



Fecal Microbiota Transplantation for the Management of Recurrent Clostridium Difficile Infections: A Systematic Review

Chinanu Ihuoma Nwankwo ^a, Salman Yousaf ^{b*},
Victor N Oboli ^c, Farzeen Sharaf ^d, Komal Naz Khalid ^e,
Franca Erhiawarie ^f, Ejiroghene Tejere ^g, Aqsa Latif ^h,
Ogochukwu Ekpeleamaka Chioma ⁱ,
Chidinma Vivian Ikekpeazu ^j, Omar Rahim ^k, Imtiaz Nazam ^l,
Toluwani Balogun ^g, Chidera Precious Chukwuneta ^m
and Chinonso Ndubuisi ⁿ

^a College of Medicine, Enugu State University of Science and Technology, Nigeria.

^b Services Institute of Medical Sciences (SIMS), Pakistan.

^c Lincoln Medical and Mental Health Center, NY, USA.

^d Liaquat University of Medical and Health Sciences, Pakistan.

^e Shifa College of Medicine, Pakistan.

^f University of Benin, Nigeria.

^g Kharkiv National Medical University, Ukraine.

^h King Edward Medical University, Pakistan.

ⁱ College of Medicine, Ebonyi State University, Abakaliki, Nigeria.

^j University of Nigeria, College of Medicine, Nigeria.

^k Kabir Medical College, Pakistan.

^l Azra Naheed Medical College, Pakistan.

^m Chukwuemeka Odumegwu Ojukwu University, Nigeria.

ⁿ Humboldt Park Health, Illinois, USA.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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*Corresponding author: E-mail: s.yousafmd@gmail.com;

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ABSTRACT

Background: Fecal microbiota transplantation (FMT) is a promising therapeutic option for managing *Clostridium difficile* infections (CDI). CDI is a significant health concern, particularly in antibiotic-resistant cases impairing the quality of life among the patient population. This systematic review aims to pool current clinical trial evidence of FMT (RBX2660) success rates when used for recurrent CDI in the clinical trial setting.

Methods: In accordance with PRISMA Statement 2020 guidelines, the following databases were systematically searched: Embase, PubMed, and Scopus. There were no time or language restrictions. The following keywords were used in all the databases: fecal, microbiota, transplantation, recurrent, *Clostridium difficile*, infection, and antibiotic-resistant. Only clinical trials, controlled or single-arm, were included in this systematic review.

Results: A total of five clinical trials, of which four were phase II, and one was phase III, were included. Seven hundred ninety-five participants were pooled across all trials. Patients were included in the trials with 1-2 recurrent CDI. In most cases, they had undergone standard antibiotic therapy before enrolling. The treatment success rate in the RBX2660 intervention group was 69.5% (335/482) compared to 49.6% (123/248) in the placebo group. The intervention was safe and effective, with no grade III or higher adverse events reported in treating recurrent CDI.

Conclusion: RBX2660, recently approved as a therapy for recurrent CDI in the United States, is a significant milestone in expanding treatment options. This study reports the potential benefits of FMT and other microbiota-based therapies. While many challenges require addressing, including sample control and patient compliance, FMT is heading toward ongoing acceptance in the broad medical community.

Keywords: Fecal microbiota; transplantation; recurrent; clostridium difficile infections; RBX2660.

1. INTRODUCTION

Fecal Microbiota Transplantation (FMT) has emerged as a promising therapeutic option for the management of recurrent *Clostridium difficile* infections (CDI) [1]. CDI is a major public health concern and is responsible for significant morbidity and mortality, particularly among older adults and patients with underlying medical conditions [2]. Despite the availability of several antibiotics for the treatment of CDI, there is a high rate of recurrence following initial therapy, which poses a significant challenge to healthcare providers and patients alike [3,4]. This has led to an urgent need for alternative treatment options that can address the underlying cause of the infection and prevent its recurrence. FMT involves the transfer of fecal material from a healthy donor into the gastrointestinal tract of a

recipient [5,6]. The primary goal of this therapy is to restore the balance of the gut microbiota, which is often disrupted by antibiotics and other factors that contribute to the development of CDI [5,6]. The procedure is typically performed via colonoscopy, nasogastric/nasoenteric tubes, or enema and is shown to be highly effective in treating recurrent CDI [7,8].

