Despite the availability of a growing number of therapeutic options for the treatment of inflammatory bowel disease (IBD), patients in remission remain at constant risk of disease relapse. Clinically, it can be difficult to distinguish between diarrhea relapses of IBD and infectious causes of diarrhea. Similarly, infection may lead to exacerbation of disease in patients with otherwise quiescent IBD. The significance of secondary infectious causes such as *Clostridium difficile* in this setting has been an area of controversy. However, there is a definite increase in both the rate and severity of *Clostridium difficile*-associated disease (CDAD) in the United States, Canada and Europe. Thus, it is likely that this organism will be encountered with increasing frequency in patients with IBD relapse. CDAD should be considered in all patients with recent exposure to antibiotics. There has been a recent documented increase in sporadic cases of CDAD as well, so patients with relapses of IBD who do not respond to therapy should be evaluated for *C. difficile*. Treatment with metronidazole or vancomycin is recommended.

**INTRODUCTION**

Despite the availability of a growing number of therapeutic options for the treatment of inflammatory bowel disease (IBD), patients in remission remain at constant risk of disease relapse. Clinically, it can be difficult to distinguish between diarrhea relapses of IBD and the presence of enteric infection. Several microorganisms can be seen in association with relapse, including *Clostridium difficile*, Campylobacter, Salmonella and Shigella species, *Escherichia coli*, *Entamoeba histolytica*, and cytomegalovirus. *Clostridium difficile* is particularly common in patients with a history of recent antibiotic use and will be the focus of this review. The significance of secondary infectious causes such as *Clostridium difficile*, as well as the importance of routine stool examination in patients with relapsed IBD remains controversial.

**EPIDEMIOLOGY**

Initial interest in an association between *C. difficile* and IBD stemmed from early studies evaluating the incidence of infection in patients with diarrhea. In one study of 56 patients presenting with diarrhea, five of nine patients testing positive for *C. difficile* were noted to have severe IBD requiring therapy with systemic steroids (1). The authors postulated that infection may have precipitated the IBD exacerbation in these patients. This was followed by several subsequent studies evaluating the incidence of *C. difficile* infec-
Other organisms detected included *Campylobacter jejuni* in one sample and *Plesiomonas shigelloides* in another. Thus, this group concluded that testing for *C. difficile* was high yield, particularly in patients with exposure to antibiotics in the preceding month.

In a recent European study of 213 patients with 237 relapses of IBD, enteric infection was detected in 25 relapses (10.5%, 24 patients) (12). *C. difficile* toxin A or B was detected by enzyme-linked immunosorbent assay (ELISA) in 13 (5.5%), seven of whom had undergone previous antibiotic treatment, while *Campylobacter* species, *Entamoeba histolytica*, Salmonella species, *Plesiomonas shigelloides*, *Strongyloides stercoralis*, and *Blastocystis hominis* accounted for the other 5% of relapses. There was a significant association between infection and the need for hospital admission. No significant difference was detected between infection and duration of disease, use of immunosuppressive drugs or corticosteroids, or foreign travel, and all relapses resolved with targeted antibiotics with or without corticosteroids. Due to the high prevalence of enteric infections in this study, particularly *C. difficile*, the authors advocated for the routine microbiological examination of stool in patients with relapsed IBD.

While these studies found no association between the use of immunosuppressive therapy and infection with *C. difficile*, earlier reports suggested a relationship between use of sulfasalazine and infection with this organism. One group reported similar rates of *C. difficile* infection in patients with or without IBD that presented with diarrhea, but noted that 67% of the IBD patients testing positive were being treated with sulfasalazine (13). Pseudomembranous colitis has also been reported in the setting of sulfasalazine use and was initially felt to be a complication of therapy, perhaps due to the antimicrobial sulphonamide component of the drug and subsequent disruption of colonic flora (14). However, in a study of 62 patients with ulcerative colitis, none of the 31 patients taking sulfasalazine became toxin or culture positive (15). Several additional studies have also failed to demonstrate an association (3,16,17), and another suggested that sulfasalazine therapy may even reduce the risk of *C. difficile* superinfection (18).
In addition to contributing to disease relapse, it is possible that *Clostridium difficile* may precipitate an initial episode of IBD. Newly diagnosed ulcerative colitis has been described following treatment of pseudomembranous colitis, with histologic findings of inflammatory infiltrate, crypt abscess formation, and gland reduction occurring despite eradication of *C. difficile* from the stool (19). Although not widely reported in the literature, personal communication from colleagues indicates that several similar cases have occurred, suggesting that the organism may play a role in triggering initial disease.

**PATHOPHYSIOLOGY**

The specific factors that may predispose patients with IBD to *C. difficile* infection, as well as the precise mechanism by which infection might lead to exacerbation of disease, are unclear. It is generally believed that enteric flora play a crucial role in the pathogenesis of inflammatory bowel disease, likely by providing a stimulus for a dysregulated T-cell response in genetically susceptible individuals. IBD patients have been shown to have higher concentrations of mucosal bacteria, increased amounts of pathogenic organisms such as *Bacteroides* and *Escherichia coli*, and decreased amounts of beneficial bacteria such as *Bifidobacterium* and *Lactobacillus* species (20–23). It is possible that this alteration of colonic flora could predispose patients to overgrowth of *C. difficile*. Additionally, activation of IBD may be triggered by factors that alter mucosal barrier function. By disrupting mucosal integrity, *C. difficile* could lead to increased exposure of the immune system to luminal contents and subsequent stimulation of the inflammatory response. Similarly, colonic epithelial dysfunction causing impaired secretion, perhaps leading to an increase in bacterial colonization and translocation, has been proposed as a potential stimulus for inflammation (24). In a rat model of colitis, intestinal exposure to *C. difficile* toxin A and other stimuli resulted in suppression of the secretory response, an increase in numbers of colonic aerobic bacteria and a greater than three-fold increase in bacterial translocation (24). Thus, it is possible that several mechanisms contribute to exacerbation of inflammation in IBD patients.

