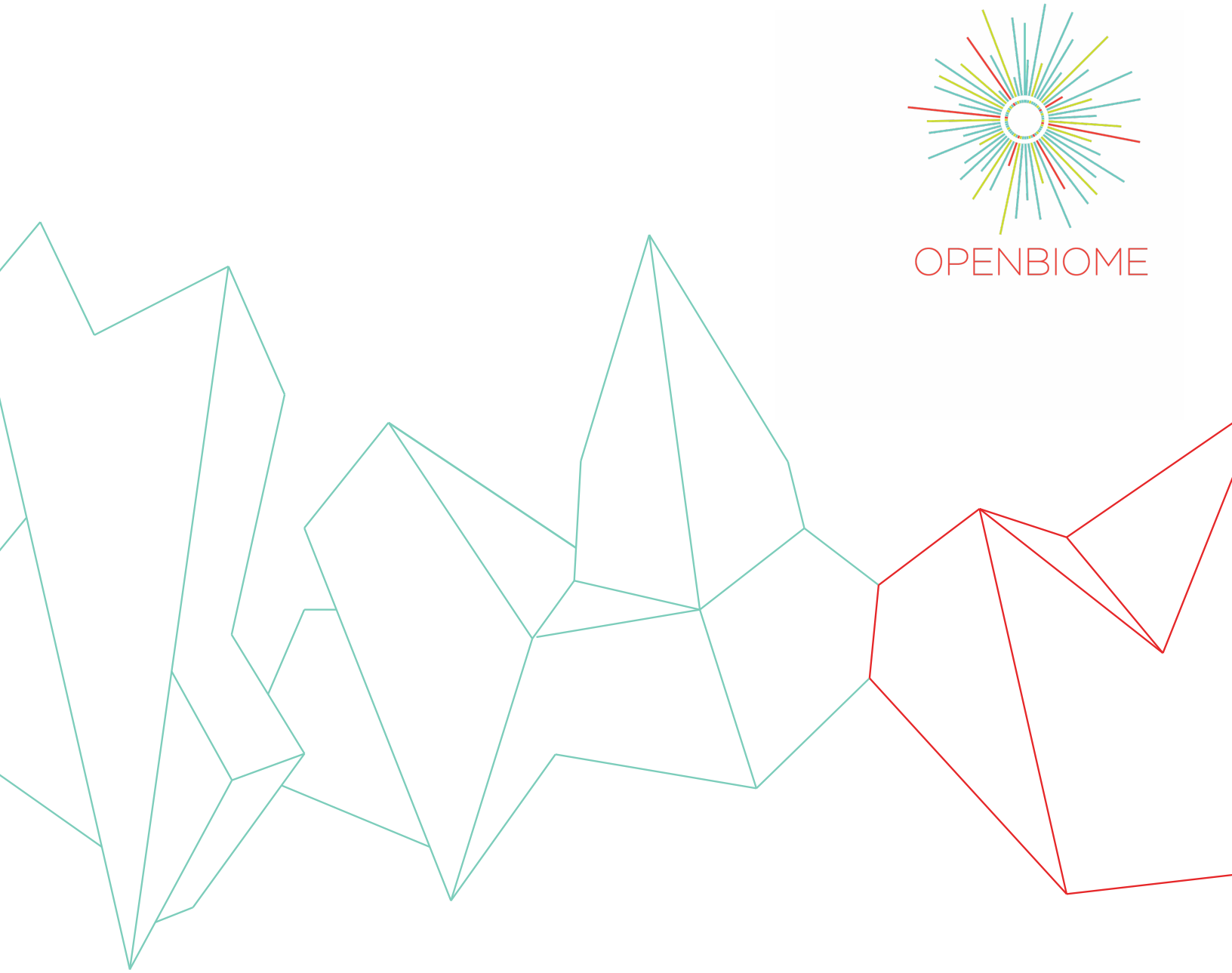

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Efficacy of Fecal Microbiota Transplantation

Current evidence on clinical cure for Fecal Microbiota Transplantation (FMT) for the treatment of recurrent *C. difficile* infection

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Abstract

Controlled clinical trials and observational studies of Fecal Microbiota Transplantation (FMT) as a treatment for *C. difficile* infection (CDI) have reported cure rates ranging from 68%-100%. However, such trials and studies have varying definitions of recurrent *C. difficile*, use different FMT formulations and delivery methods, and treat different patient populations. This paper reviews important points to consider when extrapolating existing efficacy data to the unique situation of an individual patient.

