EDITORIAL

# Capsules for Fecal Microbiota Transplantation in Recurrent *Clostridium difficile* Infection

## The New Way Forward or a Tough Pill to Swallow?

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***Clostridium difficile* infection** (CDI) has emerged as a major public health threat, with more than 450 000 cases per year in the United States alone.[1] Even among patients who initially improve with treatment, the risk of recurrent CDI (RCDI) following an initial episode is approximately 20%,[2] often resulting in hospital readmission and totaling an estimated $1.5 billion annually in health care costs.[3] Among patients who develop RCDI, 40% to 65% will experience additional recurrences.[4]

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For individuals experiencing chronic recurrences of CDI, there is no universally accepted or validated treatment algorithm. Options to reduce the risk of additional recurrence include extended courses of vancomycin,[5] probiotics, or fermented foods such as kefir; antibiotic "chasers" (short courses at the end of therapy after initial treatment is complete) with fidaxomicin or rifaximin; or anti-toxin monoclonal antibody therapy.[4] Fecal microbiota transplantation (FMT) is an increasingly common treatment to address RCDI, but widespread adoption is limited in part by the logistics of delivering the stool product.

In this issue of *JAMA*, Kao et al[6] present the results of a randomized clinical trial (RCT) in 116 patients with RCDI to determine whether FMT delivered via fecal capsules (n = 57 patients) was noninferior to FMT delivered via colonoscopy (n = 59 patients). The primary outcome was the proportion of patients without RCDI 12 weeks after FMT, and the noninferiority margin was set at 15%. At 12 weeks, 96.2% of patients in both treatment groups were recurrence free (1-sided 95% CI, −6.1% to infinity; $P < .001$), meeting criteria for noninferiority. Two participants with underlying inflammatory bowel disease experienced disease flare after FMT. Minor adverse events were comparable between groups. Although 30% of participants described FMT as "unpleasant, gross, or disgusting," 97% indicated they would undergo the treatment again if needed. Quality-of-life scores increased significantly for participants after FMT, with no significant difference between the treatment groups. The authors concluded that FMT administered via capsules was noninferior to FMT administered by colonoscopy for preventing subsequent RCDI over 12 weeks in patients who had RCDI.

As a secondary analysis, the microbial composition of the participants following FMT delivered via both routes was followed longitudinally. As had been observed in earlier studies,[7] patients with RCDI had a lower diversity fecal microbiota prior to transplantation compared with the donors. Also, as has been reported previously,[8] fecal microbial diversity increased following FMT and this was maintained for up to 12 weeks (the end of the observation period).

Although these data on FMT using capsules are encouraging and may decrease barriers to further adoption of FMT for RCDI, many broader questions remain about the efficacy of FMT. One question involves acute RCDI. In the study by Kao et al,[6] participants in the capsule and colonoscopy groups had a mean duration of RCDI prior to FMT of 3.9 and 4.6 months, respectively, after their original treatment had ended.[6] Many patients also received vancomycin for most of the period from the end of treatment to randomization. In contrast, a single-center study by Hota et al[9] evaluating FMT for acute RCDI compared 14 days of vancomycin followed by FMT with a 6-week taper of vancomycin, a more conventional treatment.[9] This open-label RCT used a 1:1 allocation between treatment groups and the primary end point was RCDI within 120 days. The study was terminated owing to futility after only 30 patients were randomized, with 58% of the vancomycin-only group remaining RCDI-free compared with 44% in the FMT group.

The study by Hota et al[9] contrasts with much of the FMT literature, including the current study by Kao et al[6] and prior RCTs, which have shown a beneficial effect. Many prior studies did not assess FMT in the acute recurrence setting and did not compare FMT with short courses of vancomycin. The first, large RCT for FMT demonstrated such a beneficial effect that it was terminated early for ethical reasons.[10] However, that initial study compared FMT with only 2 weeks of oral vancomycin, and 2 weeks of oral vancomycin has a higher failure risk than a vancomycin taper.[5] A subsequent RCT compared FMT with vancomycin for 10 days followed by a 3-week taper.[11] This trial was also stopped after a 1-year interim analysis showed FMT was more effective than this short vancomycin taper. Other RCTs that included patients receiving a prolonged course of suppressive vancomycin did not have a non-FMT group,[12,13] and as Hota et al[9] noted, "it is not known what proportion of patients would have been symptom-free had their antibiotics been simply discontinued."

Underscoring the importance of timing relative to FMT is a trial by Kelly et al.[14] This double-blind, randomized, placebo-controlled trial compared FMT from healthy donors with the patients' stool (given as a placebo) administered by colonoscopy. Although FMT was more effective than placebo overall, this outcome was only observed at 1 study site (in Rhode Island), whereas at the other study site in New York, there was no difference in

outcomes, with the placebo group achieving 90% cure. The main difference between the 2 sites was the time to FMT; the New York site had a median 16-month waiting period until FMT compared with a 6-month waiting period in Rhode Island.

In addition to vancomycin taper duration and the timing of FMT after RCDI onset, the relative importance of stool components remains ill defined. The stool-derived, purified spore product, SER-109, was associated with reduced risk of RCDI in a phase 1B trial, suggesting only the spore fraction of the microbiota may be necessary.[15]

In another approach, Ott et al[16] conducted FMT using sterile fecal filtrates that did not contain any bacteria and successfully treated 5 patients with CDI who remained symptom free after 6 months of follow-up.[16] Although no bacteria were transferred, patients demonstrated increases in microbial diversity as well as changes in the relative abundance of specific taxa. Findings of this small case series are preliminary but suggest that bacteria may not be necessary components of future stool-derived therapeutic products. What components of the sterile filtrates mediated the therapeutic effect has yet to be determined; however, bile acids and bacteriophages exist in stool, and preclinical evidence supports their possible efficacy in CDI treatment.[17,18] These preclinical studies can inform future RCTs, which will be needed to establish the relative importance and efficacy of different stool-derived components.

Currently, researchers are taking a rational, mechanistic approach to designing probiotics and fecal-derived products. For example, microbes with 7α-dehydroxylase activity can metabolize primary to secondary bile acids, which are inhibitory to *C difficile*. Thus, incorporation of such bacteria into therapeutic products may be desirable. This approach has shown merit in preclinical investigations. Buffie et al[19] showed that a consortia of bacteria capable of metabolizing primary to secondary bile acids were protective in a murine model.[19] Trials using defined microbial consortia have begun in the clinical setting.[20]

What should clinicians conclude from these contradictory data regarding FMT for CDI? Placing the trial by Kao et al[6] into the above context underscores the importance of further research about the optimal timing and format of FMT, as well as the role for rational design of defined microbial consortia. While it is encouraging that capsules appear to be a viable delivery route for FMT, a number of additional approaches still deserve consideration in future research. These include vancomycin tapers with and without "chasers" of fidaxomicin/rifaximin, defined microbial communities, and sterile fecal-derived products. If these latter approaches prove to be effective, they may supplant standard FMT and other undefined microbial consortia, making even convenient, capsule-based FMT a tough pill to swallow.

## ARTICLE INFORMATION

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