



Journal Summary: Microbiome-Based Therapies for Recurrent *Clostridioides difficile*

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In a randomized control trial by Feuerstadt et al published in the *New England Journal of Medicine*, the authors have shown the benefit of lyophilized spores from donor stool in comparison to placebo in preventing recurrence of *Clostridioides difficile* infection (CDI) in patients with ≥ 2 episodes of CDI in the last 12 months over and above standard medical therapy. In 182 patients randomized to placebo or SER-109, there were fewer recurrences at 8 weeks of follow-up in the SER-109 group vis-à-vis placebo (12% vs. 40%). This benefit was across all ages and subgroups when stratified as per antibiotics received for the acute management of CDI. This trial reemphasizes the role of microbiome modulation in the management of patients with recurrent CDI (rCDI). The strengths of this study were the inclusion of metabolomics and bile acid analysis of these patients showing concurrent engraftment along with the clinical effect.¹ This study looked at the effect of SER-109 till 8 weeks of follow-up. It would be interesting to look at the effects of this therapy beyond this period. As recurrence is a major concern for these patients, the durability of response would make this drug a favorable option for rCDI. Furthermore, the majority of the adverse events in this study were mild to moderate in nature and were similar to placebo.

C. difficile is a rod-shaped, anaerobic, Gram-positive bacterium, first described as a commensal in infants in 1935 and a pathogenic role was ascribed to this organism as an agent causing antibiotic-associated diarrhea in 1978.² CDI has become a substantial concern for hospitalized patients, especially the elderly and those with a history of treatment with broad-spectrum antibiotics due to increased severity of the disease and associated morbidity encountered in the last two decades.³ *C. difficile* is a noninvasive organism

and pathogenesis involves toxin-mediated inflammation and disease. Second, the spores of *C. difficile* are resistant to all antibiotics. Hence, even if patients get cured of the infection, spores may regeminate to cause recurrence. Moreover, exposure to spores does not necessarily lead to colonization because the major underlying pathogenic mechanisms for colonization involve gut dysbiosis due to perturbation of colonic microbiota. A diverse and complex gut microbiome is essential for the prevention of colonization, a term called colonization resistance. Despite available antibiotics used to treat CDI, the recurrence rates after CDI remain high.³ In a landmark trial by Van Nood et al, a single session of fecal microbiota transplantation (FMT) had a better resolution of infection than vancomycin (81% vs. 33%).⁴ Since then, multiple studies encompassing different routes have established the role of FMT in CDI. FMT restores the bile acid milieu in patients with rCDI. The bile acids have different effects on the growth of *C. difficile*, secondary bile acids inhibiting its growth, and primary bile acids as taurocholic acid having a progerminating effect for *C. difficile*. FMT leads to an increase in secondary bile acids and a decrease in primary bile acids by promoting its degradations and eventually has an inhibitory effect on *C. difficile*. The use of FMT is limited by its heterogeneity, variable donor screening, and recent adverse events.³

SER-109 is a microbiome-based product for rCDI. It is a lyophilized, frozen oral microbiome therapeutic that has circumvented many problems associated with FMT, making it less time-consuming, saving on resources, and is more acceptable to patients. The phase I data on SER-109 had shown a per-protocol efficacy of 86.7% in preventing recurrence of CDI in patients who have had three or more

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recurrences of CDI. This work had shown that FMT via this form was able to break the cycle of rCDI via restoring colonization resistance and establishing the safety of SER-109 across various doses.⁵ The phase II trial did not show any significant difference in recurrence vis-à-vis placebo (44.4% vs. 53.3%) albeit the benefit was shown in subgroup aged > 65 years.⁶ Reanalysis of the integrated data of both phase I and II trials concluded that rapid engraftment was quintessential for the efficacy of SER-109 as most of the recurrences occur within 3 weeks and rapid engraftment is a dose-dependent phenomenon. The major shortcoming of the phase II trial was that they used a lesser dose of SER-109 (1×10^8 spores), and hence, this phase III study used a higher dose. These trials emphasized the role of engraftment that leads to functional changes via microbe-associated metabolites. Additionally, the phase II trial included patients diagnosed with any stool assay but phase III only allowed patients diagnosed with a toxin-based stool assay.^{1,5,6}

