

Clostridium difficile colitis

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Bacteriology and Pathogenesis

Clostridium difficile is a Gram-positive spore-forming anaerobic bacillus, which is found in the stool flora of 25-80% of healthy infants but rarely in the stool of healthy adults and children over the age of 12 months.

Ingested spores of *C. difficile* survive the gastric acid barrier and germinate in the colon. Colonization of the adult intestinal tract occurs when antibiotics alter normal intestinal flora, which otherwise facilitates resistance to colonization. Between one third and two thirds of patients colonized develop clinical symptoms.

Some strains of *C. difficile* are non-toxinogenic, but the majority make two protein exotoxins, toxin A, a 308 kDa protein and toxin B, a 275 kDa protein. Toxin A binds to a specific receptor on the brush border of the intestinal epithelium, a glycoprotein with an α -linked galactose; the intestinal receptor in humans for toxin B is less well-characterized. Both toxins modify Rho proteins at a specific threonine residue by addition of a glucose molecule, leading to inactivation of the protein. This is followed by disaggregation of polymerized actin, opening of tight junctions between cells, cell rounding and subsequent cell

death. The toxins also induce the release by various cells of pro-inflammatory mediators and cytokines (such as IL-8), as well as activation of the enteric nervous system, leading to neutrophil chemotaxis and fluid secretion. Toxin B is not enterotoxic in animals (as is toxin A), but it is a much more potent cytotoxin in tissue culture than toxin A. Occasional toxinogenic strains of *C. difficile* associated with clinical illness make toxin B but contain an internal deletion in the gene for toxin A and do not make an active form of this toxin. Strains of *C. difficile* that produce neither toxin A nor B do not cause clinical illness.

Epidemiology

C. difficile is the leading cause of nosocomial enteric infection, with 17-21% of patients in two studies acquiring colonization during hospitalization; the risk of acquisition increases linearly with the length of hospital stay. Antimicrobial therapy substantially increases the probability of acquiring *C. difficile* colonization and colitis; the risk is highest in patients treated with clindamycin, ampicillin, or a cephalosporin, but virtually all antibiotics can predispose to *C. difficile* infection. Receipt of clindamycin is a particular risk factor for disease due to clindamycin-resistant *C. difficile*. *C. difficile* infection may also follow cancer chemotherapy. Patient to patient transmission of the organism

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occurs, and the organism can be cultured from many environmental surfaces in rooms of infected patients, and on hands, clothing and stethoscopes of health care workers. Outbreaks can occur in hospitals, nursing homes and other extended care facilities. A recent study estimated that a symptomatic episode of *C. difficile*-associated diarrhea (CDAD) added 3.6 days to hospital length of stay ($p=0.0003$) and \$3,669 to hospital costs ($p=0.003$), after adjusting for other relevant factors in a multivariate analysis; CDAD was not, however, an independent risk factor for increased mortality at 3 months or 1 year.

Clinical Manifestations

Colonization of the colon by *C. difficile* produces a wide variety of clinical manifestations, ranging from the asymptomatic carrier state to severe fulminant disease with toxic megacolon, perforation and death. Symptomatic patients generally develop acute watery diarrhea, abdominal pain, and fever. More severely affected patients develop colitis with distinctive pseudomembranes on sigmoidoscopy or colonoscopy.

Historically, 3% of cases have developed severe *C. difficile* colitis. A minority of patients has disease primarily in the cecum and right colon, and may present with fever, right-sided lower abdominal pain, and marked leukocytosis but little or no diarrhea. Also, *C. difficile* infection may occasionally complicate idiopathic inflammatory bowel disease.

The incidence of severe *C. difficile* colitis has recently been reported to be increasing. In a recent Canadian study, for example, investigators examined the incidence of severe *C. difficile* colitis over the period from 1991 to 2003. They defined complicated *C. difficile* colitis as toxic megacolon, perforation, shock, the need for colectomy, or death.

Overall, the incidence of complicated *C. difficile* colitis increased from 7.1% of cases in

1991 to 18.2% in 2003, and the incidence of death from *C. difficile* colitis increased from 4.7% in 1991 to 13.8% in 2003. Factors associated with complicated *C. difficile* colitis in this study included an age greater than 65 years, a white blood cell count greater than 20,000, and an elevated serum creatinine. Another study reported a recent outbreak of *C. difficile* colitis at the University of Pittsburg with increasing severity of disease; this outbreak followed the increased use of levofloxacin at that hospital. Overall, the incidence of *C. difficile* colitis rose from 2.7 per thousand hospital discharges in 1999 to 6.8 per thousand hospital discharges in 2000-2001. The incidence of severe *C. difficile* colitis rose in the same time period from 5.6% of cases to 8.8% of cases.

