed a non-significant decrease in in-hospital mortality with GIL (25% versus 41%; p=0.35) [50]. Only one of 19 patients in the GIL group failed treatment and required colectomy, but the rate of rCDI was higher with GIL (60% versus 17%; p=0.04).

Without well-established criteria to determine which patients warrant operation and which type of operation is most suitable, surgeons must apply their judgment and experience. Total abdominal colectomy with diverting ileostomy remains the traditional approach, but newer, less invasive techniques may prove acceptable or even desirable (Figure 1).

CONCLUSIONS

Patients with recent antibiotic use or hospitalization, in addition to a compromised immune system from age, comorbidities, or medications, are at the highest risk of CDI. Prompt diagnosis and treatment are critical. Oral or enteral vancomycin is part of the preferred first-line antimicrobial treatment across the disease spectrum, including mild-moderate initial cases. Novel immune therapies remain under investigation. Compared to total abdominal colectomy, diverting ileostomy with colonic irrigation may improve survival and ileostomy reversal rates, but comparisons between these two approaches may have been biased. Fecal microbiota transplantation is a promising therapy, especially for rCDI, but investigators have not yet fully elucidated its indications, adverse effects, and long-term outcomes.

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ABBREVIATIONS

CDI	*Clostridium difficile* infection
PPI	proton pump inhibitor
rCDI	recurrent *Clostridium difficile* infection
NAAT	nucleic acid amplification test
FMT	fecal microbiota transplant
NSQIP	National Surgical Quality Improvement Program
GIL	gastrointestinal lavage

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LEARNING OBJECTIVES

1. Understand the transmission of *Clostridium difficile* in hospital settings
2. Describe the recommended antibiotic treatment of *Clostridium difficile* infection
3. Discuss the roles of novel therapies such as probiotics, immunotherapy, and fecal microbiota transplant in prevention and treatment of *Clostridium difficile* infection
4. Describe the surgical options for treatment of *Clostridium difficile* infection, including the underlying rationale

QUESTIONS

1. Which of the following strains of *Clostridium difficile* is considered the most virulent?
   - **a.** NAP1
   - **b.** NAP4
   - **c.** NAP7
   - **d.** NAP11
2. Which of the following is NOT associated with *Clostridium difficile* infection (CDI)?
   - **a.** Age > 65 years
   - **b.** Recent antibiotic use
   - **c.** Non-steroidal anti-inflammatory drug use
   - **d.** Proton pump inhibitor use
3. Which of the following statements is true regarding CDI diagnosis?
   - **a.** Nucleic acid amplification testing (NAAT) identifies the amount of TcdA toxin
   - **b.** NAAT cannot readily discriminate between those with active infection and those who are colonized
   - **c.** Following resolution of symptoms, repeat NAAT should be performed to ensure cure
   - **d.** CT scan is helpful in the identification of pseudomembranes
4. Which of the following is the most appropriate treatment for mild-moderate initial CDI?
   - **a.** Oral vancomycin
   - **b.** Intravenous fidaxomicin
   - **c.** Intravenous vancomycin
   - **d.** Rectal metronidazole
5. Which of the following is an appropriate treatment for recurrent CDI?
   - **a.** 10-day course of intravenous vancomycin if the initial episode was treated with metronidazole
   - **b.** 10-day course of oral vancomycin if the initial episode was treated with vancomycin
   - **c.** Oral vancomycin taper if the initial episode was treated with vancomycin

d. Oral fidaxomicin if the initial episode was treated with metronidazole

6. Which of the following is a true statement regarding fecal microbiota transplant (FMT)?

a. FMT is associated with a cure of approximately 80%

b. FMT administered via oral capsules had a significantly lower likelihood of cure than FMT via colonoscopy

c. FMT can be administered via suppositories

d. FMT with frozen stool had a significantly lower cure rate than with fresh stool

