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The Vermiform Appendix and Recurrent *Clostridium difficile* Infection: A Curious Connection

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Clostridium difficile is a spore-forming, anaerobic, and gram-positive bacterium that causes gastrointestinal infection resulting in diarrhea and colitis.^{1,2} There has been a dramatic increase in both the incidence and the severity of *C difficile* infection (CDI) during the past decade. Recent studies demonstrate that nosocomial CDI prolongs hospital stay, even after controlling for confounding variables such as admission diagnosis, age, and burden of comorbidities, amounting to \$1–3 billion per year in extra hospital costs alone in the United States.^{3–5} The increased severity of CDI is reflected in markedly increased death rates (from 5.7 deaths per million population in 1999 to 23.7 deaths per million population in 2004), making it a leading cause of death from nosocomial infection.⁶ Recurrence of infection is one of the most challenging aspects in the management of CDI. Approximately 25% of patients experience recurrence despite initial successful treatment. The risk might be as high as 65% for those with a history of multiple prior recurrences.⁷ Recurrent CDI typically occurs 1–3 weeks after completion of treatment for the initial episode, but late recurrences up to 2 months are not infrequent.^{7–13}

Recurrent CDI is typically first treated with an additional course of metronidazole or oral vancomycin.² A wide variety of sometimes ingenious therapies have been reported for multiple recurrences of CDI including oral vancomycin given in tapering and intermittent doses, fidaxomicin, rifaximin, probiotics, non-toxinogenic *C difficile*, human monoclonal antitoxin antibodies, and a *C difficile* toxoid vaccine.^{1,2,14}

Previous studies have revealed that multiple factors were independently associated with recurrent CDI including age >65 years, severe or fulminant underlying illness (as determined by modified Horn's index), continued use of non-*C difficile* antibiotics after diagnosis of CDI, and use of acid-antisecretory medications.^{15,16} An inadequate host immune response to *C difficile* toxins has also been implicated.¹⁷

In this issue, Im et al¹⁸ report the results of their investigation into whether the absence of an appendix is associated with CDI recurrence. The authors reviewed medical records of inpatients with CDI admitted to Winthrop University Hospital, a tertiary care hospital, from 2005–2007. They used abdominal computed tomography reports and records of patients' surgical histories to identify those with and without an appendix. The primary outcome

Conflicts of interest

The authors disclose no conflicts.

studied was CDI recurrence, defined as recurrent diarrhea with a positive *C difficile* stool toxin assay in a subject with a prior episode of CDI within the past 8 weeks. A total of 254 patients with CDI and known appendix status were studied, 194 (76%) with a first episode CDI and 60% (24%) with recurrent CDI. In a multivariate analysis, the presence of an appendix was strongly associated with a lower risk of CDI recurrence ($P < .0001$; adjusted relative risk 0.40). Conversely, age >60 years was associated with increased CDI recurrence ($P = .03$; adjusted relative risk, 2.44). Thus, Im et al have made the novel and intriguing observation that prior appendectomy was strongly associated with increased risk for CDI recurrence.

The vermiform (from the Latin for worm-shaped) appendix is a thin, blind-ended tube arising from the cecum. The base of the appendix is usually located approximately 2 cm below the ileocecal valve. The appendix averages 10 cm in length, and its diameter is usually between 7 and 8 mm. The function of the appendix remains in constant debate. An old and prevailing theory is that the appendix is a useless evolutionary remnant. This theory is supported by the usual apparent lack of significant health consequences after its surgical removal. However, recent studies suggest important roles for the appendix in 2 areas, maintenance of the gut microbiota and immune function (Figure 1).^{19,20}

Studies on gut biofilms suggest that the appendix might harbor and protect bacteria that are beneficial to human colonic function.^{19,21,22} Studies with healthy human appendices removed during kidney-pancreas transplants reveal that the mucosa is lined by a biofilm.²³ The appendicular biofilm consists of an organized aggregate of microorganisms within the mucus layer that adhere to each other and to the intestinal epithelial surface.^{21–23} By using samples taken from a fresh, normal, intact, unprepared human colon of a deceased organ donor, Bollinger et al¹⁹ demonstrated that biofilms were most prominent in the appendix in terms of bacterial density and of biofilm continuity across the epithelial surface. The density and continuity of biofilms decreased progressively from the appendix to the distal end of the large bowel. These findings led to the proposal that the appendix serves as a “safe house” for commensal bacteria, providing support for bacterial growth and potentially facilitating reinoculation of the colon in the event that the contents of the intestinal tract are purged after exposure to a pathogen (or an antibiotic).²⁴

The appendix has abundant gut-associated lymphoid tissue. It has long been proposed as a functioning lymphoid organ capable of responding to the wide variety of bacterial antigens present in the human gastrointestinal tract. As such, the appendix might work as a guardian of the luminal environment, identifying and counteracting hostile external factors. Intestinal immune responses are known to be important in determining the natural history of CDI and the risk for recurrence. *C difficile* produces 2 major virulence factors, toxin A and toxin B. Symptomless carriers of toxinogenic *C difficile* and those with a single episode of CDI without recurrence show more robust adaptive antitoxin immune responses than those with symptomatic and recurrent disease.^{11,17,25}

