

Fecal microbiota transplantation and ulcerative colitis remission: A meta-analysis

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ABSTRACT

Introduction: Fecal microbiota transplantation's role in ulcerative colitis was discussed controversially. Literature regarding the route of administration lack. **Aims:** we aimed to assess the different routes of fecal microbiota transplantation in ulcerative colitis remission. **Methods:** A systematic literature search was conducted in PubMed Cochrane Library and Google Scholar from January 2011 up to September 2021. Two reviewers searched the databases for relevant articles. The terms microbiota transplantation, fecal transplantation, ulcerative colitis, inflammatory bowel disease, colonoscopy route, upper gastrointestinal route and oral capsule were used. The author's name year and country of publication, the study methodology and the results of the included studies were entered in Excel before data analysis by the most RevMan system. **Results:** Out of 762 studies retrieved, 25 full texts were screened and ten cohorts from 7 studies were included in the final meta-analysis. The colonic route (five cohorts), odd ratio, 4.06, 95% CI, 2.19-7.50, observed a higher rate of ulcerative colitis remission compared to placebo. The chi-square was 1.94 and the P-value for overall effect was < 0.0001. However, five cohorts including 35 events and 60 patients showed that fecal transplantation administered by the upper gastrointestinal tract was not different from placebo regarding clinical remission, odd ratio, 1.45, 95% CI, 0.48-4.37, P-value for overall effect, 0.51 and endoscopic remission, P-value, 0.91. **Conclusion:** Fecal microbiota transplantation administered by colonoscopy was effective in ulcerative colitis remission. However, upper gastrointestinal administration was not. Further, longer multicenter studies assessing the characters of donors, frequency and duration of microbiota administration are needed.

Keywords: microbiota transplantation, ulcerative colitis remission, route of administration.

1. INTRODUCTION

Inflammatory bowel disease has become a global burden; the disease is on the rise especially in newly industrialized countries (Ng et al., 2017). The pathogenesis is complex and multi-factorial involving genetic predisposition, environmental factors, immunological and gut microbial alteration (Anbazhagan et al., 2018). IBD is associated with intestinal and extra-intestinal complications including thromboembolism, ocular and neurological diseases, the available treatment poses a great economic burden to the healthcare systems (Rubin et al., 2021). There is a piece of growing evidence that gut microbiota disruption is associated with the development and maintenance of IBD, fecal microbiota transplantation from a healthy subject to patients with IBD was proposed as a potential novel treatment (Kump and Högenauer, 2016). The current evidence is weak regarding remission and maintenance (imdad et al., 2018; Paramsothy et al., 2017). Therefore, this review aimed to assess fecal transplantation among patients with ulcerative colitis.

2. SUBJECTS AND METHODS

Eligibility criteria according to PICOS

We included studies if they were randomized controlled studies. Prospective or retrospective studies, case-control and animal studies were excluded. The search was limited to the English language. Only studies reporting the effects of fecal transplantation (microbiota transplantation) on ulcerative colitis were eligible.

