ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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Strategies for Management of Clostridium difficile Infection in Immunosuppressed Patients

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G&H Why do Clostridium difficile infections occur in immunosuppressed patients?

DGB Researchers are currently trying to understand why some individuals become asymptomatic carriers of *Clostridium difficile* while others develop infections that can range from mild to life-threatening. At the present time, our understanding is that certain individuals are able to mount an effective immunoglobulin G response against *C. difficile* toxin A. This humoral immune response against the *C. difficile* toxin is believed to allow an individual to become an asymptomatic carrier. In contrast, people who fail to mount an immune response to *C. difficile* toxin are susceptible to infection. In general, patients on immunosuppressive therapy have a blunted ability to mount immune responses and, therefore, may be at greater risk for infection. Patients who are receiving corticosteroid therapy, in particular, have a high risk for infection.

G&H How common is C. difficile infection among immunosuppressed patients?

DGB The prevalence of *C. difficile* infection depends on which population of immunosuppressed patients is being analyzed. Current data suggest that 34% of patients who have undergone lung transplantation will develop symptomatic *C. difficile* infection shortly after transplantation; this risk may be associated with a number of factors, including immunosuppressive therapy. *C. difficile* infection may also be related to the use of antibiotics in the post–lung transplantation setting. In addition, patients who undergo lung transplantation include a disproportionate number of individuals with hypogammaglobulinemia, which can predispose individuals to lung inflammation; this congenital immunodeficiency could potentially make a patient more susceptible to *C. difficile* infection.

Of particular interest to gastroenterologists is the impact of *C. difficile* infection on patients with inflammatory bowel disease (IBD). Estimates suggest that 10% of patients with IBD will develop a symptomatic *C. difficile* infection at some point during their lifetime. The IBD medical therapies most strongly associated with development of *C. difficile* infection include maintenance immunosuppression with purine analogs and methotrexate, as well as steroid therapy. Indeed, steroid exposure is linked to a 3-fold increase in the risk of *C. difficile* infection during the following year.

G&H How do immunosuppressed patients and immunocompetent individuals differ in terms of their likelihood of developing C. difficile infection?

DGB The difference between immunocompetent individuals and immunosuppressed individuals relates to their innate ability to mount appropriate immune responses. Researchers have found that *C. difficile* carriage will vary considerably during a patient's lifetime. Up to 90% of newborns are believed to have *C. difficile* in their bowel soon after birth, but they typically do not become sick. In the majority of individuals, *C. difficile* will clear from the gastrointestinal tract, and approximately 4% of healthy adults may be asymp-

tomatic carriers of *C. difficile*. As people age, the rates of *C. difficile* carriage will rise; an unpublished study by Curry and coworkers at the University of Pittsburgh Medical Center found that 34% of adults admitted to a tertiary referral hospital were carriers of *C. difficile*.

The majority of individuals who come into contact with *C. difficile* will not become ill; the bacteria either transiently pass through the gastrointestinal tract or lead to asymptomatic carriage. However, a minority of patients become sick due to this infection. The likelihood of illness is increased in individuals with compromised immune function, either chronic immunosuppression for therapeutic purposes (in the setting of organ transplantation or inflammatory disease treatment) or transient immunosuppression (due to chemotherapy).

G&H What are the potential consequences of C. difficile infection, particularly in immunosuppressed patients?

DGB Immunosuppressed patients who contract *C. difficile* infection are at higher risk for severe disease. Studies suggest that IBD patients who are hospitalized with *C. difficile* infection have longer hospital stays, higher hospital costs, higher rates of surgery, and greater mortality. A study by Ananthakrishnan and colleagues showed that IBD patients who are hospitalized with *C. difficile* infection have a mortality rate of 4.2%, which is significantly higher than the overall mortality rate for patients hospitalized with this infection. Other studies have shown that IBD patients who ultimately required colectomy had a perioperative mortality rate of 25%; this finding suggests that surgery was delayed in individuals who were developing fulminant disease.

Because outcomes in immunosuppressed patients are generally more severe, clinicians need to be vigilant, look for the infection, and initiate appropriate treatment. Therapy typically involves decreasing the use of broad-spectrum antibiotics whenever possible and then initiating targeted therapy against *C. difficile*. Emerging data suggest that oral vancomycin is the preferred antibiotic for treatment of *C. difficile* infection in higher-risk patients, including patients who are immunosuppressed.

G&H Does the clinical presentation of C. difficile infection differ between immunosuppressed and immunocompetent patients?

DGB The clinical presentation of *C. difficile* infection is variable. Pseudomembranes, the hallmark endoscopic feature of *C. difficile* infection, are seen in approximately half of the *C. difficile* infections in the general population. In this setting, the presence of pseudomembranes during colonoscopy is an important marker of severe disease, and it should raise the question of using oral vancomycin earlier in treatment. However, IBD patients infected with *C. difficile* rarely show this clinical feature, even in the presence of severe infection.

G&H How can clinicians diagnose C. difficile infection in immunosuppressed patients?