Two factors have recently been shown to increase the probability of symptomatic disease in patients who acquire *C. difficile* colonization in the hospital: the severity of other illnesses and reduced levels of serum IgG antibody to toxin A.

Diagnosis

C. difficile can be isolated by anaerobic culture of stool, and the presence of toxin genes confirmed by PCR, but this approach is seldom used for clinical diagnosis because it takes several days and is expensive.

The gold standard for diagnosis is a tissue culture assay for the cytotoxicity of toxin B, utilizing pre-incubation with neutralizing antibody to this toxin to show the specificity of cytotoxicity. This test can detect as little as 10 picograms of toxin B in stool and has a high sensitivity (94-100%) and specificity (99%). However, the test takes 1-3 days to complete and requires tissue culture facilities. More recently, enzyme-linked immunosorbent assays (ELISAs) have been developed to detect toxin A and/or B in stool. These assays detect 100-1000 picograms of either toxin and have a sensitivity of 66-94% and a specificity of 92-98%. Because of the rapidity of

testing and ease of performance, ELISAs for toxin A and B are now used most frequently by clinical laboratories for diagnosis of *C. difficile* infection. Because toxin A-negative, toxin B-positive strains of *C. difficile* may cause clinical illness, an ELISA for detection of both toxins in clinical specimens should be used. Approximately 20% of patients may require more than one stool assay to detect toxin if the clinical suspicion of *C. difficile* infection is high. The cytotoxicity assay for toxin B will pick up an additional 5-10% of cases missed by ELISA techniques, and it occasionally may be useful to perform this test, if available, if the ELISA is negative but clinical suspicion is high.

Lower endoscopy is a rapid way to look directly for evidence of colitis and pseudomembranes, and may be useful in the very ill patient in whom rapid diagnosis is necessary. However, this is an expensive approach to diagnosis and potentially dangerous; at least 10% of cases will not be detected by flexible sigmoidoscopy, because only right-sided disease is present. Diffusely thickened or edematous colonic mucosa may sometimes be seen by abdominal CT scan and may be very suggestive of the diagnosis.

Some patients have positive assays for toxin even at the completion of successful therapy, and it is not necessary or recommended to recheck toxin assays as part of standard clinical management. There is no evidence that treatment of asymptomatic carriers of *C. difficile* provides any

Treatment

Therapy of Initial Episodes: When *C. difficile* colitis is diagnosed, the inciting antibiotic should be stopped if at all possible and antiperistaltic therapy should be avoided. Persistent or more severe symptoms require specific antimicrobial therapy for *C. difficile*. Two studies have directly compared initial therapy with metronidazole (in an oral dose of 500 mg tid or 250 mg qid) with vancomycin (500 mg qid orally), each given for ten

days, and have shown that these therapies were equally efficacious, both in resolving symptoms as well as in the subsequent risk for relapse. Another study examined different doses of vancomycin and showed that an oral dose of 125 mg qid was equivalent to 500 mg qid for 10 days, both for symptomatic response and risk for subsequent relapse. In many series of patients, therapy with either metronidazole or vancomycin was effective in resolving symptoms in more than 95% of patients, although 10-20% of patients subsequently relapsed. Because of lower cost and avoidance of selective pressure for vancomycin-resistant organisms such as vancomycin-resistant enterococci, initial therapy with metronidazole (either 500 mg PO tid or 250 mg PO qid) is currently preferred initial therapy for *C. difficile* colitis. However, some authorities prefer initial therapy with vancomycin in the more severely ill patients, or in women who are pregnant or children less than ten years of age in whom metronidazole should be avoided if possible. Metronidazole is well-absorbed from the small intestine and produces low or undetectable levels in stool as *C. difficile* diarrhea subsides, while oral vancomycin is not absorbed and produces high fecal levels even in the absence of diarrhea.

The duration of initial therapy should be 10 days (or therapy may be continued until one week after completion of the inciting antibiotic, if that cannot be stopped earlier). Oral bacitracin (20,000 to 25,000 units qid) has been shown to be as effective as vancomycin in ameliorating clinical symptoms of *C. difficile* disease, but bacitracin was less effective in eradicating the organism from stool; patients treated with bacitracin also had a higher risk of subsequent relapse. Bacitracin should be reserved for unusual situations, in which neither metronidazole or vancomycin can be used.