Two of the most abundantly produced effector molecules of the intestinal immune system, immunoglobulin A and mucin, support the growth of microbial biofilms in vitro^{26–28} and are physically associated with biofilms in vivo in human gut.²³ Type 1 fimbriae with mannose-

specific adhesins expressed by most *Escherichia coli* isolates can bind to secretory immunoglobulin A, thus contributing to biofilm formation.^{29,30} Thus, there appears to be synergy between the 2 proposed functions of the appendix in that its rich contributions to intestinal innate and adaptive immunity might also act to support biofilm formation, thereby maintaining a reserve of normal enteric bacteria.

The appendix has also received attention in inflammatory bowel disease because of an inverse relationship between appendectomy and ulcerative colitis (UC).³¹ Interestingly, the incidence of UC is lower in patients who had appendectomy for inflammatory conditions (appendicitis and lymphadenitis), but not in patients who had appendectomy for nonspecific abdominal pain. Furthermore, this inverse relationship is limited to patients who undergo appendectomy before the age of 20 years. Finally, several studies report improvement of UC after appendectomy, especially in young patients.^{32–34} The relationship, if any, between appendectomy and Crohn's disease is weak.

In summary, the study by Im et al provides new evidence that the appendix might protect against recurrent CDI. Plausible and complementary potential mechanisms of action include effects on microbial biofilms and immune defense. Recurrent CDI typically occurs shortly after initial CDI therapy is discontinued and before the normal colonic microbiota is restored. Prominent and protected biofilms within the appendix might accelerate the repopulation of the colonic lumen, restoration of colonization resistance against *C difficile*, and hence lead to fewer CDI recurrences. Alternatively or in parallel, colonic immune responses to *C difficile* and its toxins, which are known to be an important determinant of recurrence risk, might be impaired after appendectomy, leading to increased vulnerability to recurrent disease.^{17,35} The results of the study by Im et al raise fascinating questions regarding possible underappreciated functions of the vermiform appendix in CDI and its role as a biofilm reservoir and as an intestinal immune organ. However, this retrospective examination does need to be validated by prospective, controlled, multicenter studies; fortunately, such studies are eminently feasible.

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References

1. Kelly CP, LaMont JT. *Clostridium difficile*: more difficult than ever. N Engl J Med. 2008; 359:1932–1940. [PubMed: 18971494]
2. Cohen SH, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults: 2010 update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). Infect Control Hosp Epidemiol. 2010; 31:431–455. [PubMed: 20307191]
3. Kelly CP, Pothoulakis C, LaMont JT. *Clostridium difficile* colitis. N Engl J Med. 1994; 330:257–262. [PubMed: 8043060]
4. Kyne L, Hamel MB, Polavaram R, et al. Health care costs and mortality associated with nosocomial diarrhea due to *Clostridium difficile*. Clin Infect Dis. 2002; 34:346–353. [PubMed: 11774082]

