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Fixing the microbiota to treat *Clostridium difficile* infections

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Disruption of the complex gut microbiota by antibiotics renders individuals vulnerable to *Clostridium difficile* infection (CDI), one of the most important causes of diarrhea. After dormant *C. difficile* spores are orally ingested, they subsequently germinate and grow¹. The bacteria then produce toxins A and B, which damage the colonic epithelium, leading to inflammatory responses that can cause a range of symptoms, from mild diarrhea to potentially fatal colitis. The high frequency of CDI recurrence is a vexing problem², as antibiotic treatment for primary CDI can also eliminate many potentially protective commensal bacteria and thereby facilitate *C. difficile* reinfection. The strategy of using antibiotics to treat a condition originally caused by antibiotics is, at the very least, conceptually dissatisfying, and it may very well explain why first recurrence rates for CDI approach 30% and secondary recurrences are even more frequent^{2,3}. In cases of refractory disease, clinicians have resorted to prolonged, tapering or pulsed courses of antibiotics, all with incomplete success².

Given the high rates of recurrence in CDI with antibiotic treatment, reconstitution of the intestinal microbiota seems logical, but challenges to this approach are daunting. It remains unknown which commensal bacteria, or bacterial consortia, will provide protection against infection. Once this is determined, it will be important in the clinical setting to find out how to cultivate and expand these bacterial species *in vitro*, if possible, and to determine the optimal way to introduce protective bacterial species into the damaged microbiota of a patient with incurable CDI. Currently available probiotics are a heterogeneous group of microbes that provide marginal, if any, benefit to patients with CDI, and, therefore, their use is not recommended by current treatment guidelines⁴.

An alternative approach to reconstituting the colonic microbiota involves transferring feces from a healthy donor to the intestinal tract of a patient by fecal microbiota transplantation (FMT). Although FMT is not new, it is an unconventional treatment that is not commonly performed. Anecdotal reports attested to the potential effectiveness of FMT for the treatment of recurrent CDI, but a controlled comparison with conventional treatment was lacking until recently, when van Nood *et al.*⁵ published the first randomized trial comparing duodenal infusion of a fecal solution generated from a normal donor to antibiotic therapy to treat patients with recurrent CDI. FMT resulted in a significant difference in cure rate, with 94%

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of patients receiving FMT free of infection compared to 31% and 23% of patients in the conventional antibiotic arms (oral and rectal administration routes, respectively).

These findings provide clear, confirmatory evidence for the benefits of microbiota reconstitution. Going forward, questions will now turn to the details of FMT reconstitution, whether it can be further refined and whether the underlying mechanisms can be better understood. Because the composition of feces is complex and impossible to completely define with current tools, concerns about the potential transmission of undetected or unknown pathogens are difficult to allay. Furthermore, recent discoveries that the microbiota composition can influence the development of obesity, metabolic syndrome and autoimmune diseases raise additional concerns about the potential for the promotion of these after transplantation³.

There is, therefore, great interest in identifying the specific bacterial species that confer protection against CDI, with the aim of achieving the same efficacy as FMT, but with greater uniformity, easier manufacturing and administration and, perhaps, improved safety profile. Nearly 25 years ago, Tvede and Rask-Madsen successfully treated five patients with recurrent CDI—who lacked *Bacteroides* bacteria—using a mixture of ten different bacterial species⁶ and found they were recolonized with *Bacteroides* spp. after the procedure. More recent studies have also shown a correlation between protection against CDI and reestablishment of *Bacteroides* in the colon⁷, and a retrospective study comparing FMT with the administration of the Tvede10 cocktail found equivalent cure rates for recurrent CDI⁸.

Last year, a mixture of 33 bacterial strains cultured from a healthy donor—consisting of bacteria belonging to *Bifidobacterium*, *Bacteroides*, *Lactobacillus* and clostridial clusters IV and XVIa, which have all been shown to protect against CDI^{2,7,9}—cured two patients with recurrent disease¹⁰. Ten of the 33 strains belonged to the Lachnospiraceae family, a group of bacteria belonging to clostridial cluster XIVa of the Firmicutes phylum. Absence of Lachnospiraceae has been recently associated with active or severe CDI, suggesting that bacteria in this family may have distinct protective effects^{7,11}. In infected germ-free mice, one strain of Lachnospiraceae that is closely related to *Clostridium clostridioforme* decreased the colonic density of *C. difficile* by 50-fold¹¹. In another study, chronic CDI in mice could be cured by administration of a cocktail consisting of six bacterial strains, which included *Anaerostipes* sp., another member of Lachnospiraceae⁹. In this study, however, administration of cultured bacteria resulted in reexpansion of resident bacterial populations, suggesting that the administered bacterial strains facilitated the redevelopment of a complex microbiota rather than directly inhibiting *C. difficile*.