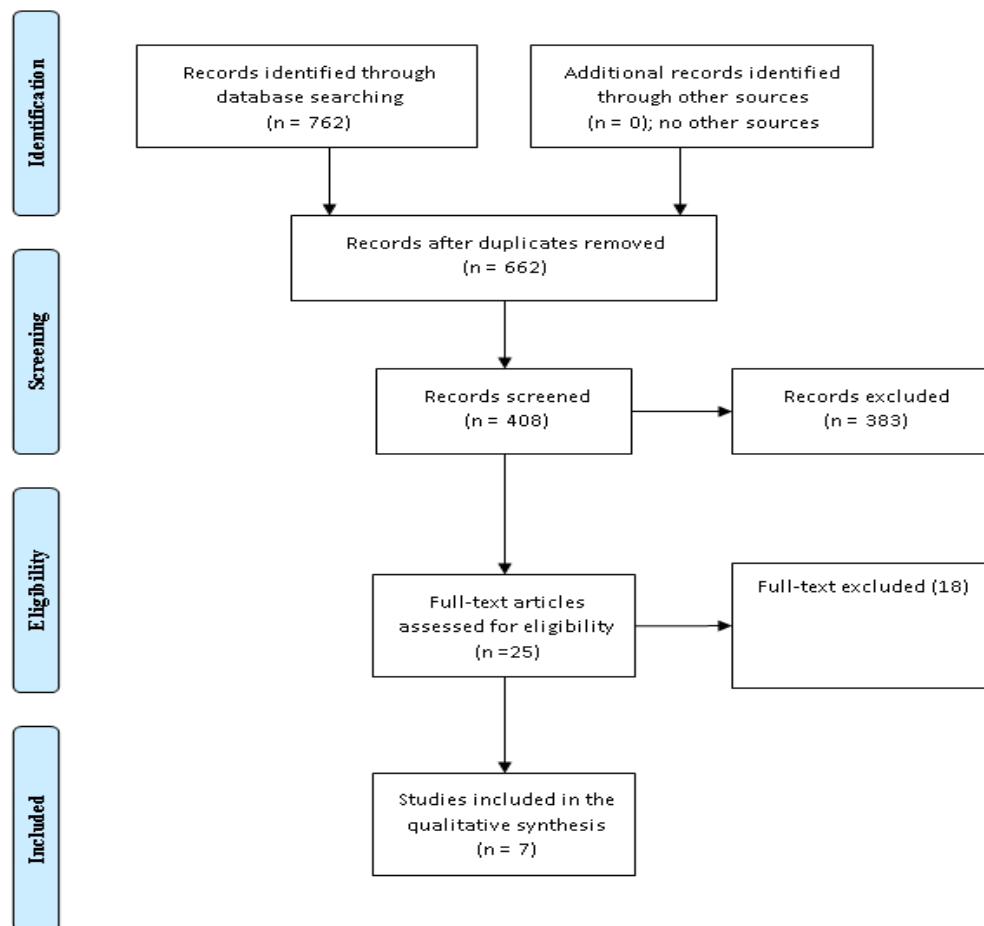


Figure 1 Fecal transplantation and ulcerative colitis remission

Outcome measures

The outcome measures were endoscopic or clinical remission of ulcerative colitis.

Literature search and data extraction

A systematic literature search was conducted in PubMed MEDLINE, Cochrane Library and Google Scholar from January 2011 up to September 2021. Two reviewers searched the databases for relevant articles. The terms microbiota transplantation, fecal transplantation, ulcerative colitis, inflammatory bowel disease, colonic route, nasogastric, nasodudenal, oral capsule were used. With the Protean "AND" and "OR". The titles, abstracts and references of the included studies were screened. Any discrepancy was solved by a consensus. Out of 762 studies retrieved, 662 stands after the removal of duplication, from them, 25 full texts were screened and only 7 studies were included in the final meta-analysis. A data sheet was used to extract the author's name year and country of publication, the study type and the results of microbiota transplantation on ulcerative colitis remission in the intervention and control arm. A modified Cochrane risk of bias assessed the quality of the included studies (Higgins et al., 2016). Tables 1-3 and Figure 1

Statistical analysis

The most recent version of the RevMan (Cochrane) system was used. The dichotomous data from four randomized trials were entered manually and a comparison was generated. The fixed effect was applied because no significant heterogeneity was observed. A P-value of <0.05 was considered significant.

Table 1 Risk of bias assessment of the included studies

Author	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other bias
Costello et al., (2019)	Unclear	Unclear	Low	Low	Low	Low	Low
Moayyedi et al., (2015)	Low	Low	Low	Low	Low	Low	Low
Paramsothy et al., (2017)	Low	Low	Low	Low	Low	Low	Low
Rossen et al., (2015)	Low	Low	Low	Unclear	Low	Low	Low

Table 2 Fecal transplantation (administered through the colon) and ulcerative colitis endoscopic remission.