5. Vonberg RP, Reichardt C, Behnke M, et al. Costs of nosocomial *Clostridium difficile*-associated diarrhoea. J Hosp Infect. 2008; 70:15–20.
6. Redelings MD, Sorvillo F, Mascola L. Increase in *Clostridium difficile*-related mortality rates, United States, 1999–2004. Emerg Infect Dis. 2007; 13:1417–1419. [PubMed: 18252127]
7. McFarland LV, Elmer GW, Surawicz CM. Breaking the cycle: treatment strategies for 163 cases of recurrent *Clostridium difficile* disease. Am J Gastroenterol. 2002; 97:1769–1775. [PubMed: 12135033]
8. Do AN, Fridkin SK, Yechouren A, et al. Risk factors for early recurrent *Clostridium difficile*-associated diarrhea. Clin Infect Dis. 1998; 26:954–959. [PubMed: 9564482]
9. Fekety R, McFarland LV, Surawicz CM, et al. Recurrent *Clostridium difficile* diarrhea: characteristics of and risk factors for patients enrolled in a prospective, randomized, double-blinded trial. Clin Infect Dis. 1997; 24:324–333. [PubMed: 9114180]
10. Gerding DN, Muto CA, Owens RC Jr. Treatment of *Clostridium difficile* infection. Clin Infect Dis. 2008; 46(Suppl 1):S32–S42. [PubMed: 18177219]
11. Kyne L, Kelly CP. Recurrent *Clostridium difficile* diarrhoea. Gut. 2001; 49:152–153. [PubMed: 11413124]
12. Maroo S, Lamont JT. Recurrent *Clostridium difficile*. Gastroenterology. 2006; 130:1311–1316. [PubMed: 16618421]
13. McFarland LV, Surawicz CM, Rubin M, et al. Recurrent *Clostridium difficile* disease: epidemiology and clinical characteristics. Infect Control Hosp Epidemiol. 1999; 20:43–50. [PubMed: 9927265]
14. Louie TJ, Miller MA, Mullane KM, et al. Fidaxomicin versus vancomycin for *Clostridium difficile* infection. N Engl J Med. 2011; 364:422–431. [PubMed: 21288078]
15. Hu MY, Katchar K, Kyne L, et al. Prospective derivation and validation of a clinical prediction rule for recurrent *Clostridium difficile* infection. Gastroenterology. 2009; 136:1206–1214. [PubMed: 19162027]
16. Garey KW, Sethi S, Yadav Y, et al. Meta-analysis to assess risk factors for recurrent *Clostridium difficile* infection. J Hosp Infect. 2008; 70:298–304. [PubMed: 18951661]
17. Kyne L, Warny M, Qamar A, et al. Association between antibody response to toxin A and protection against recurrent *Clostridium difficile* diarrhoea. Lancet. 2001; 357:189–193. [PubMed: 11213096]
18. Im GY, Modayil RJ, Lin CT, et al. The appendix may protect against *Clostridium difficile* recurrence. Clin Gastroenterol Hepatol. 2011; 9:1072–1077. [PubMed: 21699818]
19. Bollinger RR, Barbas AS, Bush EL, et al. Biofilms in the normal human large bowel: fact rather than fiction. Gut. 2007; 56:1481–1482. [PubMed: 17872584]
20. Sonnenburg JL, Angenent LT, Gordon JI. Getting a grip on things: how do communities of bacterial symbionts become established in our intestine? Nat Immunol. 2004; 5:569–573. [PubMed: 15164016]
21. Allen A, Pearson JP. The gastrointestinal adherent mucous gel barrier. Methods Mol Biol. 2000; 125:57–64. [PubMed: 10820749]
22. Atuma C, Strugala V, Allen A, et al. The adherent gastrointestinal mucus gel layer: thickness and physical state in vivo. Am J Physiol Gastrointest Liver Physiol. 2001; 280:G922–G929. [PubMed: 11292601]
23. Palestrant D, Holzknecht ZE, Collins BH, et al. Microbial biofilms in the gut: visualization by electron microscopy and by acridine orange staining. Ultrastruct Pathol. 2004; 28:23–27. [PubMed: 14967595]
24. Randal Bollinger R, Barbas AS, Bush EL, et al. Biofilms in the large bowel suggest an apparent function of the human vermiform appendix. J Theor Biol. 2007; 249:826–831. [PubMed: 17936308]
25. Kelly CP, Kyne L. The host immune response to *Clostridium difficile*. J Med Microbiol. 2011; 60:1070–1079. [PubMed: 21415200]
26. Bollinger RR, Everett ML, Wahl SD, et al. Secretory IgA and mucin-mediated biofilm formation by environmental strains of *Escherichia coli*: role of type 1 pili. Mol Immunol. 2006; 43:378–387. [PubMed: 16310051]

27. Bollinger RR, Everett ML, Palestrant D, et al. Human secretory immunoglobulin A may contribute to biofilm formation in the *gut*. *Immunology*. 2003; 109:580–587. [PubMed: 12871226]
28. Orndorff PE, Devapali A, Palestrant S, et al. Immunoglobulin-mediated agglutination of and biofilm formation by *Escherichia coli* K-12 require the type 1 pilus fiber. *Infect Immun*. 2004; 72:1929–1938. [PubMed: 15039312]
29. Friman V, Adlerberth I, Connell H, et al. Decreased expression of mannose-specific adhesins by *Escherichia coli* in the colonic microflora of immunoglobulin A-deficient individuals. *Infect Immun*. 1996; 64:2794–2798. [PubMed: 8698510]
30. Wold AE, Adlerberth I. Breast feeding and the intestinal microflora of the infant: implications for protection against infectious diseases. *Adv Exp Med Biol*. 2000; 478:77–93. [PubMed: 11065062]
31. Andersson RE, Olaison G, Tysk C, et al. Appendectomy and protection against ulcerative colitis. *N Engl J Med*. 2001; 344:808–814. [PubMed: 11248156]
32. Järnerot G, Andersson M, Franzén L. Laparoscopic appendectomy in patients with refractory ulcerative colitis. *Gastroenterology*. 2001; 120:1562–1563. [PubMed: 11339237]
33. Jo Y, Matsumoto T, Yada S, et al. Histological and immunological features of appendix in patients with ulcerative colitis. *Dig Dis Sci*. 2003; 48:99–108. [PubMed: 12645797]
34. Okazaki K, Onodera H, Watanabe N, et al. A patient with improvement of ulcerative colitis after appendectomy. *Gastroenterology*. 2000; 119:502–506. [PubMed: 10930385]
35. Lowy I, Molrine DC, Leav BA, et al. Treatment with monoclonal antibodies against *Clostridium difficile* toxins. *N Engl J Med*. 2010; 362:197–205. [PubMed: 20089970]

Fig. 1.
Risk factors for *Clostridium difficile* infection, and potential protective effects conferred by the appendix.