The use of FMT for the treatment of CDI has gained significant attention over the past decade, and numerous observational studies have demonstrated its safety and efficacy [2,9]. The success rates of FMT in treating recurrent CDI have been reported to be as high as 90%, surpassing those of traditional antibiotic therapy [10]. In addition, FMT has been shown to be associated with few adverse effects, with most patients experiencing only mild and transient

symptoms such as abdominal discomfort, bloating, and diarrhea. Despite the promising results of FMT, there has been a lack of regulatory oversight and standardization in the field, limiting its adoption as a standard care approach in healthcare. This is expected to change with the recent approval of a first-in-class microbiota-based live biotherapeutic, originally termed RBX2660, by the U.S. Food and Drug Administration (FDA) on November 30, 2022 [11]. RBX2660 is specifically indicated for the prevention of recurrent CDI in adults aged 18 or above and is expected to significantly impact the healthcare delivery system.

The approval of RBX2660 represents a major milestone in the field of FMT, particularly for patients experiencing recurrent CDI with no alternative treatments. It underscores the growing recognition of the potential benefits of microbiota-based therapies. RBX2660 has the potential to transform the management of CDI and could lead to improved outcomes with reduced healthcare costs. Moreover, RBX2660 is expected to pave the way for the development of additional microbiota-based therapies for other

conditions, further expanding the potential applications of FMT and related approaches. This systematic review aims to pool current clinical trial evidence of FMT success rates when used for recurrent CDI.

2. METHODS

Adhering to PRISMA Statement 2020 guidelines [12], a systematic search was conducted in the following databases: PubMed, Embase, and Scopus. Clinical trials published in any language without any date restrictions were included. All non-English studies were translated into English using google translate. The following keywords were used, applying the Boolean (and/or) logic: fecal, microbiota, transplantation, recurrent, *Clostridium difficile*, infection, and antibiotic-resistant. The trials were required to have an interventional arm administering RBX2660/FMT to patient populations in a clinical trial setting. Observational studies (cohorts, retrospective and prospective), case series/reports, editorials, brief reports, and secondary studies were omitted. The PRISMA flowchart is depicted in Fig. 1.

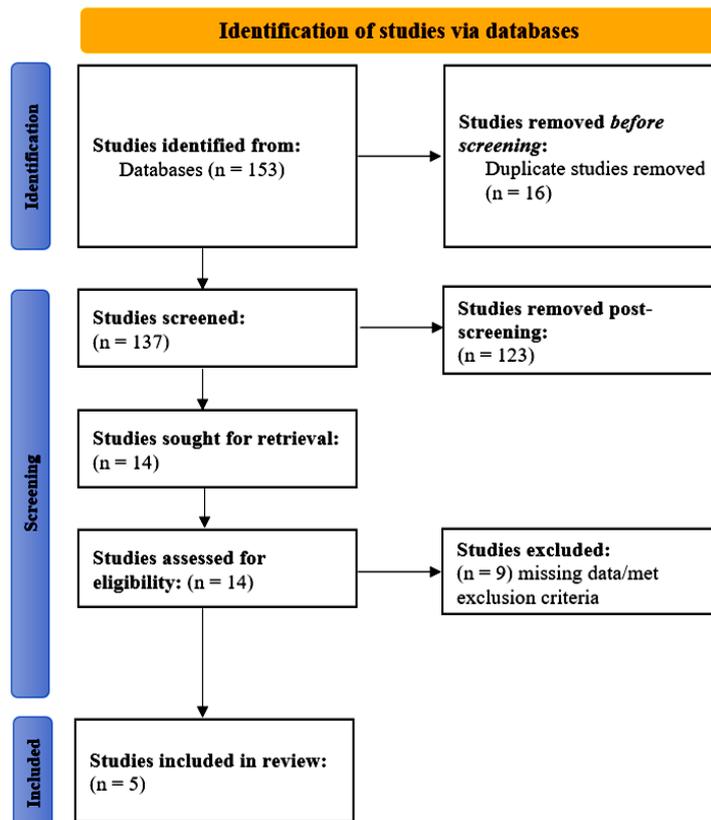


Fig. 1. PRISMA flowchart depicting the study selection process

All investigators conducted the screening of the titles and abstracts of database-identified studies. This was followed by full-text retrieval of shortlisted studies that underwent assessment. The study records were stored in EndNote X9 (Clarivate Analytics). The inter-reviewer reliability coefficient was computed in SPSS (v24, IBM). All authors conducted the data extraction into a shared spreadsheet under the following headings: author, year, title, study type, phase and identifier, participants, intervention, sample size, intervention group (I.G.) success proportions, control group (C.G.) success proportions, and key conclusions. The findings were thereby tabulated and discussed.