DGB Stool testing is mandatory for making a diagnosis of *C. difficile* infection. However, strategies for testing stool specimens are changing. Since 1984, the most commonly used testing strategy has been enzyme-linked immunosorbent assay (ELISA) testing to detect the presence of *C. difficile* toxin A and B, but the sensitivity of this assay was not as high as clinicians would have liked. New testing modalities, which use polymerase chain reaction (PCR) analysis to detect the presence of *C. difficile* in stool specimens, will likely replace ELISA testing over the next several years. However, the best strategy for using PCR testing to diagnose *C. difficile* infection has not yet been defined, and the Infectious Disease Society of America and the Society of Hospital Epidemiologists of America have not reached a consensus regarding this question. Thus, how clinicians diagnose *C. difficile* infection will continue to evolve over the next several years. Given current variations in testing, I recommend that physicians learn about the testing modalities used in their clinic, hospital, or reference laboratory. With ELISA testing, 3 samples are required to ensure that negative results are truly negative. In contrast, PCR analysis usually requires only 1 or 2 samples; however, uniformly accepted guidelines are lacking.

Endoscopy is not typically used to diagnose *C. difficile* infection, but this procedure may be performed when clinicians are trying to clarify the status of an IBD patient who is experiencing a flare; in these situations, the endoscopist should keep in mind that pseudomembranes are not seen in the majority of patients with IBD. In addition to endoscopy, all patients with IBD colitis who are experiencing a flare should undergo stool testing to determine whether superimposed infection is a contributing factor.

G&H What options are available for the treatment of C. difficile infection?

DGB First, clinicians should limit the use of broad-spectrum antibiotics whenever possible if they have suspicions about *C. difficile* infection, as the withdrawal of broad-spectrum antibiotics is always an important aspect of treatment for this condition. Patients with milder illness may recover without additional therapy once the broad-spectrum antibiotic is withdrawn. Also, clinicians should collect samples for testing and begin therapy promptly if they suspect that a patient has *C. difficile* infection; they should not wait for testing results to confirm clinical suspicions before starting treatment.

Historically, 2 antibiotics have been available for treating *C. difficile* infection. The first US Food and Drug Administration (FDA)-approved strategy for treating

C. difficile infection was oral vancomycin, which has been available since 1981. Clinical trials showed oral vancomycin to be more effective than metronidazole for treating patients with severe disease. Metronidazole has been used to treat *C. difficile* infection since 1982, although this drug never underwent formal FDA testing for this indication.

In May 2011, the FDA approved a second antibiotic for the treatment of *C. difficile* infection: fidaxomicin (Dificid, Optimer Pharmaceuticals). Trials showed that fidaxomicin is equivalent in efficacy to vancomycin, but fidaxomicin appears to have lower rates of relapse in the 30 days after the course of antibiotics is completed. However, data are lacking regarding the use of fidaxomicin in specific patient populations, including immunosuppressed individuals or patients with IBD.

G&H What are the main considerations when selecting treatments for immunosuppressed patients?

DGB In the outpatient setting, metronidazole therapy is appropriate for patients who have mild disease (after limiting use of broad-spectrum antibiotics). If these patients do not show a clinical response within 48–72 hours, clinicians should consider switching to oral vancomycin. For hospitalized patients, particularly immunosuppressed individuals (including patients with IBD), initiation of treatment with vancomycin is appropriate.

G&H Would you consider probiotics as a treatment for C. difficile infection?

DGB Probiotics have been under investigation for the treatment of antibiotic-associated diarrhea in *C. difficile* infection, but the available data are mixed. In patients with mild *C. difficile* infection who are being treated in an outpatient setting, the use of a probiotic yogurt or supplement might be considered. Some studies have shown that *Saccharomyces boulardii* can shorten the duration of antibiotic-associated diarrhea and/or decrease relapse rates in *C. difficile*–infected patients. Probiotics are not typically used in hospitalized individuals, however, as the use of probiotic compounds in severely ill individuals could lead to bacteremia and worse clinical outcomes.

G&H What steps can clinicians take to prevent C. difficile infection in immunosuppressed patients?

DGB Preventing nosocomial transmission of *C. difficile* infection is of paramount importance. We do not know why *C. difficile* infection rates have more than doubled in the past 10 years, but we do know that healthcare settings are high-risk environments for infection. *C. difficile* spores can live in the hospital or clinic environment for up to 60 days, so all healthcare personnel must be very fastidious and committed to hand washing in order to prevent transmission of *C. difficile* to patients. The best strategy is to use plain soap and water to dislodge spores from the hands or use gloves when examining patients so that healthcare providers do not carry *C. difficile* spores among patients.

Caution regarding the use of broad-spectrum antibiotics is also an important consideration, as limiting the use of broad-spectrum antibiotics has been shown to curb *C. difficile* outbreaks in hospital settings. In patients who have conditions such as IBD, use of broad-spectrum antibiotics as a treatment modality should be used cautiously and limited whenever possible.

G&H What questions need to be addressed in future studies?

DGB First, we do not know why *C. difficile* infection rates have risen dramatically over the past decade. Better understanding of the epidemiology of *C. difficile* infection will be important for developing strategies to limit infections in the future. Also, we do not understand why certain individuals mount an effective immune response and become asymptomatic carriers while others develop active infections. Understanding this difference is another important area of future study. Finally, we need to know which antibiotic strategies will be the most effective for treating *C. difficile* infection and preventing relapse. Approximately 25% of individuals experience a relapse of *C. difficile* infection, and these patients are often at higher risk for increased hospital stays, colectomy, and mortality.

G&H Are ongoing studies attempting to answer some of those questions?

DGB I hope to see more data regarding the use of fidaxomicin in the near future. Fidaxomicin is only the second agent to be approved by the FDA for the treatment of *C. difficile* infection, and it just became available this year. Also, I hope future studies will explore the possibility of creating a vaccine that could help individuals mount an immune response against *C. difficile*.

Suggested Reading

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