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AGA CLINICAL PRACTICE UPDATE: EXPERT REVIEW

Management of *Clostridium difficile* Infection in Inflammatory Bowel Disease: Expert Review from the Clinical Practice Updates Committee of the AGA Institute

Sahil Khanna,[*] Andrea Shin,[‡] and Ciarán P. Kelly[§]

[*]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota; [‡]Division of Gastroenterology and Hepatology, Indiana University, Indianapolis, Indiana; [§]Gastroenterology Division, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts

This article has an accompanying continuing medical education activity, also eligible for MOC credit, on page e60. Learning Objective–Upon completion of this activity, successful learners will be able to identify and manage *Clostridium difficile* infection in patients with inflammatory bowel disease.

The purpose of this expert review is to synthesize the existing evidence on the management of *Clostridium difficile* infection in patients with underlying inflammatory bowel disease. The evidence reviewed in this article is a summation of relevant scientific publications, expert opinion statements, and current practice guidelines. This review is a summary of expert opinion in the field without a formal systematic review of evidence.

***Best Practice Advice 1*: Clinicians should test patients who present with a flare of underlying inflammatory bowel disease for *Clostridium difficile* infection.**

***Best Practice Advice 2*: Clinicians should screen for recurrent *C difficile* infection if diarrhea or other symptoms of colitis persist or return after antibiotic treatment for *C difficile* infection.**

***Best Practice Advice 3*: Clinicians should consider treating *C difficile* infection in inflammatory bowel disease patients with vancomycin instead of metronidazole.**

***Best Practice Advice 4*: Clinicians strongly should consider hospitalization for close monitoring and aggressive management for inflammatory bowel disease patients with *C difficile* infection who have profuse diarrhea, severe abdominal pain, a markedly increased peripheral blood leukocyte count, or other evidence of sepsis.**

***Best Practice Advice 5*: Clinicians may postpone escalation of steroids and other immunosuppression agents during acute *C difficile* infection until therapy for *C difficile* infection has been initiated. However, the decision to withhold or continue immunosuppression in inflammatory bowel disease patients with *C difficile* infection should be individualized because there is insufficient existing robust literature on which to develop firm recommendations.**

***Best Practice Advice 6*: Clinicians should offer a referral for fecal microbiota transplantation to inflammatory bowel disease patients with recurrent *C difficile* infection.**

Clostridium difficile is an anaerobic, spore-forming, gram-positive bacillus.[1,2] Pathogenic strains produce 2 large protein exotoxins (toxin A and toxin B). In 1978, *C difficile* and its toxins were first identified as causing antibiotic-associated pseudomembranous colitis.[3,4] The incidence and severity of colonic disease caused by *C difficile* have increased greatly in recent years.[5] A study of *C difficile* infection (CDI) in the United States in 2011 found that there were 453,000 incident cases and 83,000 first recurrences.[6] Of greatest concern is the estimated number of CDI-associated deaths at 29,000 per annum, a death rate that exceeds the total number of deaths attributed to both multidrug-resistant gram-negative bacteria and methicillin-resistant *Staphylococcus aureus* combined.[6,7] The ascent of *C difficile* to become the most lethal acute enteric pathogen in the United States led the Centers for Disease Control to designate it as an urgent antibiotic resistance threat in 2015, 1 of only 3 pathogens to earn this attribute (http://www.cdc.gov/drugresistance/biggest_threats.html). The substantial increases in CDI incidence and mortality appear to arise from a combination of factors including increased antibiotic use, an aging population, and the emergence of highly virulent strains such as the BI/NAP1/027/toxinotype III strain.[5,8–10] Patients with inflammatory bowel disease (IBD) commonly experience exacerbations secondary to CDI, which leads to adverse outcomes in IBD patients including increased risk of hospitalization, escalation of IBD therapy, and surgery. Current major challenges of CDI include increasing incidence, frequent recurrences, and progression to severe, or even fatal, disease.[6] These complications are even more problematic when CDI arises against a background of IBD with

Abbreviations used in this paper: **CDI, *Clostridium difficile* infection; EIA, enzyme immunoassay; FMT, fecal microbiota transplantation; IBD, inflammatory bowel disease; NAAT, nucleic acid amplification tests.**

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colitis. Dilemmas for management in these patients include the choice of antibiotic therapy, and timing and need for change in immunosuppressants for IBD. This review summarizes the existing literature and provides management recommendations.

Methods

This article is not based on a formal systematic review but instead seeks to provide practical advice based on the best available evidence, including existing clinical studies, systematic reviews, and practice guidelines. The focus is on the management of both CDI and IBD in patients with underlying IBD who are infected by CDI.