**DIAGNOSIS**

Laboratory diagnosis of CDAD is based on the detection of *C. difficile* toxin in stool specimens using either a cytotoxicity assay or immunoassay. Due to its high sensitivity (94%–100%) and specificity (99%), the cytotoxicity assay is considered the “gold standard” for detection of *C. difficile* cytoxins. During this test, diluted stool is added to cell culture, resulting in a characteristic rounding of cultured fibroblasts. Results typically return in two to three days. More rapid assays are available and retain a high specificity (99%) but somewhat lower sensitivity (70%–90%). These include enzyme linked immunosorbent assays (ELISAs) for detection of *C. difficile* toxin, and are being used with increased frequency due to ease of performance, lower cost and short time for results. Typically they detect either toxin A and/or B. Those that detect toxin A but not toxin B will miss infections with strains that produce a variant of toxin A not detected by EIA (these are about 2%–3% of cases). Although relied on more heavily in the past, stool culture is now rarely used clinically for detection of *C. difficile* and does not distinguish carriers from active infection.

**TREATMENT**

Treatment of *C. difficile* infection in patients with IBD has been an area of debate, with minimal evidence available to guide management. In several early reports, authors mention that therapy for *C. difficile* with vancomycin was not given (2,3,16). Nonetheless, many of these patients improved with corticosteroids or other treatment for IBD. In one case, the patient was sent for colectomy (16). It is unclear in some cases whether or not these patients had received metronidazole. In more recent reports, targeted therapy of infection has been given with resolution of symptoms in nearly all cases, although some patients also received steroids (1,11,12,25–28). In a couple of cases, toxin cleared spontaneously without specific antibiotic therapy, and was associated with improvement in clinical outcome (11,27). Nonetheless at present, in light of an increasing severity and frequency of CDAD, therapy of *C. difficile* infection with oral metronidazole or van-
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comycin is recommended. Because diagnostic tests are imperfect, a patient who is ill and in whom C. difficile is suspected should be given empiric treatment while confirmatory tests are pending. For relapses, repeat antibiotics are indicated and can be given using pulsed or tapered dosing. The adjunctive probiotic Saccharomyces boulardii can also be considered for recurrent CDAD, although should be avoided in patients who are immunosuppressed (29).

In addition to treating C. difficile infection, antibiotic use may lead to improvement in underlying inflammatory bowel disease. Evidence suggests a role for antibiotics in septic complications of IBD, such as abscesses, fistulæ, fissures, bacterial overgrowth, peritonitis, and toxic megacolon (23). The role of antibiotics in primary or adjunctive treatment of IBD is less clear, with some studies suggesting benefit for patients with active mild to moderate colonic involvement of Crohn’s disease (23). In addition to clearing C. difficile and its related toxins, antibiotic use may lead to a decrease in luminal bacteria, decreased bacterial translocation, and improvement in underlying colitis.

Another agent with therapeutic potential is rifaximin, a poorly absorbed antibiotic with a wide range of antibacterial activity. It is currently approved by the FDA for treatment of traveler’s diarrhea due to enterotoxigenic E. coli. In preliminary studies of Crohn’s disease, treatment with rifaximin led to reduction in Crohn’s Disease Activity (CDAI) and Harvey-Bradshaw Indices, improvement of colitis in up to 63% of patients, and clinical remission in up to 59% of patients with mild to moderate disease (30–32). Small studies of patients with ulcerative colitis have shown improvement in symptoms and endoscopic indices, and have suggested a role for rifaximin in the treatment of pouchitis (33–37). Rifaximin may also be effective in the treatment of CDAD. In vitro studies have demonstrated susceptibility of C. difficile to the drug, and efficacy similar to vancomycin was reported in one randomized trial of patients with pseudomembranous colitis (38–40). Further studies evaluating the role of this agent would be of interest.

Finally, it should be noted that C. difficile infection may result in an asymptomatic carrier state. While patients colonized with nontoxigenic strains would be expected to remain asymptomatic, a subset of patients infected with toxin-producing strains also fails to develop diarrhea or colitis. This may be due to the presence of serum antibodies against toxin A, as well as other host factors that remain unclear (41). While carriers may respond to antibiotic therapy, most patients become culture positive following discontinuation and thus treatment is not routinely recommended.

CONCLUSION

While early studies found low rates of C. difficile infection in patients with relapsed IBD, available evidence now suggests an increase in the rate and severity of C. difficile-associated disease. Thus it is likely that this pathogen will be encountered increasingly in patients with active IBD. The precise mechanism by which the organism might lead to disease exacerbation is unclear, but likely involves alteration of the mucosal barrier function and subsequent stimulation of the inflammatory response. Infection with C. difficile should be considered in patients presenting with diarrheal relapses, particularly in the setting of recent antibiotic use. Sporadic cases can also occur and thus patients who do not respond to therapy should also be evaluated for concomitant C. difficile infection. Treatment with metronidazole or vancomycin should be given to all patients in whom CDAD is encountered. In addition to treating the infection, antibiotics may lead to improvement in underlying inflammation and thus a decreased severity of IBD. Recurrent infection should be treated with repeat antibiotics given in pulsed and tapered doses. Use of the adjunctive probiotic S. boulardii can also be considered, but should not be given to patients who are immunosuppressed. With especially virulent strains, a high index of suspicion for CDAD is more important than ever.

References


