ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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Clostridium difficile Infection and Inflammatory Bowel Disease

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G&H How common is *Clostridium difficile* infection in the general population, and how common is it among patients with inflammatory bowel disease?

DB *Clostridium difficile* infection has more than doubled in North America over the past 20 years. According to the Nationwide Inpatient Sample, there was a fairly sharp increase in *C difficile* infection in hospitalized patients during the first decade after 2000. In conjunction with a rise in the number of infections, a new strain of *C difficile* was identified, the epidemic BI/NAP1 strain, which involved an organism with a gene deletion resulting in higher levels of toxin production. Thus, this strain was associated with worse clinical outcomes, including higher mortality and more patients becoming ill with severe colitis requiring colectomy. Several hospitals in North America even had to close temporarily because of spore contamination due to the severity of the epidemic strain of *C difficile*.

In the background of these rising *C difficile* infection rates, researchers found that there was an even higher increase in *C difficile* infection occurring in the inflammatory bowel disease (IBD) patient population. From 2004 to 2006, an approximately 4-fold increase of *C difficile* infection in IBD patients was identified at the Medical College of Wisconsin, where I was working at the time, and patients with IBD who were coinfected with *C difficile* infection were experiencing severe flares, which resulted in extremely high rates of colectomy. This experience was mirrored in Barnes Jewish Hospital in St Louis, Missouri, where Dr Christian Stone identified a similar dramatic rise in *C difficile* infection in patients with IBD, particularly ulcerative colitis. Rates of *C difficile* infection rose throughout hospitals in North America during this time period. Looking at administrative data sets from the United States and Canada, approximately 6% of IBD patients admitted to a hospital setting had a diagnosis of *C difficile* infection during this time period. Although precise data are not known, it is likely that a significant percentage of IBD patients experienced flares of their colitis and became destabilized due to concomitant infection with *C difficile,* but did not require admission.

G&H Which IBD patients are at greatest risk of acquiring *C difficile* infection?

DB Patients at greatest risk are those who have IBD with colitis; therefore, colonic inflammation appears to be the most important risk factor. For example, a preexisting injury to the mucosa might predispose a patient to *C difficile* infection. Colonization resistance in the gut microbiome is an important biologic factor for preventing patients from becoming sick with an infection. There is growing evidence that in patients with IBD, the gut microbiome is not as diverse and healthy, or has dysbiosis, which may be one of the reasons that IBD patients have a higher-than-usual risk of contracting *C difficile*.

In addition, the use of immunosuppressive medications can predispose IBD patients to infection. Among the drugs typically used to treat IBD, corticosteroids are perhaps the most powerful in terms of increasing risk for *C difficile* infection. Administrative data have suggested that corticosteroid exposure for any dose or duration significantly increases the risk of *C difficile* infection. These data come from the British Columbia provincial database as well as a paper by Dr Sebastian Schneeweiss and colleagues. More recent research has been performed

at the University of Toronto. Dr Geoffrey Nguyen and colleagues explored *C difficile* infection in the IBD patient population at that institution and found that in addition to corticosteroids, immunomodulators and 5-aminosalicylates were independently associated with the development of *C difficile* infection.

G&H What impact does *C difficile* infection have on IBD in terms of severity?

DB *C difficile* infection produces an infectious colitis, which, when superimposed with an idiopathic colitis in an individual, creates a synergy that can make both conditions worse. IBD is destabilized by *C difficile* infection, so to bring IBD patients under control, both conditions have to be managed effectively. This means controlling the infectious problem with *C difficile* while, at the same time, addressing the flare of the underlying IBD colitis, which has been induced by the infection. This requires balancing treatment of an infectious process with potentially escalating anti-inflammatory or immunomodulatory treatment for the underlying IBD, a significant challenge that must be identified rapidly. If the clinician fails to control the infection and simply escalates immunosuppressive therapy, the patient can deteriorate, which likely accounts for some of the excess mortality that was seen in North America during 2004 and 2005. In an IBD patient who presents with colitis activity, it is tempting to simply escalate treatment for colitis, which typically means initiating intravenous corticosteroids in the hospital setting. However, intravenous corticosteroids are one of the most deleterious agents that can be used in the setting of a true *C difficile* infection. Clinicians should have a high clinical index of suspicion when managing these patients.

G&H When should *C difficile* infection be suspected in an IBD patient?