Author	Year	Country	Duration	Method	Intervention	Control	95%CI	P-value
Costello et al.,	2017	Australia	1 year	RCT	12/38	3/35	1.2-20.1	0.02
Costello et al.,	2019	Australia	1 year	RCT	12/38	3/35	1.2-20.1	0.03
Moayyedi et al.,	2015	Canada	7w	RCT	9/38	2/37	2%-33%	0.01
Paramsothy et al.,	2017	Australia	8w	RCT	11/41	3/40	1.1-11.9	0.021
Rossen et al.,	2015	Netherlands	3 years	RCT	7/23	5/25		0.51

Table 3 Fecal transplantation via the upper gastrointestinal tract and ulcerative colitis remission

Author	Year	Country	Intervention	Control	Remission
Crothers et al.,	2018	USA	4/7	8/8	Endoscopic
Crothers et al.,	2018	USA	5/7	7/8	Clinical
Crothers et al.,	2021	USA	2/6	0/6	Clinical
Rossen et al.,	2015	Netherlands	21/23	23/25	Endoscopic
Rossen et al.,	2015	Netherlands	16/23	17/25	Clinical

3. RESULTS

In the present meta-analysis, all of the five trials included showed a higher rate of ulcerative colitis remission compared to placebo (8-12), odd ratio, 4.06, 95% CI, 2.19-7.50. No heterogeneity was observed ($I^2=0$, P-value, 0.75). Thus, the fixed effect was applied. The chi-square was 1.94 and the P-value for overall effect was < 0.0001. The studies (Three from Australia, one published in Canada and one from Europe.) included 346 patients and 66 events Figure 2. However, three randomized trials (12-14) including 35 events and

60 patients showed that fecal transplantation administered by the upper gastrointestinal tract was not different from placebo regarding clinical remission, odd ratio, 1.45, 95% CI, 0.48-4.37. Mild heterogeneity was observed ($I^2=14$, P-value, 0.28). The chi-square was 1.16 and the P-value for overall effect, 0.51 Figure 3. In figure 4, two cohorts showed no effects on ulcerative colitis endoscopic remission, P-value, 0.91.

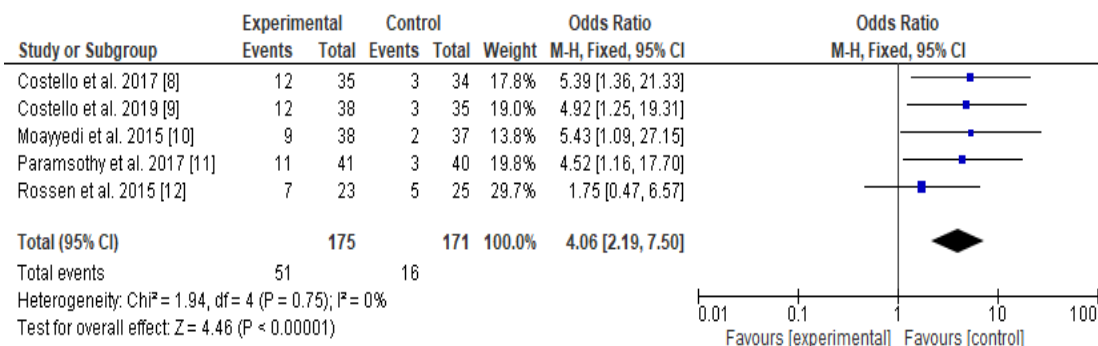


Figure 2 The effects of microbiota transplantation on ulcerative colitis remission.

