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EDITORIAL

Beyond Antibiotics: Novel Approaches in the Treatment of Recurrent *Clostridioides difficile* Infection

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Clostridioides difficile infection (CDI) is a prevalent and potentially life-threatening condition associated with the use of broad-spectrum antibiotics.[1,2] Although conventional treatments such as antibiotics and fecal microbiota transplantation (FMT) are effective, they may not work for all patients. Therefore, there is growing interest in oral microbiome therapy (OMT) as an alternative approach for recurrent CDI.[3]

OMT involves introducing a combination of bacterial species to the gastrointestinal tract to restore microbial diversity and function. OMT has the potential to inhibit the pathogen's growth and virulence.[4,5]

This article provides an overview of alternative therapies for recurrent CDI, including their proposed mechanisms of action, supporting evidence, and the challenges that need to be addressed to be widely adopted as a treatment of CDI.

Since 2000, there has been a rise in the occurrence, intensity, and failure rate of treatment of CDI.[6,7] The emergence of *C. difficile* strains with an increased mean inhibitory concentration to metronidazole has been reported and contributes to treatment failures.[8] Antimicrobial therapy is preferred for CDI, and clinical severity prediction tools are available for determining CDI severity. The 2017 Infectious Diseases Society of America (IDSA) clinical severity prediction tool categorizes mild CDI as white blood cell $<15 \times 10^9$/L and serum creatinine <1.5 times premorbid level. Severe CDI is indicated by leukocytes $\geq$15,000 cells/μL and serum creatinine ≥ 1.5 times premorbid level.[6]

CDI management involves avoiding commonly implicated antibiotics (eg, broad-spectrum penicillin, cephalosporins, clindamycin, fluoroquinolones) and favoring less implicated ones such as macrolides, aminoglycosides, sulfonamides, vancomycin, or tetracyclines. A 2014 European Society of Clinical Microbiology and Infectious Diseases guideline, based on an observational study,[9] found a positive treatment response in 135 of 154 patients on discontinuing inciting antibiotics. Failure to stop antibiotic use during and after CDI treatment may lead to recurrent CDI.[10] Supportive care measures, such as discontinuing unnecessary antimicrobial therapy, fluid and electrolyte replacement, avoiding antimotility medications, and reviewing proton pump inhibitor use, are recommended in the European Society of Clinical Microbiology and Infectious Diseases 2014 guidelines.[11,12]

Metronidazole and vancomycin have been the mainstays of CDI treatment, but recent reports indicate higher failure rates for metronidazole.[10,13–23] In a randomized, prospective, double-blind, placebo-controlled trial by Zar et al, comparing vancomycin and metronidazole, vancomycin showed significantly better clinical cure rates in severe disease.[15]

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ACG and IDSA/Society for Healthcare Epidemiology of America guidelines recommend vancomycin or fidaxomicin as first-line treatments for mild-to-moderate CDI. Although metronidazole is still an option for nonsevere CDI in low-risk patients, its efficacy is decreasing, particularly against the BI/NAP1/027 strain.[24] Recent studies show vancomycin's superior cure rates compared with metronidazole, supported by a systematic review.[9,11,25] Fidaxomicin, a bactericidal antibiotic, demonstrates noninferiority to vancomycin with lower recurrence rates.[11,12] Clinical trials advocate vancomycin's effectiveness, and combination therapy with intravenous metronidazole and per oral vancomycin is recommended.[16,17] For severe CDI, oral vancomycin and fidaxomicin are standard therapies, while rectal retention enema or intravenous metronidazole is suggested for CDI complicated by paralytic ileus per IDSA/Society for Healthcare Epidemiology of America guidelines.[6]