DB Currently, there is no easy way to differentiate an IBD colitis flare from a *C difficile* infection because they have essentially the same clinical presentation. Both of these conditions typically produce diarrhea and abdominal pain. Thus, if a person has evidence of active colitis, screening for *C difficile* infection is recommended. American College of Gastroenterology guidelines regarding the diagnosis and management of *C difficile* have specifically advocated that IBD patients undergo screening for *C difficile* when experiencing flare activity because of this concern. Patients in clinical remission with IBD that is not active do not require routine screening for *C difficile*. As mentioned above, *C difficile* is a colonizing organism in certain settings, but if the microbiome is healthy, *C difficile* is typically not a pathogen. However, when there is clinical activity with colitis and a positive stool sample, clinicians should assume that *C difficile* may play a role. Lastly, it is important to remember that an undetected infection with *C difficile* can lead to misinterpretation of therapeutic drug monitoring results in an IBD patient on biologic therapy at the time of testing.

G&H How effective are the current treatment options for these patients?

DB The current standard treatment for *C difficile* infection relies on an initial course of antibiotic therapy targeting the pathogen. The antibiotics that have been routinely used to treat *C difficile* include metronidazole, oral vancomycin, and the compound fidaxomicin (Dificid, Merck), which was approved by the US Food and Drug Administration (FDA) in 2011. The difficulty with antibiotic therapy is that the spectrum of its activity may have injurious effects on the underlying microbiome. Thus, the ideal antibiotic would be more selective and would have less effect on the microflora, which is a key component of colonization resistance.

In terms of specific agents, data comparing metronidazole and oral vancomycin in the IBD patient population suggest that oral vancomycin is a superior agent, particularly for IBD patients who are hospitalized with infection. There are limited data at this time regarding the use of fidaxomicin in the IBD patient population. The comparison of fidaxomicin and vancomycin in the general population was a component of the FDA's approval process for fidaxomicin. Fidaxomicin and vancomycin have equivalence in terms of initial efficacy; however, fidaxomicin was shown to have a lower rate of relapse in the ensuing 60 days following successful initial therapy. The lower relapse rate may be due to the fact that fidaxomicin does not lead to spore formation, which typically occurs with oral vancomycin exposure during *C difficile* treatment. Spore formation may be a mechanism of colonization with *C difficile* that can lead to clinical relapse and recurrent infections several months after cessation of therapy.

G&H How significant of an issue is relapse?

DB After treatment with metronidazole or oral vancomycin, the relapse rate in the general population is 25%. With fidaxomicin, the relapse rate is 12%. Recent data from investigators at the University of Toronto suggest that the IBD patient population has a significantly higher relapse rate following initial successful infection (approximately 34% in patients with underlying IBD). Once a patient has a relapse, the chance for successful eradication diminishes with subsequent antibiotic exposure. Recent data suggest that patients with recurrent or relapsing *C difficile* infection may benefit from fecal microbiota transplantation (FMT).

G&H How effective is FMT as a treatment option?

DB In a pivotal study, Dr Els van Nood and colleagues studied patients with recurrent and relapsing *C difficile* infection and found success rates approaching 90% with FMT. In this study from Amsterdam, The Netherlands, a screened pool of healthy donors provided fresh fecal samples, which were infused via a nasoduodenal tube. The study was stopped prematurely due to the fact that up to 2 infusions of donor feces eradicated *C difficile* infection in 94% of patients, compared with only 31% of patients who received additional courses of oral vancomycin. Based upon this success, the American College of Gastroenterology guidelines for *C difficile* treatment advocated early use of FMT following the first relapse.

Initial case reports have shown success for FMT treatment of recurrent *C difficile* infection in IBD patients as well. A study by Dr Colleen Kelly and colleagues found that FMT was effective therapy for recurrent *C difficile* infection in patients on immunosuppressive therapy for various conditions. A more recent study by Dr Monika Fischer and colleagues, which was presented in abstract form and focused on IBD patients, suggested that FMT can also be used safely and successfully in this patient population. However, the success rates of FMT treatment of recurrent *C difficile* in IBD patients are typically not as high as the greater-than-90% success rates seen in the non-IBD patient population. It is unclear why this has been the case. Considering that the trials of FMT as primary therapy for IBD have shown deterioration in some patients, this may be reflected in the subset of IBD patients who have failed FMT for the treatment of concomitant *C difficile*. Thus, at this time, FMT is not an option for the primary therapy of IBD, although it remains a focus of research protocols. Given the mixed results in a number of studies, it is too early to determine whether the use of FMT can eventually be a therapeutic intervention for patients with IBD.

G&H How does the presence of *C difficile* infection affect standard IBD treatment?