3. RESULTS

In total, five trials were included, pooling a total of 795 participants. Of these, three were randomized controlled trials, and two were open-label trials. Four trials were in Phase 2 of testing, whereas one was in Phase 3. Participants were included if they had 1-2 or more recurrent CDI and, in most cases, had undergone standard care approaches, including antibiotic therapy. The intervention was either a single dose of RBX2660 or a double dosage via enema/administered rectally. The success proportion in the intervention group was 335 out of 482 (69.5%), whereas the control group success proportion was reported as 123 out of 248 (49.6%). Overall, the intervention was considered safe and effective for recurrent CDI, and responses were retained throughout six months with no adverse events. The characteristics of the included trials, outcomes and author conclusions are listed in Tables 1-2.

Khanna and colleagues (2022) conducted a phase III, randomized, double-blind controlled trial with the primary outcome of treatment success [13]. The investigators assessed for the absence of CDI diarrhea within two months of the study duration. 320 individuals were screened, of which 289 were randomly assigned, and 267 underwent a blinded treatment protocol. RBX2660 was administered as a single-dose enema to 180 patients, whereas 87 patients received a placebo. Post Bayesian analysis, a treatment success rate was determined to be 70.6% with RBX2660 as compared to 57.5% with placebo. Despite being well tolerated, the adverse events were reportedly higher with the intervention compared to the placebo, where mild gastrointestinal events were reported. The response was sustained throughout the course of six months.

Orenstein et al. (2022) led an open-label Phase II, prospective multicenter trial enrolling patients who experienced two or more recurrent CDI episodes [14]. The participants received up to two doses of RBX2660 given one week apart. The treatment efficacy with RBX2660 was reportedly 78.9% compared to the historical control group, which had a success rate of 30.7%. The composition of the interventional group's fecal microbiome showed diversity before and after treatment with durable outcomes two years post-treatment. The authors concluded that the microbiome changes were consistent with restorative changes implicated in resisting *C. difficile* recurrence.

Kwak and colleagues (2020) conducted a double-blind, randomized, multicenter, placebo-controlled Phase IIb study [15]. Participants were enrolled to receive either one or two doses of RBX2660 via enema or placebo and were assessed for changes in microbiome and resistance to antibiotics. All patients presented with recovered diversity of the gut microbiome and decreased antibiotic-resistance genes. The treatment success in the interventional group was 56.8% compared to 43.2% in the placebo group. The authors also did shotgun metagenomic sequencing, where the correlation between taxonomic transplantations and resistome was determined. Antibiotic-resistant organisms were eradicated in patients undergoing RBX2660 administration, and the patients' microbiome and colonization changed post-fecal microbiota transplantation.

Blount et al. (2019) conducted a double-blinded, randomized, and placebo-controlled Phase IIb trial [16]. The fecal bacterial microbiome was characterized before and after the treatment among RBX2660 and placebo-controlled groups. Post-treatment, Clostridia, Bacteroides, and alpha diversity increased among the intervened group. Statistical testing indicated extensive and rapid remodeling among patients who were intervened with RBX2660. The treatment success rate was in the fecal microbiota group compared to those receiving placebo. Overall, RBX2660 led to sustained restorative microbiome changes, which were hypothesized to help with CDI recurrence and organism colonization.

Langdon and colleagues (2021) conducted an open-label, multicenter, non-randomized Phase II trial [17]. The safety and efficacy of RBX2660 were assessed for RBX2660 use in

recurrent CDI. Fecal specimens of 29 participants were studied, where 16 patients received one dose and 13 received two doses. The findings elucidated that the successful prevention of CDI recurrence with RBX2660 was related to the taxonomic

convergence of patient and donor microbiota as weighted by uniFrac distance. The single-arm treatment success rate of patients was 87.1%. Overall, RBX2660 led to a reduction in antibiotic-resistant Enterobacteriaceae within 2 months of retrieval.