Researchers and clinicians are exploring strategies to address recurrent *C. difficile* infections (rCDI), including nonantibiotic therapies, such as precision microbiome therapy. Innovative approaches are sought to improve CDI treatment, considering FMT outdated. Wilcox et al conducted trials with actoxumab and bezlotoxumab, monoclonal antibodies used with standard antibiotic therapy.[19,20] Bezlotoxumab (10 mg/kg infusion) significantly reduced the recurrence rate (17%) compared with placebo (28%), while the addition of actoxumab did not impact the recurrence rate.[19,20] SER-109, an experimental oral microbiome treatment, showed reduced recurrence rates of CDIs in a Phase 3 study compared with placebo.[21] Compared with the existing first-line treatment, SER-109 showed favorable outcomes, with only 12% of patients experiencing recurrent CDI. In comparison, the placebo resulted in recurrence in 40% of patients.[10] RBX2660 is a microbiota-based therapy derived from healthy human fecal donations. It effectively reduces CDI recurrence and restores the microbiome configuration.[26]

FMT's mechanisms include repopulating the gut with healthy bacteria, stimulating the immune system, and strengthening mucosal immunity. FMT treats gut dysbiosis and reduces the recurrence of CDI, and has been shown to decrease the mortality rate of severe CDI.[23] In 1958, Eiseman et al successfully treated pseudomembranous colitis with fecal enemas. FMT was first used for recurrent CDI in 1983 and 2013 and was approved by the US Food and Drug Administration.[26–28] The IDSA's 2021 guidelines recommend FMT for adults with rCDI when antibiotic treatment fails.[29]

Numerous studies show the benefits of FMT. In a systematic review of 371 patients from 27 case series, FMT has exhibited a success rate of about 92% in patients with rCDI.[30] A clinical trial showed 90% resolution of CDI following FMT as opposed to only 26% of patients recovering following a course of vancomycin.[31] van Nood et al showed that FMT is far superior compared with vancomycin alone or vancomycin with gastric lavage.[32] The first FMT registry was formed in 2021 to assess the efficacy of FMT in North America. The initial results showed a cure rate of 90% in patients after the first infusion, with recurrence in the next 6 months occurring only in 4% of the patients.[33]

FMT can be done through upper gastrointestinal tract routes (enteric tubes or oral capsules) or lower gastrointestinal tract routes (retention colonoscopy). Studies comparing different routes of FMT administration have yielded varying results, with Furuya-Kanamori et al showing lower gastrointestinal administration as the most efficient method. At the same time, Postigo and Kim found no significant difference in effectiveness between the two.[34,35] In addition, a trial by Kao et al showed that using capsules was not inferior to colonoscopy.[36] These findings suggest that both upper and lower gastrointestinal approaches can be equally effective for FMT.

Oral capsules for FMT, containing frozen stool samples and an acid-stable cryoprotectant, offer a noninvasive approach.[36] In a trial by Jiang et al, FMT demonstrated an 86% cure rate with no recurrence. Single oral dose recipients showed a 63% improvement, while the 2-dose subgroup had a 91% cure rate, resulting in an overall 84% cure rate for oral capsule FMT.[37] FMT has gained interest due to its efficacy and safety demonstrated in multiple randomized control trials for treating recurrent CDI, with a success rate of 92%.[38,39]

Open Biome formed Finch Therapeutics in cooperation with a former company, Crestovo, to develop CP101, an oral live biologic treatment for CDI. CP101 is an oral capsule that contains healthy donor stools, increasing microbiome diversity and preventing recurrent CDI.[40] In a post hoc analysis of the PRISM3 trial, an oral microbiome treatment (CP101) showed a high cumulative cure rate of 85.0% at week 8 for recurrent CDI patients, with a higher rate of 88.2% observed in the active treatment group compared with placebo.[39] FMT has been widely used in conventional medicine for the past decade as the most common modality for microbiome restoration in the treatment of recurrent CDI.[41,42]

