# ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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## *Clostridium difficile* Infection in Patients with Inflammatory Bowel Disease

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### **G&H** What is the burden of disease associated with *Clostridium difficile* infection in the general population?

**DGB** The burden of disease due to *Clostridium difficile* infections is significant. The number of *C. difficile* infections in North America has more than doubled in the past decade, and there are now more than 500,000 infections annually in the United States. Significant morbidity and mortality are associated with these infections, with approximately 13,000 individuals dying annually as a result of *C. difficile* infection. The cost of care is also markedly elevated when *C. difficile* occurs among hospitalized patients; thus, *C. difficile* infection has a major impact on both clinical outcomes and overall healthcare costs.

Inpatient statistics show that up to one third of hospitalized patients at academic medical centers may be carriers of *C. difficile*, and approximately 6–7% of these individuals will develop an active infection. At the University of Pittsburgh Medical Center, approximately 27,000 patients are admitted per year; approximately 9,000 of these patients are carriers of *C. difficile*, and approximately 500 patients develop active *C. difficile* infections. Asymptomatic carriage is also quite common in the geriatric population, with up to 50% of individuals in nursing homes being carriers of *C. difficile*.

### **G&H** What is the burden of disease associated with *C. difficile* infection in patients with inflammatory bowel disease?

**DGB** Patients with ulcerative colitis and Crohn's disease have increased risks of developing *C. difficile* infection and having worse outcomes, including higher rates of colectomy and death. While data on outpatients with *C. difficile* infection are lacking, hospitalization data show a rise in the percentage of US patients with inflammatory bowel disease (IBD) who suffer from *C. difficile* infection, with an increasing trend from 2004 to the present. Furthermore, analysis of a registry database of approximately 1,300 IBD patients suggests that 10% of IBD patients will develop a *C. difficile* infection at some point in their lifetime, and half of these individuals will experience a recurrence of this infection.

### **G&H** What factors affect a patient's risk of developing *C. difficile* infection?

**DGB** Among the general population, younger patients typically have lower rates of *C. difficile* infection, while older patients have significantly higher rates of infection: Approximately 70% of patients with *C. difficile* infection are over the age of 60 years, and 52.2% of patients are over the age of 70 years. In addition, *C. difficile* infection in the general population continues to be associated with antibiotic use, exposure to healthcare facilities, and immunosuppression. Transplant recipients and oncology patients who are undergoing chemotherapy are at a particularly high risk of developing *C. difficile* infection, which suggests that disturbances in immune function—whether due to iatrogenic effects of chemotherapy or immunosuppressive drugs—can increase an individual's risk of infection by blocking certain aspects of immunity. One hypothesis is that humoral immunity is a critical factor in the development of asymptomatic carriage of

*C. difficile*; specifically, individuals who are able to mount an immunoglobulin G response against *C. difficile* toxin A seem to be more likely to become asymptomatic carriers, while individuals who fail to mount a humoral immune response to *C. difficile* toxin A are at higher risk for manifesting an active infection.

### **G&H** Do the risk factors for *C. difficile* infection differ for patients with IBD?

**DGB** Among IBD patients, approximately three quarters of *C. difficile*–infected patients have not been hospitalized; instead, these individuals are outpatients who were doing well prior to developing community-acquired *C. difficile* infection. Similarly, antibiotic exposure is not mandatory for development of *C. difficile* infection in IBD patients. At our center, approximately 60% of patients could identify antibiotic exposure in the 2 months preceding the documented *C. difficile* infection, but a substantial minority of patients (40%) did not have documented antibiotic exposure immediately preceding their infection. Finally, IBD patients tend to be younger than *C. difficile*–infected patients in the general population.

### **G&H** How can clinicians minimize the impact of *C. difficile* infection among patients with IBD?

**DGB** Clinicians need to be alert to the possibility of *C. difficile* infection when IBD patients are hospitalized. Estimates suggest that *C. difficile* infection may lead to colectomy in 20–40% of colitis admissions, and high rates of *C. difficile* infection are seen among patients at IBD centers, especially patients with ulcerative colitis or Crohn's disease involving the colon. These groups are most susceptible to *C. difficile*, so clinicians should look for evidence of this infection whenever such patients present with worsening of their condition. Gastroenterologists also need to keep in mind that the traditional risk factors for *C. difficile* infection may not be present in IBD patients. For example, many IBD patients with *C. difficile* infection are younger individuals and/or outpatients with no recent hospitalization or healthcare exposure. Finally, approximately 10% of *C. difficile* infections occur at the time of IBD diagnosis; in these cases, *C. difficile* causes a precipitating infection that parallels the diagnosis of IBD colitis.

In addition to considering *C. difficile* infection as a possible diagnosis in IBD patients, all healthcare personnel should strive to reduce nosocomial transmission of *C. difficile*. Spores of *C. difficile* can lay dormant in the environment for up to 60 days, and these spores are often found on surfaces in patient rooms and on the skin of infected patients. Thus, clinicians need to remain vigilant about soap-and-water hand washing, as this practice is the cornerstone for prevention of horizontal transmission in the hospital. Hospital personnel can also wear gloves to prevent transmission of *C. difficile* among patients.

### **G&H** What treatments are currently available for *C. difficile* infection?

**DGB** Currently, there are 2 medications that have been approved by the US Food and Drug Administration (FDA) for the treatment of *C. difficile* infection: Oral vancomycin was approved in the early 1980s, and a newer drug, fidaxomicin (Dificid, Optimer Pharmaceuticals), was approved last year. Historically, clinicians have also used metronidazole for the treatment of *C. difficile* infection; although it never received FDA approval for this indication, a number of studies have shown its efficacy for the treatment of *C. difficile* infection.