How does the normal microbiota provide resistance against CDI? In one hypothesis, antibiotic treatment can deplete obligate anaerobic bacterial populations, resulting in a loss of short-chain fatty acids (SCFAs), including acetate, butyrate and propionate. However, although SCFAs have been shown to influence the generation of a mucosal regulatory T cell subset¹², administration of SCFAs to mice does not diminish infection with *C. difficile*^{9,11}.

An alternative mechanism for microbiota-mediated suppression of CDI involves bacterial modification of bile salts (Fig. 1). Primary bile salts, such as taurocholic acid, in the

duodenum can act as germinants for *C. difficile* spores within minutes¹³. A subset of colonic bacteria modify primary bile acids by deconjugating, for example, taurocholic acid to choline, which can then be further converted by a smaller subset of colonic bacteria to secondary bile salts, such as deoxycholate¹³, which strongly inhibit vegetative growth of *C. difficile*¹⁴. These findings led Sorg and Sonenshein to propose that antibiotic-mediated depletion of bacterial species that convert primary to secondary bile salts could enhance *C. difficile* spore germination and vegetative growth¹³. Related studies in the mouse ileum and cecum support this model¹⁵, and recent work has now begun to dissect the complex pathways involved in *C. difficile* sporulation¹⁶, a process that is necessary for *C. difficile* transmission from infected to susceptible mice¹⁷. Moreover, a recently identified *C. difficile*-encoded bile acid receptor has been shown to be required for spore germination and the establishment of infection¹⁸.

Although CDI continues to be a major challenge with substantial impact on morbidity and mortality, there is hope on the horizon. Microbiota-mediated protection against CDI has been outlined, but the microbial contributors to this process remain incompletely defined. Until we make more progress in this area, FMT will remain an important option for the treatment of CDI. In the future, however, we are likely to move toward targeted probiotic administration and perhaps even more targeted therapies that interfere with *C. difficile* spore germination, vegetative growth and toxin-mediated epithelial damage.

References

1. Rupnik M, Wilcox MH, Gerding DN. Nat Rev Microbiol. 2009; 7:526–536. [PubMed: 19528959]
2. Kelly CP, LaMont JT. N Engl J Med. 2008; 359:1932–1940. [PubMed: 18971494]
3. Kassam Z, Lee CH, Yuan Y, Hunt RH. Am J Gastroenterol. 2013; 108:1538. [PubMed: 24005359]
4. Cohen SH, et al. Infect Control Hosp Epidemiol. 2010; 31:431–455. [PubMed: 20307191]
5. van Nood E, et al. N Engl J Med. 2013; 368:407–415. [PubMed: 23323867]
6. Tvede M, Rask-Madsen J. Lancet. 1989; 1:1156–1160. [PubMed: 2566734]
7. Shahinas D, et al. MBio. 2012; 3:e00338–12. [PubMed: 23093385]
8. Emanuelsson F, Claesson BE, Ljungstrom L, Tvede M, Ung KA. Scand J Infect Dis. 2013; 46:89–97. [PubMed: 24354958]
9. Lawley TD, et al. PLoS Pathog. 2012; 8:e1002995. [PubMed: 23133377]
10. Petrof EO, et al. Microbiome. 2013; 1:3. [PubMed: 24467987]
11. Reeves AE, Koenigsnecht MJ, Bergin IL, Young VB. Infect Immun. 2012; 80:3786–3794. [PubMed: 22890996]
12. Smith PM, et al. Science. 2013; 341:569–573. [PubMed: 23828891]
13. Sorg JA, Sonenshein AL. J Bacteriol. 2008; 190:2505–2512. [PubMed: 18245298]
14. Sorg JA, Sonenshein AL. J Bacteriol. 2010; 192:4983–4990. [PubMed: 20675492]
15. Giel JL, Sorg JA, Sonenshein AL, Zhu J. PLoS ONE. 2010; 5:e8740. [PubMed: 20090901]
16. Fimlaid KA, et al. PLoS Genet. 2013; 9:e1003660. [PubMed: 23950727]
17. Deakin LJ, et al. Infect Immun. 2012; 80:2704–2711. [PubMed: 22615253]
18. Francis MB, Allen CA, Shrestha R, Sorg JA. PLoS Pathog. 2013; 9:e1003356. [PubMed: 23675301]

Figure 1.

Bile salts may have an impact on CDI pathogenesis. Primary bile salts produced by the liver are released into the small intestine where they circulate, acting as germinants for *C. difficile* spores to transform into vegetative bacteria. In the cecum, primary bile salts are converted to secondary bile salts by members of the normal intestinal microflora. Secondary bile salts inhibit the vegetative growth of *C. difficile*, thus circumventing subsequent toxin production and colitis. In CDI, perturbation of the intestinal microflora leads to decreased conversion of primary to secondary bile salts, in turn leading to increased vegetative growth by *C. difficile* and subsequent toxin-mediated colitis.