

# ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Diseases

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## Management of *C. difficile* Infection in IBD

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**G&H** Could you discuss the increasing incidence of *Clostridium difficile* infection in patients with inflammatory bowel disease?

**DB** In the 1980s, it was believed that *C. difficile*, an anaerobic, spore-forming, gram-positive bacteria, did not contribute to colitis flare in patients with inflammatory bowel disease (IBD). This past dogma does not appear to hold true anymore; we now believe that *C. difficile* infection will preferentially affect IBD patients.

Over the past 6 years, *C. difficile* infection has doubled in incidence in North American hospitals, including the United States and Canada. This increase has been well documented by the Centers for Disease Control and Prevention in the United States. During this time period, we have seen a dramatic increase in the incidence of IBD patients who have contracted *C. difficile*. We had previously reported a marked increase in *C. difficile* infections in IBD patients at the Medical College of Wisconsin's major teaching college hospital, Froedtert Memorial Lutheran Hospital, and an additional report from the Washington University of St. Louis by Dr. Christian Stone showed very similar findings. These two reports were published in 2007 in *Clinical Gastroenterology and Hepatology* in back-to-back articles.

Because both of these papers were based on referral hospitals, an additional report was published in *Gut* last year by Dr. Ashwin Ananthakrishnan, a gastroenterol-

ogy fellow who worked with me at the Medical College of Wisconsin, using the nationwide inpatient sample, which is a survey of 20% of short-stay hospitals in the United States. During that same time period, there was a significant rise in *C. difficile* infections among patients with IBD, primarily patients with forms of IBD colitis. The nationwide inpatient sample also demonstrated that IBD patients who suffer from *C. difficile* infection have an increased morbidity, longer hospital stays, and an increased mortality of 4.2% compared to *C. difficile* infections in non-IBD patients.

**G&H** Which IBD patients have a higher risk for contracting *C. difficile*?

**DB** The IBD patients who are most at risk are individuals with IBD colitis, either ulcerative colitis or Crohn's colitis. On multivariate logistic regression analysis, we also determined that patients on a maintenance immunosuppression strategy appeared to be most likely to contract the infection. Antibiotic exposure was not required for *C. difficile* infection to be contracted by the IBD patient population. Based upon a 2005 cohort that we reported on in *Clinical Gastroenterology and Hepatology*, only 61% of the patients who were ultimately found to have *C. difficile* infection had, in fact, used antibiotics in the two months preceding the infection. The vast majority of patients were young, otherwise healthy outpatients who contracted *C. difficile*.

In addition, past history of *C. difficile* infection is important. Approximately 10% of the IBD patients followed at my former center at the Medical College of

Wisconsin were found to have a history of *C. difficile* at some point in their life, and approximately half of those individuals had suffered from a recurrent infection.

Patients who have undergone ileoanal pouch reconstruction (ie, J pouch) are also at risk for *C. difficile* infection, according to research conducted by Dr. Bo Shen at the Cleveland Clinic, who documented that these individuals can, in fact, harbor *C. difficile* enteritis in their reconstructed ileoanal pouch. We had previously reported that *C. difficile* infection could occur in the small intestine in patients with ileostomies. *C. difficile* enteritis has historically been associated with extremely high rates of mortality.

#### **G&H** How effective is diagnostic testing for *C. difficile* infection in IBD patients?

**DB** The detection of *C. difficile* can be challenging, as diagnostic tests may have a low sensitivity. In our 2005 patient cohort published in *Clinical Gastroenterology and Hepatology*, approximately half of the IBD patients who were found to have *C. difficile* were detected on the first stool enzyme-linked immunosorbent assay (ELISA) analysis for *C. difficile* toxins A and B. A second stool analysis increased the detection rate to approximately 70% of the patients, whereas the third sample brought the detection rate to approximately 80% and the fourth stool analysis to approximately 90%. Treating physicians should be prepared to obtain multiple stool testing to confirm a diagnosis with the use of ELISA for detecting *C. difficile* toxins A and B.