Table 1. Characteristics of the included trials

Author, Year	Title	Study Type	Phase and Identifier	Participants
Khanna, 2022	Efficacy and Safety of RBX2660 in PUNCH CD3, a Phase III, Randomized, Double-Blind, Placebo-Controlled Trial with a Bayesian Primary Analysis for the Prevention of Recurrent <i>Clostridioides difficile</i> Infection	Double-blind, placebo-controlled RCT	Phase 3 (NCT03244644)	Adult patients with ≥ 1 recurrent CDI; positive stool assay for <i>C. difficile</i> ; previously treated with standard-of-care approaches (antibiotics)
Orenstein, 2022	Durable reduction of <i>Clostridioides difficile</i> infection recurrence and microbiome restoration after treatment with RBX2660: results from an open-label phase 2 clinical trial	Prospective, multicenter, open-label trial	Phase 2 (NCT02589847)	Experienced either ≥ 2 recurrences of CDI, treated by standard-of-care antibiotic therapy, after a primary CDI episode, or ≥ 2 episodes of severe CDI requiring hospitalization
Kwak, 2020	Impact of investigational microbiota therapeutic RBX2660 on the gut microbiome and resistome revealed by a placebo-controlled clinical trial (PUNCH CD2)	Multicenter, double-blind, placebo-controlled RCT	Phase 2b (NCT02299570)	Adults who have undergone at least two rounds of standard-of-care oral antibiotic therapy or with at least two episodes of severe CDI resulting in hospitalization
Blount, 2019	Restoration of Bacterial Microbiome Composition and Diversity Among Treatment Responders in a Phase 2 Trial of RBX2660: An Investigational Microbiome Restoration Therapeutic	Double-blind, placebo-controlled RCT	Phase 2B (NCT02299570)	Adults with 2 or more CDI recurrences
Langdon, 2021	Microbiota restoration reduces antibiotic-resistant bacteria gut colonization in patients with recurrent <i>Clostridioides difficile</i> infection from the open-label PUNCH CD study	Open-label, multicenter, non-randomized trial	Phase 2 (NCT01925417)	Patients with at least 2 recurrent CDI episodes or at least 2 severe episodes resulting in hospitalization

Table 2. Key findings and author conclusions

Author, Year	Intervention	N	I.G. Success Proportions	C.G. Success Proportions	Key Author Conclusions
Khanna, 2022	Single dose RBX2660 (microbiota suspension)	267	126 of 180 participants (70%)	53 of 87 participants (60.9%)	The intervention (RBX2660) was safe and effective and reduced recurrent CDI. Responses were retained throughout the 6 months.
Orenstein, 2022	<2 doses of RBX2660 administered rectally one week apart	217	112 of 142 participants (78.9%)	23 of 75 participants (30.6%)	RBX2660 was safe and efficacious, meeting primary endpoints as compared to historical control groups. Microbiome changes were also witnessed against <i>C. difficile</i>
Kwak, 2020	Single dose of RBX2660, or double dosage of RBX2660 administered via enema	150	25 of 44 participants (56.8%)	19 of 44 participants (43.2%)	RBX2660 administration led to more complete and rapid improvement in microbiome, resistome, and ARO colonization upon transplanting microbiota compared to control (saline)
Blount, 2019	Double dosage of RBX2660 (group A); Double dosage of placebo (group B); 1 dose of RBX2660 followed by 1 dose of placebo (Group C).	127	25 of 41 in group A (61%) and 20 of 44 in group B (45.5%) (participants)	28 of 42 participants (67.3%)	Singular dosage of RBX2660 compared to dual was found to be more significant compared to placebo; restorative microbiome changes were observed with reduction in infection recurrence and colonization
Langdon, 2021	Single or double dosage of RBX2660 via enema	34	27 of 31 participants (87.1%)	NR	Microbiota-therapeutics reduced organism resistance/gene abundance in the gut microbiome. RBX2660 via enema was effective and safe with no adverse events reported

Abbreviations: CDI: *C. Difficile* Infection; C.G.: Control Groups; I.G.: Interventional Groups

4. DISCUSSION

The recent approval of RBX2660 by the FDA is a major breakthrough in managing recurrent CDI, a significant public health concern in the United States and worldwide. The high recurrence rates following traditional antibiotic therapy for CDI have led to the search for alternative treatment options. FMT has emerged as a promising therapeutic option, as reported in this systematic review. RBX2660 is expected to lead to a new era in the management of CDI and may have far-reaching implications for treating other conditions influenced by the gut microbiome [18,19]. One of

the primary advantages of FMT is its ability to restore the balance of the gut microbiota, which is often disrupted by antibiotics and other factors that contribute to the development of CDI [20]. The human gut microbiome is a complex ecosystem that plays a critical role in the maintenance of human health, and disruption of this ecosystem has been linked to a wide range of conditions, including inflammatory bowel disease, obesity, and various autoimmune disorders [21]. FMT has been shown to be an effective means of restoring the balance of the gut microbiome and could have significant implications for managing these conditions [22].