7. Which of the following is NOT involved as part of diverting ileostomy and colonic irrigation?

a. Diagnostic laparoscopy

b. Intraoperative lavage with polyethylene glycol

c. Postoperative antegrade irrigation with polyethylene glycol

d. Postoperative retrograde (per rectum) vancomycin enemas

8. Which of the following is a true statement regarding surgical outcomes for CDI?

a. Total abdominal colectomy is associated with 20% 30-day mortality

b. The standard NSQIP calculator overestimates CDI-related surgical mortality

c. Diverting ileostomy can be successfully completed in only 50% of cases

d. Ileostomy reversal appears to be more common after diverting ileostomy than after total abdominal colectomy

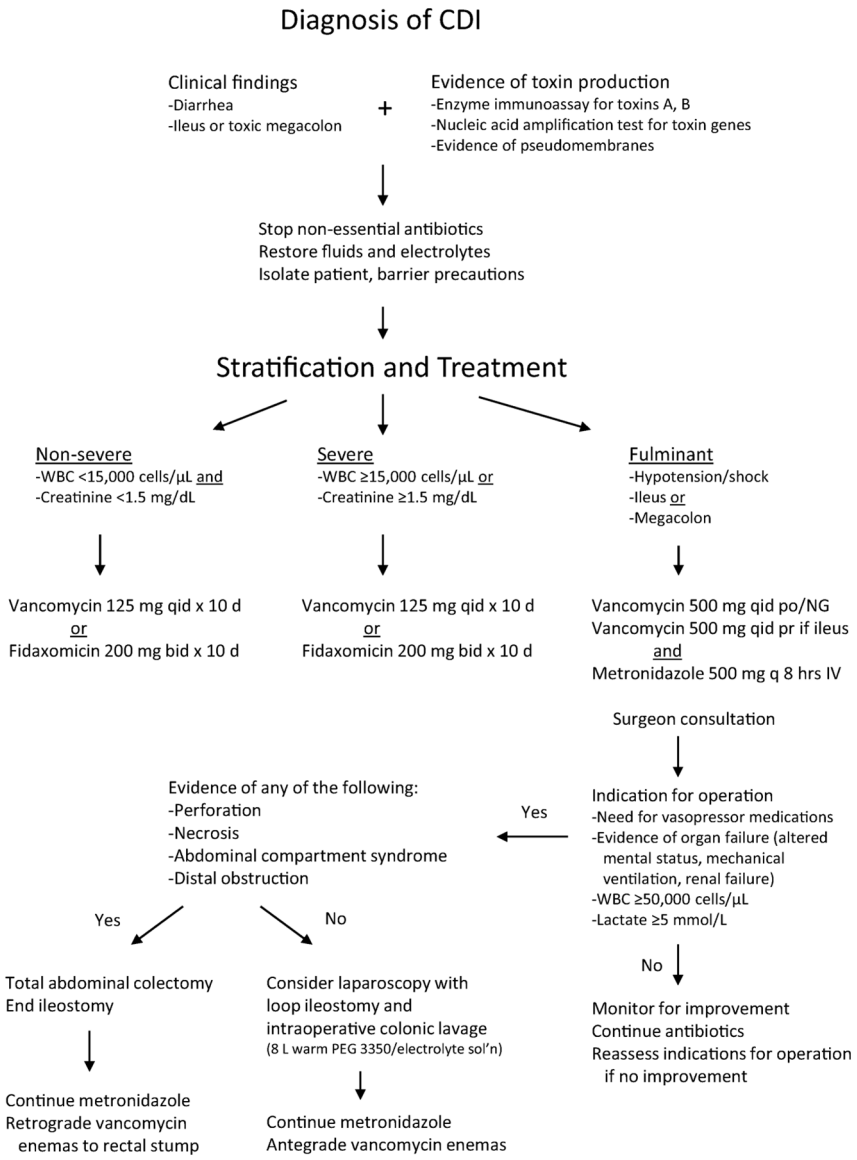

Figure 1.
Schema for management of Clostridium difficile colitis.