RBX7455 is an oral capsule therapy for CDI made using the same process as REBYOTA. In a phase 1 study, 30 adults with prior CDI episodes were given RBX7455 capsules, without needing bowel preparation. Divided into 3 groups, they took varying doses over different durations. The study showed promising results: group 1 had a 90% recurrence-free rate over 8 weeks, group 2 had 80%, and group 3 had 100%. In addition, after 6 months, microbiome analysis revealed increased levels of beneficial bacteria such as *Bacteroides* and nonpathogenic Clostridia.[43,44] Khanna et al conducted a phase 1 study with varying dosages of RBX7455 in patients with recurrent CDI. The study found that RBX7455 at different dosages effectively prevented rCDI, with success rates of 80%–100% at 8 weeks and no dose dependency. Changes in microbiota composition were observed in responders to RBX7455. The adverse effects were mainly gastrointestinal. The study concluded that RBX7455 was safe and effective in delaying CDI onset for up to 8 weeks,

with no further recurrences for 6 months, and influenced responders' microbiome composition.[44]

In conclusion, rCDI is a severe medical condition with high morbidity and mortality, and FMT has been proven as an effective therapy for rCDI in randomized control trials. Recent research has also shown promising results with an oral microbiome treatment, CP101, demonstrating a high cumulative cure rate. Furthermore, RBX7455 has also shown efficacy in preventing rCDI, with success rates ranging from 80% to 100%. The success of these therapies highlights the importance of microbiome restoration in treating CDI. Further research is needed to fully understand the mechanisms and potential adverse effects of FMT, CP101, and RBX7455. Still, they offer promising options for patients with recurrent CDI and provide clinicians with new treatment possibilities.

While valuable, the studies mentioned have limitations. Jiang et al's study was single center with small sample size, limiting generalizability. The placebo-controlled design of the PRISM3 trial may not reflect real-world conditions. Khanna et al's open-label study with a single arm introduces bias and limits comparisons. Moreover, all studies have short follow-up periods, leaving long-term effects and safety unknown. Further research is needed to address these limitations and comprehensively understand CDI treatment.