Endoscopic appearance of *C. difficile* infection with the classic pseudomembranous eruption on the mucosal surface is not typically found in the IBD patient population. The fact that both an IBD flare and a *C. difficile* infection will frequently manifest with identical symptoms makes it essential for clinicians to consider and test for the possibility of this infection. An IBD patient who is suffering from a true infection in the colon will deteriorate without appropriate antibiotic treatment.

#### **G&H** How, specifically, does *C. difficile* infection complicate the severity and management of IBD?

**DB** *C. difficile* infection elevates the severity of the patient's status. Approximately 60% of IBD patients who contracted *C. difficile* infection required hospitalization in our published report from *Clinical Gastroenterology and Hepatology*. As previously discussed, the nationwide inpatient sample data suggested increased hospital stays, increased lengths of stays, and an increased mortality rate of 4.2% in IBD patients. I suspect that much of the mortality increase comes from the difficulty in establishing

the diagnosis, as alluded to above, because 10% of IBD patients may manifest concomitant *C. difficile* infection at the time of their initial IBD presentation. We believe that *C. difficile* will precipitate an IBD colitis flare, and both the infection and the IBD will ultimately need treatment for the patient to recover.

In terms of the IBD treatment itself, it is important to keep in mind that the traditional treatment approach for an IBD patient experiencing colitis flare is broad, generalized immunosuppression with intravenous steroids, which will, in fact, worsen the *C. difficile* infection substantially if it is not treated with appropriate antibiotics. *C. difficile* infection in IBD represents an infectious complication where we must target the pathologic bacteria with the appropriate antibiotic strategy. Thus, IBD patients who contract *C. difficile* infection are at a remarkably increased risk for hospitalization as well as colectomy, a conclusion that was supported in the previously discussed paper by Dr. Ananthkrishnan. Over 118 IBD patients died from a *C. difficile*-related infection in the year 2004 in the nationwide inpatient sample. By extrapolating from this sample, we can estimate that, at the present time, over 500 IBD patients die annually as a result of *C. difficile* infection. Accordingly, between the years 2004 and 2008, we can estimate that as many as 2,500 IBD patients have died from *C. difficile* infection in the United States. It is, therefore, essential that treating clinicians keep this infection high on their radar screens in order to make the diagnosis and offer appropriate antibiotic therapy to control the synergistic inflammation that will oftentimes flare in the setting of IBD colitis.

#### **G&H** In other words, untreated *C. difficile* infection could cause an IBD patient to become refractory to the IBD treatment?

**DB** That is exactly the problem; *C. difficile* will not allow a patient experiencing colitis flare to resolve with immunosuppression alone. That is why it is essential for physicians treating IBD patients to be well acquainted with this new challenge. It is important for the treating physician to consider the possibility of *C. difficile* infection in the patient and to be persistent with testing in order to clarify whether the infection is contributing to the patient's deterioration.

#### **G&H** How is *C. difficile* infection usually treated in IBD patients?

**DB** *C. difficile* infection has been historically treated with the antibiotic metronidazole. This treatment approach had a 90% success rate roughly 10 years ago. Presently, it is commonly believed that there is an increased failure rate

with metronidazole therapy approaching 50%. We have limited data regarding the optimal treatment approach for patients with IBD who have contracted *C. difficile* infection, as examination of this patient population is fairly new. Oral metronidazole is currently considered to be reasonable for outpatients. We have come to realize that in patients suffering from more severe infection, and certainly in inpatients who are sick enough to warrant hospitalization, the oral antibiotic vancomycin may actually be more effective, at dosages as high as 500 mg orally four times a day. There have been data, not from the IBD patient cohort but from hospitalized patients who have been treated with both oral metronidazole and oral vancomycin, showing that vancomycin is superior. For mild patients, again based upon data not from the IBD patient cohort, we suspect that oral vancomycin is equivalent in efficacy to metronidazole.