While clinicians continue to use all 3 of these drugs for the treatment of *C. difficile* infection, there have been some recent changes in the therapeutic responses of these drugs. In older studies, metronidazole showed equivalence with vancomycin; however, more recent data suggest that metronidazole may not be quite as effective in patients who are severely ill. Thus, vancomycin has emerged as the preferred antibiotic for individuals with severe *C. difficile* infection. Vancomycin is also recommended as the first-line treatment for IBD patients who are admitted to the hospital with evidence of a colitis exacerbation, as this drug has yielded superior outcomes among individuals in referral hospital populations.

At present, clinicians have less experience with fidaxomicin than vancomycin, but available data on fidaxomicin are encouraging. In the FDA registration trial for fidaxomicin, this drug was shown to be noninferior to vancomycin, meaning that patients achieved equivalent results in terms of response to initial therapy with either drug. This trial also included a novel endpoint, referred to as "global cure," which was defined as the recurrence of *C. difficile* infection within 30 days after cessation of the initial course of antibiotic therapy. Rates of recurrence were significantly lower in patients who received fidaxomicin (approximately 13%) compared to patients who received vancomycin, where rates of *C. difficile* recurrence are typically 25%. Thus, fidaxomicin may yield lower rates of *C. difficile* recurrence in the month following cessation of therapy. Despite these encouraging findings, the consensus is that clinicians should still use vancomycin as the first-line therapy for IBD patients with evidence of severe *C. difficile* infection, as there are no data regarding the use of fidaxomicin in the IBD patient population.

In addition to antibiotic therapy, fecal microbiome transplantation is also being explored as a way to restore a healthy microbiome in the lower gastrointestinal tract of patients who have experienced recurrent *C. difficile* infections. Patients who have experienced multiple recurrences

of *C. difficile* infection and who are struggling to discontinue antibiotic therapy are potential candidates for fecal microbiome transplantation. According to reports that have been published in the past few years, fecal microbiome transplantation has a success rate approaching 90% in patients with recurrent *C. difficile* infection. Data on the use of fecal microbiome transplantation among IBD patients are currently very limited, but this procedure may also emerge as a treatment strategy for IBD patients who are suffering from recurrent *C. difficile* infections.

### G&H Does your treatment approach differ for patients over the age of 65 years?

**DGB** No, I do not alter my treatment approach based on the patient's age. Instead, the best way to stratify treatment is based on the severity of the patient's illness. Clinicians do not yet have completely unified criteria for stratifying cases as mild, moderate-to-severe, or severe-complicated, but consensus in this area is growing and will hopefully emerge in the near future. In general, mild disease is diarrheal illness without any other symptoms; patients with mild disease are appropriate candidates for first-line therapy with metronidazole (500 mg 3 times daily for 10–14 days). In contrast, patients with moderate-to-severe disease typically have diarrheal illness in combination with another sign or symptom, such as abdominal pain, a low albumin level, or an elevated white blood cell count. These individuals should be treated with vancomycin (125 mg orally 4 times a day for 10–14 days). Vancomycin is also recommended as the first-line therapy for patients who are pregnant, due to the theoretical potential that metronidazole might contribute to birth defects.

### G&H Are there any other factors clinicians should consider when selecting a treatment?

**DGB** Treatment of *C. difficile* infection in the IBD patient population often poses specific challenges. For example, treatment of patients who have undergone a diverting ostomy is difficult because antibiotics that are taken orally may have difficulty reaching the downstream bowel distal to the ostomy in these patients. Thus, individuals with a diverting ostomy should receive rectal therapy in order to guarantee that the antimicrobial agent reaches the area where it is needed; vancomycin enemas can be used in this setting. While vancomycin is not sold as an enema, the parenteral vancomycin that is normally used for intravenous treatment can be reformulated by hospital-based pharmacies or compounding pharmacies, and the resulting enema formulation can then be self-administered by the patient. A typical regimen for treatment of *C. difficile* infection would be 500-mg vancomycin enemas 3 times daily for approximately 14 days.

Also, clinicians should keep in mind that metronidazole will have very low availability to reach the distal bowel segment in patients who have diverting ostomies. There is some low-level passage of metronidazole through the inflamed tissue, but the levels of metronidazole in the mucosa will drop dramatically as the tissue starts to heal. This limitation is one reason why vancomycin enemas are preferred in these patients.

### G&H What additional research is needed in this area?

**DGB** First, we do not completely understand why the number of *C. difficile* infections has risen so dramatically over the past decade. There is a concern that the use of antibiotics by the animal industry may have led to *C. difficile* becoming a food pathogen, with *C. difficile* spores passing to individuals through ingested food. However, further research is needed to determine whether such concerns are well founded.

In addition, the life cycle of *C. difficile* is not completely understood. Perhaps as many as 90% of newborns are colonized with *C. difficile*, and this asymptomatic carriage may persist to the age of 2 years. However, individuals frequently lose *C. difficile* from the gut microbiome before reaching adulthood, with only approximately 4–5% of healthy young adults being asymptomatic carriers of *C. difficile*. Once individuals advance into the geriatric age group, however, the rates of *C. difficile* carriage again rise significantly: Up to 50% of nursing home residents and residents of long-term care facilities may be carriers of *C. difficile*. How and why this recolonization occurs and why only a small percentage of these individuals develop an active *C. difficile* infection are major unanswered questions that need to be explored further.

## Suggested Reading

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