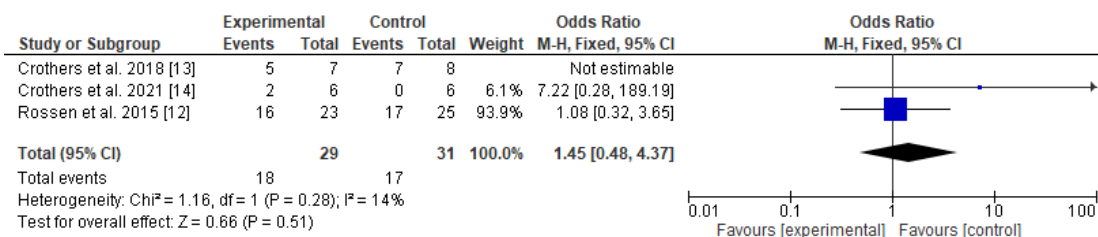


Figure 3 Upper gastrointestinal route and ulcerative colitis clinical remission

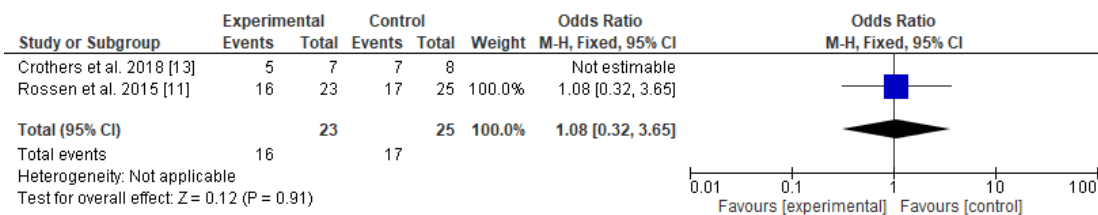


Figure 4 Upper gastrointestinal route and ulcerative colitis endoscopic remission

4. DISCUSSION

In the current meta-analysis, fecal microbiota transplantation administered by the lower gastrointestinal tract was effective in inducing ulcerative colitis remission in agreement with Narula et al., (2017) who concluded similar results. Another meta-analysis included only two randomized controlled trials and concluded the efficacy of fecal transplantation (Shi et al., 2016). Tang and colleagues demonstrated the superiority of fecal transplantation administered through the lower but not the upper gastrointestinal tract and in similarity with the current findings (Tang et al., 2020).

Recurrence rates after remission

A series of 12 patients with moderate to severe UC showed complete remission in nine patients. However, six relapsed and the response to second fecal transplantation was poor (Dang et al., 2020). A recent RCT showed the efficacy of single fecal transplantation in a patient with recurrent UC (Fang et al., 2021); a meta-analysis showed even worsening of inflammatory bowel disease after fecal transplantations. However, the study pooled studies on IBD and Clostridium difficile. Furthermore, marked heterogeneity was observed (Qazi et al., 2017).

Route of administration

The current meta-analyses showed no effect of fecal transplantation administered by the upper gastrointestinal tract. However, nasogastric and nasodudenal tend to have a higher rate of minor side effects compared to the colonic route (Ianiro et al., 2018). A

meta-analysis reported the superiority of mixed multiple donors through the lower gastrointestinal tract, while a single donor transplant through the upper gastrointestinal tract was not superior to a placebo (Suskind et al., 2015; Tang et al., 2020). The available studies showed the transient improvement (Cold et al., 2019) and maintenance of clinical remission of encapsulated fecal microbiota transplantation in patients with ulcerative colitis (Steube et al., 2019).

5. CONCLUSION

Fecal microbiota transplantation administered by the lower gastrointestinal tract but not the upper route was effective in ulcerative colitis remission. Further studies with longer duration and assessing the characters of donors, frequency and duration of microbiota are needed.

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Author's contribution

Hyder Osman Mirghani, Abdulaziz Abdullah AlShalawi and Mohammad Omar Algabri the concept, Turki Suleman Albalawi, Ahmed Mohammed F Albalawi and Abdulaziz Nasser Saleh Albalawi, drafted the introduction, Omar Sabah Alzamhari, Muteb Muflih M Alshahrani, Mohammed Ahmed I Albalawi searched the literature and drafted the methods. Hyder Osman Mirghani, data analysis and drafting the results, Ahmed Mohammed F Albalawi, Hatem Hamad Mohammed Alquthami, Waleed Muslih B Albalawi discussed the results. All the authors revised the manuscript critically and approved it before submission.

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Conflict of interest

The authors declare that there is no conflict of interests.

Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

REFERENCES AND NOTES

1. Anbazhagan AN, Priyamvada S, Alrefai WA, Dudeja PK. Pathophysiology of IBD associated diarrhea. *Tissue Barriers* 2018; 6(2):e1463897. doi: 10.1080/21688370.2018.1463897
2. Cold F, Browne PD, Günther S, Halkjaer SI, Petersen AM, Al-Gibouri Z, Hansen LH, Christensen AH. Multi donor FMT capsules improve symptoms and decrease fecal calprotectin in ulcerative colitis patients while treated – an open-label pilot study. *Scand J Gastroenterol* 2019; 54:289–296.
3. Costello SP, Hughes PA, Waters O, Bryant RV, Vincent AD, Blatchford P, Katsikeros R, Makanyanga J, Campaniello MA, Mavrangelos C, Rosewarne CP, Bickley C, Peters C, Schoeman MN, Conlon MA, Roberts-Thomson IC, Andrews JM. Effect of Fecal Microbiota Transplantation on 8-Week Remission in Patients with Ulcerative Colitis: A Randomized Clinical Trial. *J Am Med Assoc* 2019; 321(2):156-164. doi: 10.1001/jama.2018.20046
4. Costello SW, Bryant R, Katsikeros R. Short duration, low intensity pooled faecal microbiota transplantation induces remission in patients with mild-moderately active ulcerative colitis: A randomised controlled trial. *J Crohns Colitis* 2017; 11:S23.
5. Crothers J, Kassam Z, Smith M. Tu1893 - a double-blind, randomized, placebo-control pilot trial of fecal microbiota transplantation capsules from rationally selected donors in active ulcerative colitis. *Gastroenterology* 2018; 154(6):S-1050–S-1051. doi: 10.1016/s0016-5085(18)33519-4
6. Crothers JW, Chu ND, Nguyen LTT, Phillips M, Collins C, Fortner K, Del Rio-Guerra R, Lavoie B, Callas P, Velez M, Cohn A, Elliott RJ, Wong WF, Vo E, Wilcox R, Smith M, Kassam Z, Budd R, Alm EJ, Mawe GM, Moses PL. Daily, oral FMT for long-term maintenance therapy in ulcerative colitis: Results of a single-center, prospective, randomized pilot study. *BMC Gastroenterol* 2021; 21(1):281. doi: 10.1186/s12876-021-01856-9
7. Dang XF, Qing-Xi W, Yin Z, Sun L, Yang WH. Recurrence of moderate to severe ulcerative colitis after fecal microbiota transplantation treatment and the efficacy of re-FMT: A case series. *BMC Gastroenterol* 2020; 20(1):401. doi: 10.1186/s12876-020-01548-w