***Disclaimer:** The guidance presented here are general principles drawn from the experience and medical opinions of OpenBiome's clinical team. Physicians should use their own discretion when evaluating their patients and consider each patient's unique medical needs*

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What is the evidence to date on the efficacy of FMT for the treatment of *C. difficile* infection?

The use of FMT for *C. difficile* infection has largely been studied in patients whose infections recurred after at least one round of antibiotics. In controlled clinical trials and observational studies, reported clinical cure rates have ranged from 68% to100%.[1]

The first randomized controlled trial (RCT) comparing FMT to vancomycin for patients with recurrent CDI reported a clinical cure rate of 81% with FMT and 31% with vancomycin.[2] The trial was stopped early for benefit, as it was determined that it would be unethical to withhold the FMT treatment from the control group receiving standard of care. Following publication of the trial, several RCTs have replicated these findings.

To date, there have been ten RCTs that have evaluated FMT in a total of 657 patients with CDI. Five RCTs compared FMT with placebo (including autologous FMT) or vancomycin treatment (284 patients).[2–11] In a systematic review and meta-analysis, FMT was statistically significantly more effective (Relative Risk (RR), 0.41; 95% Confidence Interval (CI), 0.22-0.74).[1]

These findings from controlled clinical trials are consistent with the real-world experience of FMT. At OpenBiome, we request that physicians report de-identified patient outcomes 8 weeks post-FMT. Overall, we have observed cure rates of 79% in 5,155 cases across 1,176 facilities (manuscript in preparation).

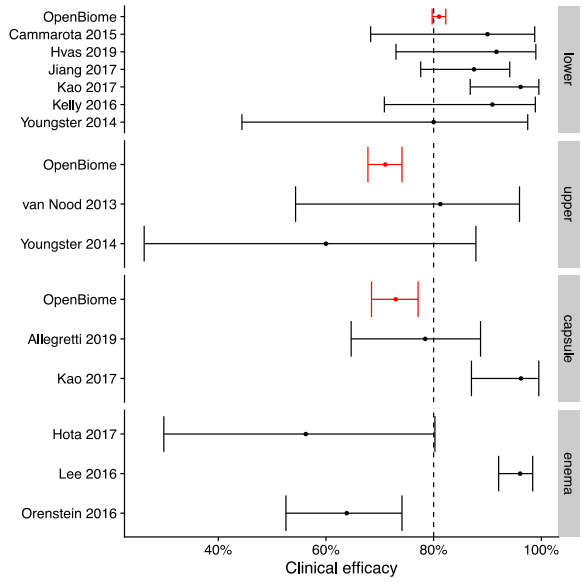

Figure 1 OpenBiome FMT clinical efficacy compared to FMT RCTs

The American Gastroenterological Association (AGA) National FMT Registry (NCT03325855) aims to collect long-term effectiveness and safety outcomes from patients undergoing FMT.[12] The majority of patients (67%) included in the registry to date have received an FMT using OpenBiome material. Other sources include hospital-based stool banks and patient-identified donors. Results reported from the registry have supported the findings from controlled clinical trials. At their one-month check-in, 200 of 222 patients (90%) had resolved their *C. difficile* infection after their FMT (Table 1). Response to FMT was durable; out of 112 patients who were cured after one month and attended a six-month follow-up, 108 (96%) remained cured (Table 1).

