Mixed Bag: How *C. Difficile* Can Cause Pouchitis

Michael J. Stewart¹

Published online: 11 December 2019

© Springer Science+Business Media, LLC, part of Springer Nature 2019

Clostridium difficile infection (CDI), a major cause of healthcare associated infections, has become a consistent frustration of hospital-based clinicians. Worldwide, the highest rates of hospital-associated CDI occur in North America, where an estimated 7.14 of 1000 hospital admissions are complicated by CDI [1]. *Clostridium difficile* is a fastidious spore-forming gram-positive anaerobic bacterium that causes infections ranging from mild diarrhea to fulminant colitis. One of the strongest risk factors for CDI is prior antibiotic exposure resulting presumably from the disruption of the intestinal microbiota, although a number of other risk factors have been identified.

Infection with *C. difficile* occurs more commonly in patients with inflammatory bowel disease (IBD) compared to those without [2, 3]. The symptoms of active IBD and CDI can be clinically indistinguishable. Delayed recognition and treatment of CDI can result in serious morbidity as well as complicate treatment of the underlying IBD. Thus, early identification of CDI in IBD patients is of particular importance. Further, among hospitalized IBD patients, there have been repeated and consistent data associating CDI with increased mortality and longer, more costly hospital admissions [2, 3].

Patients with ulcerative colitis appear to be at higher risk of developing CDI than those with Crohn's disease [2, 4]. Though the risk of CDI in IBD has been well characterized in the literature, there are limited data assessing the risk of CDI specifically in patients with ileal-pouch anal anastomosis (IPAA), as these patients are generally scarce and have been excluded from many clinical studies. Until recently, the description of CDI in IPAA patients has been limited to case reports and case series, which were reviewed in detail by Seril and Shen in 2014 [5]. A recent population-based

study using administrative data identified 3470 IBD patients admitted to hospital with pouchitis, estimating that CDI occurs in 2.6% of these admissions [6]. Furthermore, there is a literature showing that CDI of the pouch may be manifest with more systemic symptoms (e.g., fever, night sweats, and weight loss) and is associated with higher rates of recurrent CDI and refractory infection [5].

In this issue of *Digestive Diseases and Sciences*, Gosai et al. further explore CDI among IPAA patients in a retrospective review of 160 IBD patients with pouchitis admitted to a tertiary care center over a three-year time period [7]. Of these patients, 72 underwent *Clostridium difficile* PCR testing over 96 hospital admissions with 16 (22%) diagnosed with CDI. In addition to patient and clinical factors that have previously been associated with CDI, the authors evaluated the association between body mass index (BMI) and CDI. Prior data from the same group had suggested that obesity and the obesity-related diseases, non-alcoholic fatty liver disease (NAFLD) and obstructive sleep apnea (OSA) were associated with increased risk of CDI among IBD patients with IPAA [6]. In contrast, the current study by Gosai et al. found that obesity was independently associated with a lower risk of CDI according to multivariable analysis. The prior association with obesity was identified in data available through a large national administrative database, whereas the current study reports the experience at a single expert center with detailed patient information. While administrative data can be very helpful at identifying signals within large groups of patients, the availability and reliability of patient-level data is often limited.

Among patients with CDI, all were symptomatic with the majority (81%) reporting diarrhea, and half (50%) reporting abdominal pain. All of these patients had symptomatic relief with initiation of antibiotic treatment. Biochemical data typically associated with CDI severity (e.g., white blood count, albumin) were not assessed in this study.

The typical risk factors that clinicians evaluate when considering CDI in non-IPAA patients were not replicated in this study. Specifically, the use of antibiotics, corticosteroids, biologic medications, and proton pump inhibitors, as

✉ Michael J. Stewart
michael.stewart@dal.ca

¹ Division of Digestive Care and Endoscopy, Department of Medicine, Dalhousie University, QEII - Victoria Building, 9th Floor Victoria Building, 1276 South Park Street, Halifax, NS B3H 2Y9, Canada

well as certain comorbidities and advancing age were not associated with CDI in this cohort of IPAA patients. The only variable that was independently associated with CDI was BMI > 25, which was protective against the development of CDI. While it is possible that the sample size of this study was inadequate to assess the associations among these related conditions, it is possible that the clinical presentation of CDI in IPAA patients differs from both the general population and other IBD patients. In fact, this latter possibility is in keeping with other small studies that have failed to identify the typical CDI risk factors among patients who have undergone colectomy and subsequently develop CDI [8, 9].

