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-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 symp-
matic carriers of \textit{C. difficile}. As people age, the rates of \textit{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 \textit{C. difficile}.

The majority of individuals who come into contact with \textit{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).

\textbf{G\&H} What are the potential consequences of \textit{C. difficile} infection, particularly in immunosuppressed patients?

\textbf{DGB} Immunosuppressed patients who contract \textit{C. difficile} infection are at higher risk for severe disease. Studies suggest that IBD patients who are hospitalized with \textit{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 \textit{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 \textit{C. difficile}. Emerging data suggest that oral vancomycin is the preferred antibiotic for treatment of \textit{C. difficile} infection in higher-risk patients, including patients who are immunosuppressed.

\textbf{G\&H} Does the clinical presentation of \textit{C. difficile} infection differ between immunosuppressed and immunocompetent patients?

\textbf{DGB} The clinical presentation of \textit{C. difficile} infection is variable. Pseudomembranes, the hallmark endoscopic feature of \textit{C. difficile} infection, are seen in approximately half of the \textit{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 \textit{C. difficile} rarely show this clinical feature, even in the presence of severe infection.

\textbf{G\&H} How can clinicians diagnose \textit{C. difficile} infection in immunosuppressed patients?

\textbf{DGB} Stool testing is mandatory for making a diagnosis of \textit{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 \textit{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 \textit{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 \textit{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 \textit{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 \textit{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.

\textbf{G\&H} What options are available for the treatment of \textit{C. difficile} infection?

\textbf{DGB} First, clinicians should limit the use of broad-spectrum antibiotics whenever possible if they have suspicions about \textit{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 \textit{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 \textit{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.

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.

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.

Suggested Reading