Therapy of severe C. difficile colitis: A fraction of patients will have severe *C. difficile* colitis, manifest by colonic wall thickening and dilatation, pseudomembranes, abdominal tenderness, ileus,

marked leucocytosis and severe toxicity; some of these patients develop toxic megacolon, perforation, sepsis, need for colectomy, or death.

In the presence of severe ileus or toxic megacolon, intravenous metronidazole (given as 500 mg iv q8h) produces fecal concentrations above the inhibitory concentration for *C. difficile* and may be used for initial therapy instead of oral antibiotic. One series of nine patients reported use of vancomycin administered by rectal enema or catheter in patients with persistent symptoms of severe *C. difficile* colitis and ileus, despite 5-7 days of standard antibiotics (including IV metronidazole). In this series, 2-3 g of vancomycin rectally per day was used, divided in doses every 4-12 hours, and 8 of 9 patients improved. This approach has not been studied in a controlled fashion, however, and so the role of rectal vancomycin is still inadequately defined in severe *C. difficile* colitis.

In another report of 2 patients with severe CDAD whose symptoms persisted despite 5-12 days of standard antibiotics, IVIG (0.2-0.3 g/kg as a single dose) was given, with improvement in symptoms. Again, however, no controlled data on this approach are yet available. Some patients with severe CDAD, particularly those with toxic megacolon, may require colectomy.

Therapy of relapsing C. difficile colitis: Although most patients with *C. difficile* colitis respond rapidly to initial therapy, relapse of disease occurs in approximately 10-20% of patients. Relapse generally occurs within the first few weeks after initial therapy, and often in the first few days. The risk of relapse is significantly higher in patients who fail to develop a protective IgG response to toxin A during initial illness. The first relapse of *C. difficile* colitis can be treated with another 10-14 day course of either oral metronidazole or vancomycin, either of which produces a response rate of approximately 95%. A smaller number of patients have multiple relapses. One study showed a relapse rate of 24% after an

initial episode of *C. difficile* colitis, but a relapse rate of 65% after treatment of recurrent disease. In another study, standard courses of vancomycin or metronidazole resulted in relapse rates of 40-50% in patients with recurrent CDAD.

Antimicrobial resistance as the mechanism for relapse is uncommon and one hypothesis is that spores of *C. difficile* persist in the colon or the environment of the patient and subsequent germination in the intestine produces vegetative forms and clinical illness.

The approach to therapy of patients with multiple relapses of *C. difficile* colitis has not been examined by randomized, prospective, controlled clinical trials, so that the best therapeutic approach is uncertain. Anion exchange resins (such as cholestyramine 4 grams 3 times a day) have been used to bind *C. difficile* toxins in addition to antimicrobial therapy, but little prospective controlled data are available to support this approach.

Another approach to the therapy of relapsing *C. difficile* disease has been to combine *Saccharomyces boulardii* (dosed at 500 mg orally 2id and given for 4 weeks), beginning 4 days before the end of a 10 day course of standard antimicrobial therapy such as vancomycin. In one study, this combination reduced the relapse rate in patients with prior relapses compared with vancomycin alone. However, results with this approach were not as good as published studies examining a tapering vancomycin regimen described below, and *S. boulardii* is not easily available in the United States. Other probiotics, including *Lactobacillus* strain GG, have been added to antimicrobial therapy of relapsing *C. difficile* colitis, but again, this is supported by only small scale or non-controlled studies.

Several reports document improved results for relapsing CDAD with: (1) a tapering regimen of vancomycin (generally 500 mg-2 g per day tapered to 125-750 mg per day over 3-4 weeks); or (2) a pulsed dosing regimen of 10-14 days of standard

vancomycin, followed by 125-500 mg of vancomycin every 2-3 days for 3 weeks. The best results for recurrent CDAD are reported in a study that used tapering doses of vancomycin over a 6 week period; this regimen may allow spores to germinate during the days between vancomycin therapy, with killing of the vegetative forms on re-exposure. This approach cured all 22 patients who had had multiple previous relapses, with follow-ups as long as a year. The regimen employed was as follows:

- Week 1: Vancomycin 125 mg qid
- Week 2: Vancomycin 125 mg bid
- Week 3: Vancomycin 125 mg qd
- Week 4: Vancomycin 125 mg qod
- Weeks 5,6: Vancomycin 125 mg q3d

The combination of vancomycin and rifampin (600 mg PO bid) for 10 days has yielded good results in a few small studies of relapsing *C. difficile* colitis.

A small number of patients with refractory *C. difficile* disease have responded to antimicrobial therapy in conjunction with an infusion of intravenous immunoglobulin at a dose of 0.2-0.3g/kg, but this therapy has not yet been validated.

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