Patients with IPAA generally represent a small subset of both the inpatient and outpatient IBD population; this study did not include ambulatory patients or those who were admitted for < 24 h. Nevertheless, the sample size of 160 patients, while small, is similar to previously published cohort studies [8, 9]. A small number of hospital admissions in this study (16 of 218) were for reasons other than pouchitis or an IBD flare; thus, the primary reason for admission may have been unrelated to symptoms of pouchitis or IBD. This could confound the data, although it seems likely it would only underestimate the risk of CDI among symptomatic IPAA patients.

Among the 160 patients admitted to hospital with pouchitis, only 72 (45%) underwent testing for *Clostridium difficile*. Of the 88 patients who were not tested, many had symptoms that could raise the suspicion for CDI, including diarrhea, abdominal/perianal pain, and nausea/vomiting. These findings are not particularly surprising in light of a recent multicenter study that found the rate of testing for *Clostridium difficile* in IBD patients admitted to hospital varied from 61 to 91% between Canadian cities [10]. Further, a large French cohort found that *Clostridium difficile* testing was only performed in 59% of patients admitted to hospital specifically due to a flare of IBD [11].

This study confirms prior research that *Clostridium difficile* complicates a significant proportion of hospital admissions for pouchitis in IBD patients following IPAA. Available patient and clinical data associated with the risk of CDI, though limited, suggest that they may differ from the general population and even other patients with IBD. Larger studies are required to further characterize CDI of the pouch.

This study also highlights the importance of maintaining a high degree of suspicion among IPAA patients admitted with signs and symptoms of active IBD or pouchitis, since 10% of the total patients and 22% of the tested patients in this cohort were diagnosed with CDI. Considering the high

rates of CDI, the significant increased morbidity and mortality in IBD patients, and lack of accepted risk factors for CDI in IPAA patients, *Clostridium difficile* testing should be performed in all symptomatic IPAA patients, especially in those with a BMI > 25.

References

1. Balsells E, Shi T, Leese C, et al. Global burden of *Clostridium difficile* infections: A systematic review and meta-analysis. *J Glob Health*. 2019;9:407.
2. Nguyen G, Kaplan GG, Harris ML, Brant SR. A national survey of the prevalence and impact of *Clostridium difficile* infection among hospitalized inflammatory bowel disease patients. *Am J Gastroenterol*. 2008;103:1443–1450.
3. 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;17:976–983.
4. Joshi NM, Marks IH, Crowson R, Ball D, Rampton DS. Incidence and outcome of *Clostridium difficile* infection in hospitalized patients with inflammatory bowel disease in the UK. *J Crohn's Colitis*. 2017;11:70–76.
5. Seril DN, Shen B. *Clostridium difficile* infection in the postcolectomy patient. *Inflamm Bowel Dis* 2014;2014:2450–2469.
6. Kistangari G, Lopez R, Shen B. Frequency and Risk Factors of *Clostridium difficile* Infection in Hospitalized Patients with Pouchitis: A Population-based Study. *Inflamm Bowel Dis*. 2017;23:661–671.
7. Gosai F, Covut F, Alomari M, Hitawala A, Singh A, Kisangani G, et al. Obesity is associated with decreased risk of *clostridium difficile* infection in hospitalized patients with pouchitis. *Dig Dis Sci*. (Epub ahead of print). <https://doi.org/10.1007/s10620-019-05888-w>.
8. Shen BO, Jiang ZD, Fazio VW, et al. *Clostridium difficile* Infection in Patients With Ileal Pouch-Anal Anastomosis. *Clin Gastroenterol Hepatol*. 2008;6:782–788.
9. Li Y, Qian J, Queener E, Shen B. Risk factors and outcome of PCR-detected *clostridium difficile* infection in ileal pouch patients. *Inflamm Bowel Dis*. 2013;19:397–403.
10. Nguyen GC, Murthy SK, Bressler B, et al. Quality of Care and Outcomes among Hospitalized Inflammatory Bowel Disease Patients: A Multicenter Retrospective Study. *Inflamm Bowel Dis*. 2017;23:695–701.
11. Regnault H, Bourrier A, Lalande V, et al. Prevalence and risk factors of *Clostridium difficile* infection in patients hospitalized for flare of inflammatory bowel disease: A retrospective assessment. *Dig Liver Dis*. 2014;46:1086–1092.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.