8. Fang H, Fu L, Li X, Lu C, Su Y, Xiong K, Zhang L. Long-term efficacy and safety of monotherapy with a single fresh fecal microbiota transplant for recurrent active ulcerative colitis: A prospective randomized pilot study. *Microb Cell Fact* 2021; 20(1):18. doi: 10.1186/s12934-021-01513-6
9. Higgins JP, Savovic J, Page MJ, Strene JA. (The development group for RoB 2.0). Revised Cochrane risk of bias tool for randomized trials 2016. (RoB2.0). doi: 10.1002/14651858.CD201601
10. Ianiro G, Maida M, Burisch J, Simonelli C, Hold G, Ventimiglia M, Gasbarrini A, Cammarota G. Efficacy of different faecal microbiota transplantation protocols for *Clostridium difficile* infection: A systematic review and meta-analysis. *United European Gastroenterol J* 2018; (8):1232-1244. doi: 10.1177/2050640618780762
11. Imdad A, Nicholson MR, Tanner-Smith EE, Zackular JP, Gomez-Duarte OG, Beaulieu DB, Acra S. Fecal transplantation for treatment of inflammatory bowel disease. *Cochrane Database Syst Rev* 2018; 11(11):CD012774. doi: 10.1002/14651858.CD012774.pub2
12. Kump P, Högenauer C. Any Future for Fecal Microbiota Transplantation as Treatment Strategy for Inflammatory Bowel Diseases? *Dig Dis* 2016; 34(1):74-81. doi: 10.1159/000447379
13. Moayyedi P, Surette MG, Kim PT, Libertucci J, Wolfe M, Onischi C, Armstrong D, Marshall JK, Kassam Z, Reinisch W, Lee CH. Fecal Microbiota Transplantation Induces Remission in Patients With Active Ulcerative Colitis in a Randomized Controlled Trial. *Gastroenterology* 2015; 149(1):102-109.e6. doi: 10.1053/j.gastro.2015.04.001
14. Narula N, Kassam Z, Yuan Y, Colombel JF, Ponsioen C, Reinisch W, Moayyedi P. Systematic Review and Meta-analysis: Fecal Microbiota Transplantation for Treatment of Active Ulcerative Colitis. *Inflamm Bowel Dis* 2017; 23(10):1702-1709. doi: 10.1097/MIB.0000000000001228
15. Ng SC, Shi HY, Hamidi N, Underwood FE, Tang W, Benchimol EI, Panaccione R, Ghosh S, Wu JCY, Chan FKL, Sung JJY, Kaplan GG. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: A systematic review of population-based studies. *Lancet* 2017; 390(10114):2769-2778. doi: 10.1016/S0140-6736(17)32448-0
16. Paramsothy S, Kamm MA, Kaakoush NO, Walsh AJ, van den Bogaerde J, Samuel D, Leong RWL, Connor S, Ng W, Paramsothy R, Xuan W, Lin E, Mitchell HM, Borody TJ. Multi donor intensive faecal microbiota transplantation for active ulcerative colitis: A randomised placebo-controlled trial. *Lancet* 2017; 389(10075):1218-1228. doi: 10.1016/S0140-6736(17)30182-4
17. Paramsothy S, Paramsothy R, Rubin DT, Kamm MA, Kaakoush NO, Mitchell HM, Castaño-Rodríguez N. Faecal Microbiota Transplantation for Inflammatory Bowel Disease: A Systematic Review and Meta-analysis. *J Crohns Colitis* 2017; 11(10):1180-1199. doi: 10.1093/ecco-jcc/jjx063
18. Qazi T, Amaratunga T, Barnes EL, Fischer M, Kassam Z, Allegretti JR. The risk of inflammatory bowel disease flares after fecal microbiota transplantation: Systematic review and meta-analysis. *Gut Microbes* 2017; 8(6):574-588. doi: 10.1080/19490976.2017.1353848
19. Rossen NG, Fuentes S, van der Spek MJ, Tijssen JG, Hartman JH, Duflo A, Löwenberg M, van den Brink GR, Mathus-Vliegen EM, de Vos WM, Zoetendal EG, D'Haens GR, Ponsioen CY. Findings from a Randomized Controlled Trial of Fecal Transplantation for Patients with Ulcerative Colitis. *Gastroenterology* 2015; 149(1):110-118.e4. doi: 10.1053/j.gastro.2015.03.045
20. Rubin DT, Griffith J, Zhang Q, Hepp Z, Keshishian A. The Impact of Intestinal Complications on Health Care Costs among Patients with Inflammatory Bowel Disease Treated With Anti-Tumor Necrosis Factor Therapies. *Inflamm Bowel Dis* 2021; 27(8):1201-1209. doi: 10.1093/ibd/izaa270
21. Shi Y, Dong Y, Huang W, Zhu D, Mao H, Su P. Fecal Microbiota Transplantation for Ulcerative Colitis: A Systematic Review and Meta-Analysis. *PLoS One* 2016; 11(6):e0157259. doi: 10.1371/journal.pone.0157259
22. Steube A, Vital M, Grunert P, Pieper DH, Stallmach A. Long-term multi donor faecal microbiota transfer by oral capsules for active ulcerative colitis. *J Crohns Colitis* 2019; 13:1480-1481.
23. Suskind DL, Singh N, Nielson H, Wahbeh G. Fecal microbial transplant via nasogastric tube for active pediatric ulcerative colitis. *J Pediatr Gastroenterol Nutr* 2015; 60(1):27-9. doi: 10.1097/MPG.0000000000000544
24. Tang LL, Feng WZ, Cheng JJ, Gong YN. Clinical remission of ulcerative colitis after different modes of faecal microbiota transplantation: A meta-analysis. *Int J Colorectal Dis* 2020; 35(6):1025-1034. doi: 10.1007/s00384-020-03599-7