DISCLOSURES

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REFERENCES

1. McFarland LV, Evans CT, Goldstein EJC. Strain-specificity and disease-specificity of probiotic efficacy: A systematic review and meta-analysis. *Front Med.* 2018;5:124.
2. Hota SS, Achkar JP. Review of *Clostridium difficile* infection: Treatment with faecal microbiota transplantation. *Gastroenterol Hepatol.* 2017;13(2):104–7.
3. Ponce-Alonso M, Marquina D, Suárez-Cadenas E, González-Rivera M. Oral microbiota and probiotics: A novel approach in the management of *Clostridium difficile* infection. *Nutrients.* 2020;12(3):733.
4. Tariq R, Pardi DS, Tosh PK, Walker RC. Fecal microbiota transplantation for recurrent *Clostridium difficile* infection: Update and perspectives. *Expert Rev Gastroenterol Hepatol.* 2019;13(9):871–9.
5. Rao K, Young A, Malhotra N, Nugent K, Ozcan S. Oral microbiome: Unveiling the fundamentals. *J Oral Maxillofac Pathol.* 2019;23(3):374–80.
6. Wiström J, Norrby SR, Myhre EB, et al. Frequency of antibiotic-associated diarrhoea in 2462 antibiotic-treated hospitalized patients: A prospective study. *J Antimicrob Chemother.* 2001;47(1):43–50.
7. Guh AY, Adkins SH, Li Q, et al. Risk factors for community-associated *Clostridium difficile* infection in adults: A case-control study. *Open Forum Infect Dis.* 2017;4(4):ofx171.
8. Brown KA, Khanafer N, Daneman N, Fisman DN. Meta-analysis of antibiotics and the risk of community-associated *Clostridium difficile* infection. *Antimicrob Agents Chemother.* 2013;57(5):2326–32.
9. Kelly CP. Can we identify patients at high risk of recurrent *Clostridium difficile* infection? *Clin Microbiol Infect.* 2012;18(Suppl 6):21–7.
10. Feuerstadt P, Louie TJ, Lashner B, et al. SER-109, an oral microbiome therapy for recurrent *Clostridioides difficile* infection. *N Engl J Med.* 2022;386(3):220–9.
11. McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults and children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). *Clin Infect Dis.* 2018;66(7):e1–48.
12. Thomas C, Stevenson M, Riley TV. Antibiotics and hospital-acquired *Clostridium difficile*-associated diarrhoea: A systematic review. *J Antimicrob Chemother.* 2003;51(6):1339–50.
13. Deshpande A, Pasupuleti V, Thota P, et al. Community-associated *Clostridium difficile* infection and antibiotics: A meta-analysis. *J Antimicrob Chemother.* 2013;68(9):1951–61.
14. Johnson S, Samore MH, Farrow KA, et al. Epidemics of diarrhoea caused by a clindamycin-resistant strain of *Clostridium difficile* in four hospitals. *N Engl J Med.* 1999;341(22):1645–51.
15. Britton RA, Young VB. Role of the intestinal microbiota in resistance to colonization by *Clostridium difficile*. *Gastroenterology.* 2014;146(6):1547–53.
16. Sorg JA, Sonenshein AL. Bile salts and glycine as cogerminants for *Clostridium difficile* spores. *J Bacteriol.* 2008;190(7):2505–12.
17. Rea MC, Sit CS, Clayton E, et al. Thuricin CD is a posttranslationally modified bacteriocin with a narrow spectrum of activity against *Clostridium difficile*. *Proc Natl Acad Sci U S A.* 2010;107(20):9352–7.
18. Britton RA, Young VB. Interaction between the intestinal microbiota and host in *Clostridium difficile* colonization resistance. *Trends Microbiol.* 2012;20(7):313–9.
19. Wilcox MH, Gerding DN, Poxton IR, et al. Bezlotoxumab for prevention of recurrent *Clostridium difficile* infection. *N Engl J Med.* 2017;376(4):305–17.
20. Bowman JA, Utter GH. Evolving strategies to manage *Clostridium difficile* colitis. *J Gastrointest Surg.* 2020;24(2):484–91.
21. McGovern BH, Ford CB, Henn MR, et al. SER-109, an investigational microbiome drug to reduce recurrence after *Clostridioides difficile* infection: Lessons learned from a phase 2 trial. *Clin Infect Dis.* 2021;72(12):2132–40.
22. Blount KF, Shannon WD, Deych E, Jones C. Restoration of bacterial microbiome composition and diversity among treatment responders in a phase 2 trial of RBX2660: An investigational microbiome restoration therapeutic. *Open Forum Infect Dis.* 2019;6(4):ofz095.
23. Hocquart M, Lagier JC, Cassir N, et al. Early fecal microbiota transplantation improves survival in severe *Clostridium difficile* infections. *Clin Infect Dis.* 2018;66(5):645–50.
24. Miller M, Gravel D, Mulvey M, et al. Health care-associated *Clostridium difficile* infection in Canada: Patient age and infecting strain type are highly predictive of severe outcome and mortality. *Clin Infect Dis.* 2010;50(2):194–201.
25. Pépin J, Saheb N, Coulombe MA, et al. Emergence of fluoroquinolones as the predominant risk factor for *Clostridium difficile*-associated diarrhea: A cohort study during an epidemic in Quebec. *Clin Infect Dis.* 2005;41(9):1254–60.
26. Eiseman B, Silen W, Bascom GS, Kauvar AJ. Fecal enema as an adjunct in the treatment of *Pseudomembranous enterocolitis*. *Surgery.* 1958;44(5):854–9.
27. Zhang F, Luo W, Shi Y, Fan Z, Ji G. Should we standardize the 1,700-year-old fecal microbiota transplantation? *Am J Gastroenterol.* 2012;107(11):1755–56.
28. Schwan A, Sjölin S, Trottestam U, Aronsson B. Relapsing *Clostridium difficile* enterocolitis cured by rectal infusion of homologous faeces. *Lancet.* 1983;2(8354):845.
29. Johnson S, Lavergne V, Skinner AM, et al. Clinical practice guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 Focused update guidelines on management of *Clostridioides difficile* infection in adults. *Clin Infect Dis.* 2021;73(5):e1029–44.

