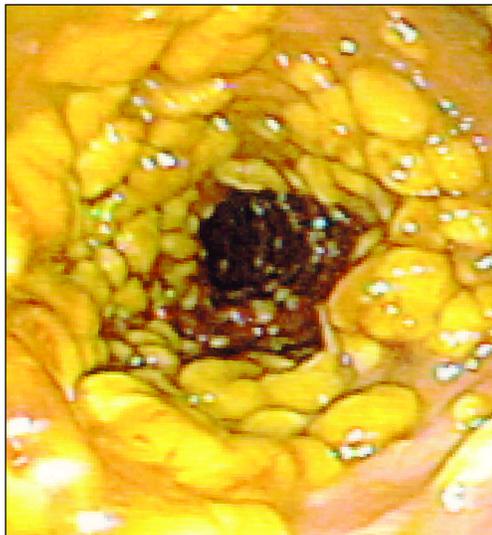


## Relapsing *Clostridium Difficile* Colitis

by Robert J. Bonasera, Jenifer K. Kramer, Sammy Ho



**Gross endoscopic view.** Description: pseudomembranes appear as yellow adherent plaques, 2–10 mm in diameter, scattered over the colonic mucosa interspersed with hyperemic mucosa.

The above image was captured during a sigmoidoscopy of an 82-year-old woman who was complaining of yellowish, watery diarrhea and left lower quadrant pain. Her past medical history included congestive heart failure, diabetes, and chronic renal insufficiency. Two weeks previous, she was discharged from a local hospital where she had been treated with antibiotics for pneumonia. During that hospital course, she acquired *Clostridium difficile* colitis, and was treated with metronidazole. Upon discharge, she remained on oral metronidazole and completed a 14-day regimen of the medication. The patient had resolution of her symptoms, however, within a week of completing her treatment the diarrhea had returned. Of

note on physical examination was a moderately tender lower abdomen, more so on the left side. Her oral temperature was 100.8, and her white blood cell count was 19.1. Stool cytotoxin assays for *Clostridium difficile* were positive. On sigmoidoscopy, biopsies of the above lesions (refer to illustration) were obtained and the histological findings were consistent with pseudomembranous colitis. The patient was again treated with oral metronidazole, 500 mg TID for fourteen days. She was provided with complete resolution of her symptoms.

Infection with *Clostridium difficile* can manifest in a number of ways. Depending upon the condition of the host, it can be as benign as an asymptomatic carrier state or as severe as toxic megacolon requiring colectomy. These two conditions represent the extremes of the clinical spectrum. The typical presentation is that of watery diarrhea, lower abdominal pain and low-grade fevers starting either during or shortly after

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antibiotic administration. All antibiotics can predispose to colonization; however, the more common culprits are clindamycin, ampicillin, amoxicillin and the cephalosporins (1).

Establishing a diagnosis of *Clostridium difficile* infection most often involves a bioassay of the stool that can detect the cytotoxins released by the organism. This is considered the gold standard. This cytotoxin assay carries with it a high sensitivity (94%–100%) and specificity (99%), however it is relatively expensive and results are not obtainable before 24–48 hours (2). In contrast to the cytotoxin assays, immunoassays such as the ELISA based assay are gaining popularity due to their lower cost, technical ease to perform, and the fact that they require less time to reach a conclusive result. A main criticism is that the sensitivity of the immunoassay is less than that of the cytotoxin assay. Due to this disparity, the cytotoxin assay will pick up an additional 5%–10% of cases that will be missed by the immunoassay(2). The role of endoscopy in patients with suspected *C. difficile* colitis is not well defined. Relapsing infections, severe disease, or a diagnosis that is in doubt are situations that commonly lead to an endoscopic examination. Pseudomembranes are not required to make a diagnosis, however, their presence in a patient with antibiotic associated diarrhea is considered pathognomonic for *C. difficile* infection. In addition, other non-specific endoscopic findings include friability, erythema, edema, and small ulcerations. It is of value to note that there will be rectosigmoid sparing in up to 10% of these cases, if possible a colonoscopy is preferable to a sigmoidoscopy in light of this need to examine the proximal colon(3).

The first step in treating these patients is to stop the causal antibiotic. This may be sufficient to ameliorate symptoms in patients with mild disease. There are no steadfast rules which dictate who should be treated, however, there is a consensus that patients with significant comorbidities or moderate-severe disease are to be treated. The first line treatment is oral metronidazole 500 mg TID  $\times$ 10–14 days. Oral vancomycin can be considered the alternative first line agent at 125 mg QID  $\times$ 10–14 days. Both are equally efficacious in treating the infection, however, vancomycin is more expensive and the selection of vancomycin resistant enterococci is an issue (4). Oral bacitracin, 250,000U