DB As mentioned above, when a person has active *C difficile* infection in the setting of a colitis flare, clinicians should be cautious using powerful immunosuppressive strategies, specifically corticosteroids. Corticosteroids can be helpful in patients with severe colitis; however, a person with a superimposed infection can destabilize if corticosteroids are used without appropriate antibiotic therapy. Thus, when an infection is identified, or when there is a high index of suspicion that a patient has an infection, clinicians should adjust their therapeutic plans to address the infection and potentially not use the highest doses of corticosteroids.

Unfortunately, clear, definitive data do not exist at this time to guide clinicians in terms of the best treatment approach when it comes to IBD flares that occur or are worsened by concomitant *C difficile* infection. It has been suggested that the use of anti–tumor necrosis factor (TNF) alpha agents can be helpful in patients with significant IBD flares that have occurred in the setting of *C difficile* infection. Thus, clinicians have to individualize treatment approaches. Research that my colleagues and I conducted at the Medical College of Wisconsin suggested that using half-maximal intravenous corticosteroids in people admitted to the hospital with concomitant antibiotic therapy (oral vancomycin) was a more effective approach than using standard high doses of IBD corticosteroids in the setting of colitis flare. Also effective was the use of anti-TNF alpha agents as a rescue approach in patients with *C difficile* who have not had an adequate clinical response to intravenous corticosteroids over 48 hours; however, this finding is based only on observational data.

G&H How many people are asymptomatic carriers of *C difficile*?

DB The majority of people who have *C difficile* in their body are asymptomatic carriers. Approximately 90% of newborns will have asymptomatic carriage of *C difficile* in their gastrointestinal tract. *C difficile* carriage usually clears by approximately age 2 years, and then re-acquisition of *C difficile* will occur as people go through childhood, adolescence, and adulthood. In the healthy adult population, the rate of *C difficile* carriage varies between 4% and 8%. In geriatric populations, the rate of *C difficile* carriage rises. People in nursing homes and long-term care facilities have an approximately 50% *C difficile* carriage rate. In the acute care hospital setting, 34% of inpatients are carriers of *C difficile*. Not all of these individuals have an active infection, but the rates of carriage rise as people grow older and have exposure to the health care system.

G&H Should IBD patients use any preventive measures to avoid *C difficile* infection?

DB Caution is advised with the use of antibiotics in IBD patients who have a history of *C difficile* infection as well as in people at risk of contracting the infection due to their occupation. In particular, health care workers should be careful due to the high *C difficile* carriage rates in nursing homes and acute care hospital settings. Soap-and-water handwashing is one of the most effective approaches for dislodging *C difficile* spore contamination on the skin that can lead to inoculation when a person is eating. Alcohol-based hand gels are not effective for killing spores. Wearing gloves during patient contact is another way to prevent

spore contamination. In addition, careful handwashing with soap and water should be practiced by IBD patients who are new parents (as they may be exposed to *C difficile* during diaper changing) and IBD patients who are visiting individuals in a hospital or nursing home.

G&H Are there any special considerations that should be kept in mind when managing patients with both IBD and *C difficile* infection?

DB If an IBD patient requires antibiotic therapy and then suddenly develops diarrheal illness over the next several weeks, that is a high-risk individual, and it may be appropriate to start therapy empirically. Once antibiotic therapy has been initiated, polymerase chain reaction testing for *C difficile* infection can turn negative within several days, so there may be a false-negative stool test result. Commitment to a full course of therapy once it has been initiated and the patient is improving clinically is appropriate. Testing for cure is not typically needed, and there are no data suggesting that a test for cure is appropriate in the IBD patient population. Some patients with IBD may require longer courses of antibiotic therapy, as the standard 10- to 14-day treatment course may not be adequate for clearance of spores in the IBD patient population, and we do not have clear data at this time in terms of guiding treatment. Thus, antibiotic therapy can be extended in this cohort, and clinicians should consider pulse taper regimens for vancomycin. Patients with IBD who have failed to eradicate infection and have had relapsing infections are appropriate candidates for FMT. For the hospitalized IBD patient population, oral vancomycin and fidaxomicin are superior agents, but only limited data are available at this time.

G&H What are the next steps in research?

DB Understanding the microbiome in the IBD patient population is one of the most important research goals in this area. Achieving this goal will likely provide insight into the patients who have the most risk for developing *C difficile* infection and for relapsing infections. The immunologic factors that lead to colonization and mounting an immunoglobulin G immune response against *C difficile* toxin A (which is part of the immunologic ability to become an asymptomatic carrier) may be disturbed in patients with IBD. Understanding underlying immune function in the IBD patient population and the ability of these patients to control infection is also important.