Recurrence is an area of major concern with CDI as 25 to 30% of the patients have recurrence after the first episode and 60% after two or more recurrences.^{7,8} But relapse needs to be differentiated from recurrence. Again, Eyre et al had shown in their work that the majority of recurrences (80%) were relapses and only one-fifth were reinfections. Moreover, recurrences are more common with certain strains of *C. difficile* such as ribotype-027 which has been associated with recurrences and a poorer outcome. This study did not look into this aspect of the disease.⁹ Ribotype-027 is known to be an outbreak strain associated with CDI outbreaks in various hospitals across the globe. It remains important to ascertain

whether the recurrence in these patients represents the relapse of the previous strain or reinfection by a new strain that could have been answered by bacterial subtyping using whole-genome sequencing (WGS). Eyre et al had used WGS in 1,223 cases to show that more than one-third of cases of *C. difficile* were from another case in a hospital setting, and 45% of the isolates were genetically unrelated to any previous infection or mode of transmission.¹⁰

Moreover, the asymptomatic carriage with nontoxigenic strains of *C. difficile* (NTCD) is associated with fewer chances of recurrence by competing with toxigenic strains for the same niche, and carriage of toxigenic strains of *C. difficile* has been associated with more recurrence.¹¹ The proportion of patients with this carriage could underestimate or overestimate the recurrence rate with *C. difficile* and hence the efficacy of SER-109. This was studied in a landmark trial where NTCD were given in either 10^4 to 10^7 doses for 7 to 14 days and the overall recurrence rate, when compared with placebo, was 11% versus 30% and importantly when colonization with NTCD occurred, the recurrence rate in comparison to when there was no colonization was 2% versus 31% (►Table 1).¹¹

Many other microbiome-based therapies have shown encouraging results in the last decade for the prevention of rCDI (►Table 1). There have been encouraging phase I or II results with various formulations showing good efficacy for preventing recurrence and concordant colonization with microbiome therapy (►Table 1).

To conclude, the authors have utilized their learnings from phase I and phase II data to come up with this landmark trial.

Table 1 Microbiome-based therapies for recurrent *Clostridioides difficile* infection¹²

Serial no	Microbiome therapeutic	Formulation details	Trial results
1.	SER-109	A lyophilized oral capsule consisting of bacterial spores	Phase III trial showed lower CDI recurrences vis-à-vis placebo (12% vs. 40%)
2.	CP-101	A full spectrum oral microbiome therapeutic derived from healthy donors	Phase II trial showed efficacy in prevention of rCDI when compared with placebo of 74% vs. 61%
3.	SER-262	A multistrain oral microbiome therapeutic consisting of bacterial spores from 12 strains prepared via fermentation (no human donor)	Phase Ib trial showed lower recurrence rates for CDI vis-à-vis placebo (6.25% vs. 28.6%)
4.	RBX 7455	Lyophilized, nonfrozen gut microbiota formulation administered orally that is room temperature stable	Phase I single-center trial showed the efficacy of 80% to 100% in preventing recurrent CDI with the shift in microbiome structure (increase in Clostridia and Bacteroidia)
5.	VE 303	Live bacterial consortium stored as a capsule in powdered form for oral administration	Phase I: VE 303 bacteria had durable colonization following administration
6.	MET-2	Microbiota formulation derived from a healthy donor stool that can be delivered orally or via colonoscopy	Phase I: 84% of patients did not have recurrence by day 130
7.	VP 20621 (NTCD-M3)	Oral suspension of spores from the nontoxigenic <i>C. difficile</i> (NTCD) strain M3	Phase II trial: Recurrence rate of 13% vs. 30% in NTCD-M3 vs. placebo
8.	RBX 2660	Microbiome therapeutic suspension delivered via enema derived from donor stool	Phase II trial: Prevention of CDI recurrence vis-à-vis placebo at 8 weeks (78.8% vs. 51.8%). Phase III trial finished enrolment

Abbreviations: CDI, *Clostridioides difficile* infection; NTCD, nontoxigenic *Clostridioides difficile*; rCDI, recurrent *Clostridioides difficile* infection.

Phase II data elucidated the mechanism of action of this novel drug with the role of engraftment and associated changes in bile acid concentrations. The authors utilized the same in planning this study using a higher dose of SER-109. This study again emphasized the two-pronged strategy for managing rCDI, utilizing antibiotics to cure the infection and microbiome modulation to prevent a recurrence. The findings of this study may have implications for other diseases associated with microbiome disruption.

Ethical Statement

Not applicable.

Author Contributions

A.C. wrote and approved while S.K. revised and approved the manuscript.

Data Availability Statement

There are no associated data.

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Conflict of Interest

None.

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