Epidemiology of *Clostridium difficile* Infection in Inflammatory Bowel Disease

In the late 1970s, toxigenic *C difficile* was identified as a causative agent in antibiotic-associated colitis and pseudomembranous colitis.[3,4] Shortly thereafter, an increased risk for colonization with toxin-producing *C difficile* was noted in individuals with IBD, leading to an active debate as to whether *C difficile* toxins may be a cause for IBD or IBD flares.[11] In more recent years, as the incidence and severity of CDI has increased in the general population, even greater increases have been described in patients with IBD.[12–14] In 2004, 7% of CDI cases diagnosed at one institution occurred in patients with underlying IBD; in 2005, this proportion had increased to 16% (Figure 1*A*).[15] During the same time period the overall rates of CDI in hospitalized IBD patients increased from 1.8% to 4.6%. Almost all patients with CDI had a prior history of IBD with colitis (91%).[15] Similar trends have been seen in other studies (Figure 1*B*).[13] The increasing incidence of CDI mainly afflicts patient with ulcerative colitis, increasing from 2.4% of admissions in 1998 to 3.9% in 2004; rates were lower in patients with Crohn's disease (0.8% increasing to 1.2%).[16] In another study, the overall rates of CDI were higher in patients with ulcerative colitis than Crohn's disease, and nearly 8 times greater overall in IBD than in non-IBD patients (Figure 2).[17] These differences may reflect the lower incidence of colitis in Crohn's disease and hence less widespread colonic dysbiosis.

It is important to note that CDI arising in patients with IBD may have several atypical features (Table 1). Patients with IBD who present with symptoms or signs suggesting a colitis flare should be evaluated for the presence of toxigenic *C difficile* in their stool. A history of recent antibiotic use is not a requirement for testing.

Pathogenic Mechanisms

The potential first step in the pathogenesis of CDI consists of disruption of the normal colonic bacterial

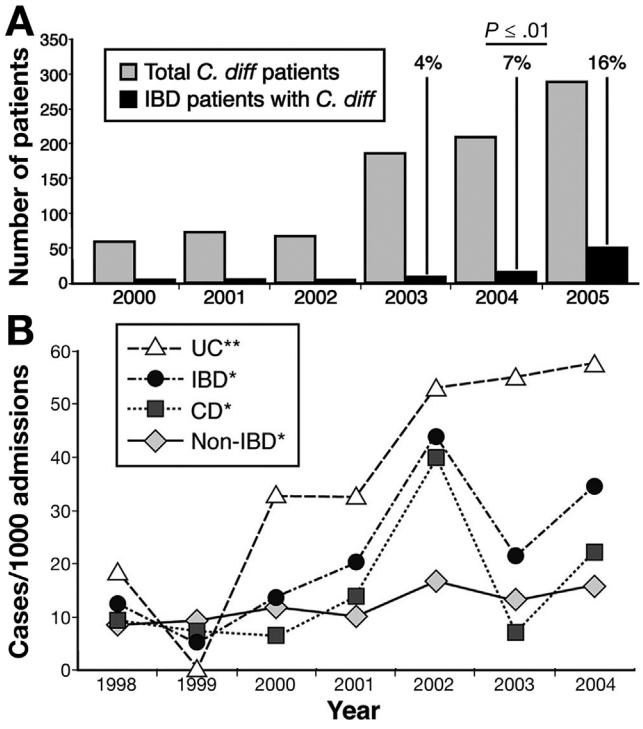

Figure 1. (*A*) Increasing proportion of IBD patients with *C difficile* (*C diff*) infection compared with the total number of *C difficile*–infected patients at a single referral hospital from 2000 to 2005. Published with permission from Elsevier.[15] (*B*) *C difficile* infection incidence at Barnes–Jewish Hospital increased from 1998 to 2004; ulcerative colitis (UC) patients appear primarily to account for the increase observed in the IBD population as a whole. *$P < .001$ and **$P = .08$ comparing the first and last 3 years of data. Published with permission from Elsevier.[13]

populations by antibiotic therapy (Figure 3).[1,18] This interferes with the colonization resistance against CDI that naturally is conferred by the gut microbiome. If exposure to *C difficile* spores then occur, as is common in

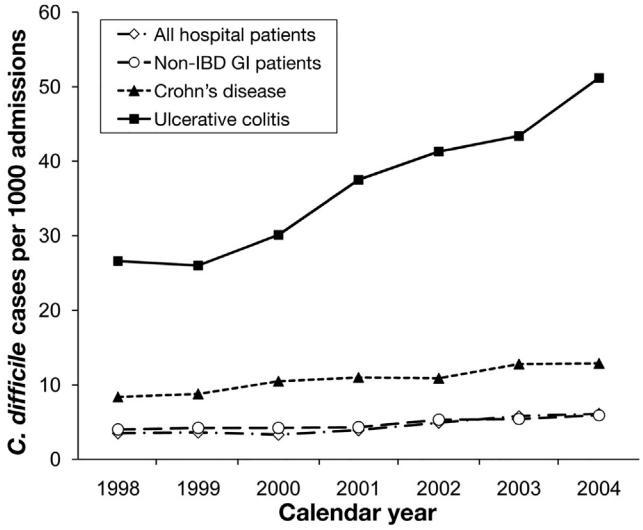

Figure 2. Increasing rates of *C difficile* infection among hospitalized IBD patients compared with non-IBD gastrointestinal (GI) patients, and a representative sample of all hospital discharges. Published with permission from Elsevier.[17]