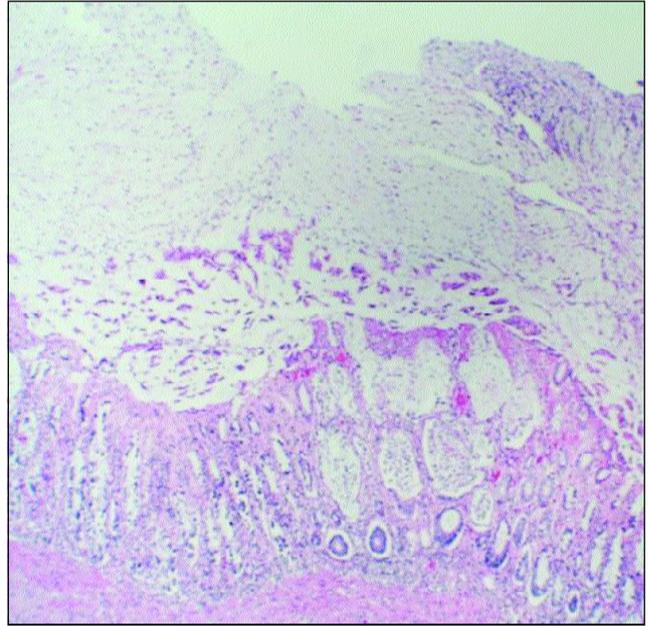
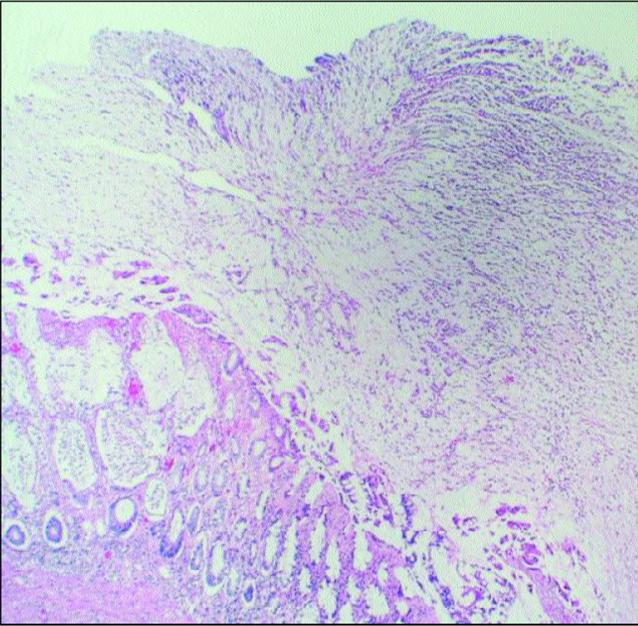
**Table 1**  
**Vancomycin tapering and pulsed regimen(5)**

Week 1:	125 mg QID
Week 2:	125 mg BID
Week 3:	125 mg QD
Week 4:	125 mg every other day
Week 5 & 6:	125 mg every third day

QID is also effective, albeit rarely used due to its unavailability.

The problem of relapsing infections is not uncommon in these patients. It occurs in 10%–25% of patients treated with metronidazole or vancomycin (1). By definition, complete symptom resolution is experienced during antimicrobial therapy. Symptoms return most commonly within a few days after therapy is completed, however, it can be as long as eight weeks afterwards. Relapsing infections is not due to antibiotic resistant organisms. To date, *C. difficile* resistance to metronidazole or vancomycin has not been found (5). One very plausible theory is that the organism finds a safe haven within the colonic diverticuli in its spore form. Low levels of antibiotic in the diverticuli, in addition to the protective spore state allow for organism survival during treatment. Upon cessation of treatment, spores transform back to their vegetative, toxin producing state. Another explanation would be a sub-optimal immune response in patients who have these relapses. One study found that asymptomatic carriers of *C. difficile* had higher antibody levels against enterotoxin A. Furthermore, those who had relapses were found to have lower levels of this antibody (6).

The treatment of a patient with relapsing *C. difficile* infection consists of repeating the initial regimen. It is prudent to confirm the diagnosis by whatever means available before beginning the treatment. An issue of contention arises in patients who have multiple relapsing infections. The vancomycin tapering and pulsed dosing regimen has been found to be efficacious in this patient population (Table 1). The rationale for this treatment is consistent with the paradigm of the spores being protected in diverticuli, only to reactivate and cause disease upon cessation of treatment. In a study by Tedesco, et al, they used a regimen consisting of a tapering dose



**Microscopic biopsy.** Description: epithelial ulceration with the classic “volcano” exudates of fibrin and neutrophils.

of vancomycin for 21 days, and then pulse doses of vancomycin every other day for 7 days, and then every 3rd day for 14 days. Twenty-two patients, all of whom had multiple relapses of pseudomembranous colitis were treated. All patients were provided with relief of their symptoms with a mean follow-up time of six months (7). Administering the antibiotic every other or every third day allows the spores to vegetate (become active) on the off days of therapy, and subsequently be exposed when the antibiotics are taken again. Another alternative therapy for patients with multiple relapses is anion-binding resins. Cholestyramine and colestipol are recommended to be used as adjuncts to antimicrobial therapy as studies have shown that they are not effective when used exclusively. Therapy with microorganisms is another potential treatment option. Although less well studied, the premise is logical. The goal is to re-establish colonic flora equilibrium, or at least reintroduce the organisms which help defend against *C. difficile*. There are reports on the use of fecal enemas, oral *Lactobacillus*, and a yeast by the name of *Saccharomyces boulardii*. Although anecdotal success has been reported, these agents are not FDA approved and no good evidence is available to support their use (7).

Further investigation is needed to elucidate risk factors that predispose patients to relapsing infections with *Clostridium difficile*. Furthermore, the optimal treatment for the population with multiple relapses is still unknown. The answers to these questions will contribute greatly towards lowering the incidence of these relapsing infections as well as alleviating some of the cost and patient suffering associated with this clinical dilemma.

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