30. Lawley TD, Clare S, Walker AW, et al. Targeted restoration of the intestinal microbiota with a simple, defined bacteriotherapy resolves relapsing *Clostridium difficile* disease in mice. *PLoS Pathog.* 2012;8(10):e1002995.
31. Cammarota G, Masucci L, Ianiro G, et al. Randomized clinical trial: Faecal microbiota transplantation by colonoscopy vs. vancomycin for the treatment of recurrent *Clostridium difficile* infection. *Aliment Pharmacol Ther.* 2015;41(9):835–43.
32. van Nood E, Vrieze A, Nieuwdorp M, et al. Duodenal infusion of donor faeces for recurrent *Clostridium difficile*. *N Engl J Med.* 2013;368(5):407–15.
33. Elkrief A, Routy B. First clinical proof-of-concept that FMT can overcome resistance to ICIs. *Nat Rev Clin Oncol.* 2021;18(6):325–6.
34. Furuya-Kanamori L, Doi SA, Paterson DL, et al. Upper versus lower gastrointestinal delivery for transplantation of fecal microbiota in recurrent or refractory *Clostridium difficile* infection: A collaborative analysis of individual patient data from 14 studies. *J Clin Gastroenterol.* 2017;51(2):145–50.
35. Postigo R, Kim JH. Colonoscopic versus nasogastric faecal transplantation for the treatment of *Clostridium difficile* infection: A review and pooled analysis. *Infection.* 2012;40(6):643–8.
36. Kao D, Roach B, Silva M, et al. Effect of oral capsule- vs colonoscopy-delivered fecal microbiota transplantation on recurrent *Clostridium difficile* infection: A randomized clinical trial. *JAMA.* 2017;318(20):1985–93.
37. Jiang ZD, Jenq RR, Ajami NJ, et al. Safety and preliminary efficacy of orally administered lyophilized faecal microbiota product compared with frozen product given by enema for recurrent *Clostridium difficile* infection: A randomized clinical trial. *PLoS One.* 2018;13(11):e0205064.
38. Kelly CR, Khoruts A, Staley C, et al. Effect of fecal microbiota transplantation on recurrence in multiply recurrent *Clostridium difficile* infection: A randomized trial. *Ann Intern Med.* 2016;165(9):609–16.
39. Trubiano JA, Cheng AC, Korman TM, et al. Australasian Society of Infectious Diseases updated guidelines for the management of *Clostridium difficile* infection in adults and children in Australia and New Zealand. *Intern Med J.* 2016;46(4):479–93.
40. Khanna S, Kelly CR, Louie T, et al. S131 CP101, an Investigational orally administered microbiome therapeutic, increases intestinal microbiome diversity and prevents recurrent *C. difficile* Infection: Results from a randomized, placebo-controlled trial. *Am J Gastroenterol.* 2021;116(1):S57.
41. Allegretti JR, Kelly CR, Fischer M, Cohen T, Budree S, Khanna S. Cp101, An investigational microbiome therapeutic for the prevention of recurrent *C. Difficile* infection: A combined analysis of the Prism3 (randomized placebo-controlled) and Prism-Ext (open-label) trials. Abstract Tu1519. *Gastroenterology.* 2022;162(7):S-995-6.
42. Voth E, Khanna S. Fecal microbiota transplantation for treatment of patients with recurrent *Clostridioides difficile* infection. *Expert Rev Anti Infect Ther*. 2020;18(7):669–76.
43. Khanna S. Microbiota restoration for recurrent *Clostridioides difficile*: Getting one step closer every day. *J Intern Med.* 2021;290(2):294–309.
44. Khanna S, Pardi DS, Jones C, Shannon WD, Gonzalez C, Blount K. RBX7455, a non-frozen, orally administered investigational live biotherapeutic, is safe, effective, and shifts patients' microbiomes in a phase 1 study for recurrent *Clostridioides difficile* infections. *Clin Infect Dis.* 2021;73(7):e1613–20.