**G&H** Has antibiotic plus immunomodulator therapy or combination antibiotic therapy been examined in these patients?

**DB** Treatment of the concomitant IBD colitis is also quite important, and we do recommend increasing medical therapy for the IBD. However, there is one caveat: the maximal dose of intravenous steroids should not be used. In order for the body to clear the *C. difficile* infection, a humoral immune response to *C. difficile* toxin A has to be generated. It is believed that the high dosages of intravenous steroids used in the treatment of IBD colitis may actually blunt the body's ability to produce an antibody response against toxin A, making it extremely difficult to clear the infection. In certain situations, we will consider the use of intravenous anti-tumor necrosis factor (TNF)- $\alpha$  antibody therapy in patients who are suffering from severe colitis as an approach to avoid surgical management (colectomy).

Intravenous metronidazole can be added to oral vancomycin treatment, and our regimen for using the intravenous metronidazole is, in part, based upon the fact that it might be better tolerated by patients. In addition, it is important for patients with *C. difficile* infection to maintain an oral diet. Sustaining oral diet and intake will allow healthy bacteria to be maintained in the gut and, hopefully, will diminish *C. difficile* colonization. A patient who is told to withhold from oral food or fluids may actually give the *C. difficile* infection a growth advantage.

**G&H** Are probiotics effective in IBD patients with *C. difficile* infection?

**DB** As probiotics have been examined in the general population of individuals with *C. difficile* infection, but

not yet specifically in the IBD patient cohort, a variety of probiotic strategies have been used anecdotally. Some patients have reported improvement with *Lactobacillus* probiotic strains. *Saccharomyces boulardii* reagents have also been shown to be successful in a series of patients without IBD and *C. difficile* infection, and we frequently use this regimen in our practice.

**G&H** Is *C. difficile* relapse a significant challenge in these patients?

**DB** *C. difficile* relapse is a very difficult problem and oftentimes portends a bad outcome and surgical intervention (colectomy). Among the 2005 cohort of IBD patients who contracted *C. difficile*, close to half experienced a relapse, and among those patients, half required colectomy.

**G&H** What is the colectomy rate, overall, in patients with IBD and *C. difficile*?

**DB** According to a series of abstracts evaluating treatment approaches, including colectomy, the colectomy rate has decreased from 45% to 34% to 4% among IBD patients who were hospitalized for *C. difficile* superinfection between the years 2004–2006 at my former center. We attributed this success to the use of vancomycin as the major antibiotic strategy for patients, very aggressive testing to confirm the diagnosis, and empiric therapy for *C. difficile* patients who had a prior history of *C. difficile* or who had broad-spectrum antibiotic exposure, which would have been a likely precipitating event for the *C. difficile* infection. In addition, as mentioned previously, the escalation of IBD therapy with anti-TNF- $\alpha$  antibody strategy was also helpful in patients with severe colitis. *C. difficile* is known to elicit a TNF- $\alpha$  cytokine response at the bowel, which may effectively be targeted with this therapeutic approach.

**G&H** What are the main research needs in this area?

**DB** We need to better understand the *C. difficile* epidemic in general. It is currently not understood whether the BI/NAP1 epidemic strain of *C. difficile*, which has been implicated in the increased severity of infection in North America, is also responsible for the increased level of illness in IBD patients who have contracted this infection.

Identifying the optimal treatment strategy for IBD patients with *C. difficile* infection is also extremely important. The data available so far have been limited to only a few referral hospitals and administrative

databases. The development of additional strategies, including alternative antibiotics and compounds such as nitazoxanide or rifaximin is also of interest to provide additional treatment strategies to the IBD patient population. Rescue strategies with intravenous immunoglobulin also warrant further evaluation for the IBD patient cohort. There are some new therapeutic strategies that use toxin binders in an attempt to ameliorate the *C. difficile* infection, but, again, these have not yet been explored in this patient population.

### Suggested Reading

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