criteria, require a toxin enzyme immunoassay positive test, showed good efficacy compared to placebo [3]. In addition, the primary outcome in this VA study was defined broadly as diarrhea with or without a positive *C. difficile* test. Less than half of those with suspected recurrence who submitted stool for testing were positive, and treatment failure was judged based on clinical symptoms alone. This is not acceptable for an RCT, considering the high rate of post-infection IBS, which almost certainly resulted in misclassifying patients who did not suffer an actual CDI recurrence as treatment failures. Although enrolling from the entire VA system was the intent, local investigators with less experience in the management of CDI may have been more likely to initiate antibiotics based on patient complaints of diarrhea. The more concerning issue is the extended washout period of 6 ± 4 days between completing anti-CDI antibiotics and FMT capsule dosing. FMT capsules are typically delivered 48–72 hours after stopping antibiotics, patients in this study had a delay as long as 14 days between completing treatment and receiving FMT. Although the optimal length of time for washout is currently unknown, within days of completing treatment, spores can germinate, allowing vegetative forms to produce toxin and CDI recurrence. Current FMT guidelines [4] recommend 1–3 days for washout, with bowel laxative to purge residual vancomycin from the colon recommended for shorter washout. Some patients in this study may have already started to experience recurrence prior to oral dosing and were destined for clinical failure. We believe that this study, a double-blind, placebo-controlled RCT, should be considered in a proper context as a cautionary tale, examining all the lessons that could be learned from the pitfalls of the study design.

Note

Potential conflicts of interest. J. R, A. declares the following interests: Scientific Advisory Board participation for Iterative Scopes and Finch Therapeutics. Consulting for Pandion, Merck Servatus, Janssen, AbbVie, Pfizer, Bristol Myer Squibb, Summit Therapeutics, Seres Therapeutics, Ferring. Grant support from Merck, Janssen and Pfizer. M. F. declares consulting for Seres Therapeutics, Ferring, AbbVie, Pfizer, Bristol Myer Squibb, Eli Lilly. DSMB member: Rebiotix. C. R. K. has no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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Clostridioides difficile: Treating Sustained Antibiotic Responders With Fecal Microbiota Transplantation Does Not Improve Efficacy

To the Editor—Drekonja et al [1] describe a randomized placebo-controlled trial with lyophilized fecal microbiota transplantation (FMT) capsules to prevent recurrent *Clostridioides difficile* infection (rCDI). We believe the results should be interpreted cautiously due to trial design aspects, such as the exclusion criteria and primary endpoint.

Patients with rCDI face high morbidity and mortality, are notoriously difficult to treat with antibiotics alone, and often require additional therapies such as FMT [2]. Given the high risk of rapid recurrence, current guidelines recommend initiating FMT within 4 days after completing antibiotic treatment for rCDI [3].

Inclusion in the trial required successful antibiotic treatment of rCDI and no signs of recurrence 2–14 days after antibiotics completion. This made patients with refractory disease or early recurrence ineligible, and 2563 (87%) of 2931 potential participants were not included. This likely caused a serious selection bias that severely limits the generalizability of the results. In essence, the study reports the effect of FMT versus placebo in a small subset of patients responding to antibiotics and without early recurrence. If patients had been included regardless of their response to antibiotics or symptom recurrence following its cessation, the results would reflect real-world clinical practice and would have provided valuable data for comparing FMT and placebo for recurrence prevention. The conclusion might even have aligned with the multiple previous studies demonstrating the superiority of FMT [2].

The primary endpoint was definite or possible rCDI or death within 56 days of randomization. While we agree with the authors that a pragmatic study with patient-centered outcomes is desirable, we find the broad definition of possible recurrence problematic. This definition included all patients with symptoms (diarrhea) regardless of test results, and also patients with no stool samples and patients with negative tests using both polymerase chain reaction (PCR) and enzyme immunoassay (EIA) toxin tests.

Factors such as FMT dosing, processing, and donor potentially influenced the observed outcomes [4, 5]. The dosing regimen of 5 FMT capsules administered once was much lower than in previous studies [4]. Unlike most studies using

frozen FMT capsules, this study used lyophilized FMT capsules, highlighting the need to evaluate new processing methods [4]. The study included only 4 donors, and if the fecal donations of only 1 or 2 of these were associated with low cure rates, this could contribute to the lack of efficacy [5].

In short, the trial population does not reflect most patients with rCDI. The study investigates the use of FMT in the small subset of patients with a sustained response to antibiotics—a response that clinicians have no chance of reliably predicting. We find the trial incomparable to previous randomized controlled trials and literature that included all patients regardless of antibiotic response. Clinical decisions to minimize recurrence risk should necessarily be made during and not after acute antibiotics therapy. Given the severity of rCDI, this includes considering timely FMT as an exit strategy. The present study should not change clinical guidelines as the existing literature establishes FMT as the most effective treatment of rCDI [2, 6, 7].

Notes

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Fecal Microbiota Transplantation in *Clostridioides difficile* Infections: Rethinking the Approach by Patient Profile in Light of New Evidence

To the Editor—We read with great interest the recent study by Drekonja et al [1], who assessed the efficacy of fecal microbiota transplantation (FMT) versus placebo in a large cohort of patients with *Clostridioides difficile* infection (CDI). Their findings, which indicated a lack of significant benefit from FMT in the first recurrence of CDI, are especially noteworthy given the well-established efficacy of FMT in recurrent CDI cases since van Nood et al first demonstrated its high potential of interest in 2013 [2].

A recent Cochrane review, which included 6 randomized, controlled trials and 320 patients, has reaffirmed FMT's role in recurrent CDI and showed both safety and efficacy in reducing recurrence risk [3]. However, Drekonja et al challenge FMT as an initial treatment in recurrent cases, a stance that is somewhat at odds with evidence from Baunwall et al, who demonstrated a significant benefit of FMT versus placebo even after a single CDI recurrence [4]. A recent French cohort study, which tracked 617 patients over 5 years, similarly supported FMT efficacy in first recurrence cases and reported an 85.1% success rate for FMT administered after the first CDI episode, irrespective of recurrence history [5].

It is worth noting that Drekonja et al's study population had higher rates of chronic kidney disease (13.2% versus 6.5%) and included immunocompromised patients (14.9% versus 4%) in the FMT group, potentially influencing outcomes. Patients with chronic kidney failure or nonsevere refractory CDI have been identified in other studies as more likely to experience FMT failure [5]. Given this, we believe dedicated randomized trials to assess FMT efficacy in specific high-risk