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Suggested Reading

Ananthakrishnan AN, McGinley EL, Saeian K, Binion DG. Temporal trends in disease outcomes related to *Clostridium difficile* infection in patients with inflammatory bowel disease. *Inflamm Bowel Dis*. 2011;17(4):976-983.

Kelly CR, Ihunnah C, Fischer M, et al. Fecal microbiota transplant for treatment of *Clostridium difficile* infection in immunocompromised patients. *Am J Gastroenterol*. 2014;109(7):1065-1071.

Louie TJ, Miller MA, Mullane KM, et al; OPT-80-003 Clinical Study Group. Fidaxomicin versus vancomycin for *Clostridium difficile* infection. *N Engl J Med*. 2011;364(5):422-431.

van Nood E, Vrieze A, Nieuwdorp M, et al. Duodenal infusion of donor feces for recurrent *Clostridium difficile*. *N Engl J Med*. 2013;368(5):407-415.

Yanai H, Nguyen GC, Yun L, et al. Practice of gastroenterologists in treating flaring inflammatory bowel disease patients with *Clostridium difficile*: antibiotics alone or combined antibiotics/immunomodulators? *Inflamm Bowel Dis*. 2011;17(7):1540-1546.

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References

1. Hsu HL, Hsiao CH, Liu KL. Henoch-Schönlein purpura. *Clin Gastroenterol Hepatol*. 2010;8(8):e83-e84.

2. Sharma A, Wanchu A, Kalra N, Singh S, Bambery P. Successful treatment of severe gastrointestinal involvement in adult-onset Henoch-Schönlein purpura. *Singapore Med J*. 2007;48(11):1047-1050.

3. Blanco R, Martínez-Taboada VM, Rodríguez-Valverde V, García-Fuentes M, González-Gay MA. Henoch-Schönlein purpura in adulthood and childhood: two different expressions of the same syndrome. *Arthritis Rheum*. 1997;40(5):859-864.

4. Mills JA, Michel BA, Bloch DA, et al. The American College of Rheumatology 1990 criteria for the classification of Henoch-Schönlein purpura. *Arthritis Rheum*. 1990;33(8):1114-1121.

5. Tancrede-Bohin E, Ochonisky S, Vignon-Pennamen MD, Flageul B, Morel P, Rybojad M. Schönlein-Henoch purpura in adult patients. Predictive factors for IgA glomerulonephritis in a retrospective study of 57 cases. *Arch Dermatol*. 1997;133(4):438-442.

6. Novák J, Márki-Zay J, Csiki Z, Sebesi J, Takáts A, Sipka S. Schoenlein-Henoch purpura in adulthood (gastrointestinal manifestation and endoscopy) [in German]. *Z Gastroenterol*. 2001;39(9):775-782.

7. Ashton H, Frenk E, Stevenson CJ. Therapeutics. XV. The management of Henoch-Schonlein purpura. *Br J Dermatol*. 1971;85(2):199-203.

8. Karagozian R, Turbide C, Szilagyi A. Henoch-Schonlein purpura presenting with ileal involvement in an adult. *Dig Dis Sci*. 2004;49(10):1722-1726.

9. Yoshikawa N, Yamamura F, Akita Y, Sato T, Mitamura K. Gastrointestinal lesions in an adult patient with Henoch-Schönlein purpura. *Hepatogastroenterology*. 1999;46(29):2823-2824.

10. Uppal SS, Hussain MA, Al-Raqum HA, et al. Henoch-Schönlein's purpura in adults versus children/adolescents: a comparative study. *Clin Exp Rheumatol*. 2006;24(2 suppl 41):S26-S30.

11. García-Porrúa C, Calviño MC, Llorca J, Couselo JM, González-Gay MA. Henoch-Schönlein purpura in children and adults: clinical differences in a defined population. *Semin Arthritis Rheum*. 2002;32(3):149-156.

12. Ronkainen J, Koskimies O, Ala-Houhala M, et al. Early prednisone therapy in Henoch-Schönlein purpura: a randomized, double-blind, placebo-controlled trial. *J Pediatr*. 2006;149(2):241-247.

13. Narin N, Akçoral A, Aslin MI, Elmastas H. Ranitidine administration in Henoch-Schönlein vasculitis. *Acta Paediatr Jpn*. 1995;37(1):37-39.