Despite the promise of FMT, many challenges still need to be addressed before it can become a widely accepted treatment option [23]. One of the primary challenges is the lack of standardization and regulation in the field, which has led to concerns about the safety and efficacy of the procedure. The recent approval of RBX2660 is expected to address some of these concerns, as it is the first FMT product to be approved by the FDA. However, additional research is still needed to establish the optimal protocols for FMT and identify the most appropriate donor populations. Another challenge is the limited availability of donor material and the need for stringent screening and testing to ensure the procedure's safety [23]. The use of frozen and standardized donor material, as is the case with RBX2660, is expected to help address some of these challenges. However, there is still a need for ongoing efforts to increase the availability and safety of donor material [23]. There is also an incessant need to develop alternative approaches to FMT, such as synthetic microbiota or microbiota-derived products, that could overcome some of the challenges associated with the use of donor material.

Despite these challenges, the potential benefits of FMT are significant, and there is growing recognition of the need to explore this approach further. In addition to its potential applications in the treatment of CDI, FMT may also have applications in the treatment of other conditions, such as inflammatory bowel disease, irritable bowel syndrome, and even neurological disorders [24]. The gut-brain axis, which is the bidirectional communication network between the gut microbiome and the central nervous system, is an area of active research, and FMT could play an important role in modulating this axis [25]. The success of FMT in the treatment of CDI has also led to renewed interest in the role of the gut microbiome in overall health and disease. As we continue to gain a better understanding of the complex interactions between the gut microbiome and various physiological processes, it is likely that we will identify new therapeutic targets and approaches. This could lead to the development of personalized medicine approaches that are tailored to an individual's unique microbiome profile, further expanding the potential applications of FMT and related approaches [26].

There are several limitations in this systematic review that should be acknowledged. First, the relatively small number of included trials (n=5)

and the total pooled participants (n=795) may limit the generalizability of the findings. Larger-scale studies are needed to confirm the efficacy and safety of RBX2660 for recurrent CDI management. Second, the heterogeneity in the design and methods among the included trials may introduce inconsistencies in the results. Three of the included trials were randomized controlled trials, while two were open-label trials. Moreover, four trials were in Phase 2, and only one was in Phase 3. The variations in trial design and methodology make it difficult to draw definitive conclusions regarding the overall effectiveness of RBX2660. Third, the intervention methods across the trials were not uniform. Some trials administered a single dose of RBX2660, while others used a double dosage via enema or rectal administration. Differences in dosing regimens may impact the outcomes and success rates, which could influence the pooled results. Fourth, the duration of follow-up and assessment of outcomes varied among the included trials. While some trials reported outcomes up to six months or even two years post-treatment, others had shorter follow-up periods. The variability in follow-up durations may affect the assessment of long-term safety and efficacy of RBX2660 treatment. Fifth, the use of different control groups and comparison treatments in the included trials may introduce additional inconsistencies in the results. Some trials used historical controls or placebo groups, while others had no control group. The lack of a consistent control group may limit the ability to make accurate comparisons between studies. Finally, the potential for publication bias should be considered, as studies with negative results may be less likely to be published. This could lead to an overestimation of the efficacy and safety of RBX2660 in this systematic review.

Despite these limitations, the results of this systematic review provide valuable insights into the potential benefits of RBX2660 as a treatment for recurrent CDI. However, more robust and consistent evidence from large-scale, well-designed trials is needed to strengthen the conclusions drawn from this review.

5. CONCLUSION

In conclusion, the recent approval of RBX2660 by the FDA is a major milestone in managing recurrent CDI and underscores the potential benefits of FMT and other microbiota-based therapies. However, it is important to note that the findings presented in this systematic review

are limited due to the small sample size across the included trials, and these results must be interpreted with caution. Further research with larger sample sizes is needed to validate and confirm the efficacy and safety of RBX2660 and FMT for recurrent CDI.

While many challenges still need to be addressed, such as sample control, patient compliance, and standardization of procedures, the potential benefits of FMT are significant and could have far-reaching results. FMT represents a promising and effective therapeutic option for managing recurrent CDI. However, its limitations should not be overlooked, and future studies should strive to address these concerns to ensure the optimal implementation and broader acceptance of FMT as a viable treatment option.

With the growing recognition of the potential benefits of microbiota-based therapies, FMT will likely continue to gain acceptance as a viable treatment option for a wide range of conditions, paving the way for a new era of personalized medicine for specialized patient populations. Nonetheless, it is crucial to continue research efforts and address the limitations and challenges associated with FMT to fully realize its potential in improving patient outcomes and quality of life.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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