Registry data also demonstrated that, although most CDI cases resolved after an initial FMT, repeat FMTs or subsequent antibiotic regimens could be used to achieve cure after failure of the initial FMT. Of the 11 patients who failed to respond to their initial FMT that were followed to 6 months, 7 (64%) resolved their infection either through metronizadole and/or vancomycin (6 (86%)) or repeat FMT (1 (14%)). This is consistent with case studies showing that sequential FMT treatments can help treat severe and fulminant C. difficile infections.[13,14]

Table 1 Clinical cure of *C. difficile* infection one month and six months after FMT for participants in the AGA National FMT Registry

Outcome reported at 1 month	**N (%)**
Cure	**200 (90)**
Failure	**22 (10)**

Outcome reported at 6 months	**N (%)**
Initial cure Remained cured at 6 months Recurrent CDI on or before 6 months	**112 (91)** 108 (96) 4 (4)
Initial failure at 1 month Remained failure at 6 months Subsequent cure by 6 months	**11 (9)** 4 (36) 7 (64)

Note: Failure of FMT is defined by continuation or new onset of *C. difficile* symptoms after 8 weeks. Recurrent symptoms may be due to relapse of the initial infecting strain or, more rarely, reinfection with a new strain. An analysis of 134 paired stool isolates from patients with recurrent CDIs demonstrated that in 88 percent of cases isolates obtained 2 to 8 weeks apart were identical, suggesting recurrence due to the initial infecting strain.[15] Isolates obtained 8 weeks to 11 months apart were identical in 65 percent of the cases. It is also possible but not common, for patients to be infected with multiple strains of *C. difficile*.[16,17]Studies of FMT in children are more limited. The North American Society for Pediatric Gastroenterology, Hepatology & Nutrition (NASPGHAN) has reported outcomes from a registry of pediatric patients who have undergone FMT for CDI. To date, clinical cure two months after FMT occurred in 271 out of 335 (81%) subjects.[18] There have been no randomized controlled trials in pediatric patients to date.

While there are weaknesses in these data, as with any real-world evidence, including underreporting and misclassification bias, data from real-world clinical experience is an important addition to data from controlled clinical trials, and supports our understanding of the safety and efficacy of FMT and microbial therapeutics.

Considerations when reviewing evidence on FMT

The evidence on the short-term clinical cure rates of FMT are good. However, there are important points to consider when interpreting this evidence in the context of an individual patient.

Variability in clinical trials—including differences in donor screening as well as FMT preparation and delivery—potentially limits the generalizability of findings on efficacy: FMT remains an investigational therapy and can be secured from multiple sources including universal stool banks, hospital-based stool banks, and commercial companies conducting clinical trials. Given the varied sources of FMT, formulations, concentrations, and delivery modalities, inferences about the generalizability of clinical cure rates from clinical trials and observational studies can be challenging.

Delivery modality and dosage are important: Clinical trials and real-world experience suggest that enema delivery has the lowest clinical cure rate while colonoscopic delivery has the highest clinical cure rate (Figure 1). Clinical cure rates using upper delivery (nasoenteric/gastric tube or esophagogastroduodenoscopy) and capsules appear to be less efficacious compared to colonoscopic delivery but potentially more efficacious than enema delivery.

Specifically, in a randomised study primarily comparing the efficacy of fresh and frozen FMT in treatment for recurrent CDI, only 52.8% of patients in the 'frozen' arm and 50.5% of patients in the 'fresh' arm of the study (n= 57/108 and 56/111 respectively) experienced resolution of symptoms after a single enema, by modified intention to treat analysis.[10] Additionally, resolution rates in both arms only reached >80% after at least three enemas.[10] A recent randomised study demonstrated similar rates of recurrence of CDI in patients with recurrent CDI treated with either a single FMT enema or a six week vancomycin taper (9/16 patients with recurrence vs 5/12 respectively).[9] However, enemas do have specific advantages, such as being a treatment option where full colonoscopy is contraindicated. It is also possible to give multiple infusions relatively easily. These lower cure rates by enema are likely driven by poor retention of material. Colonoscopic delivery allows for higher dosage and direct delivery to the site of infection.

An OpenBiome retrospective analysis found that FMT by colonoscopy (85.8% clinical cure, n=1441) was superior to that by upper endoscopy (74.1 clinical cure, n=201).[19] These results extend the findings of a smaller study showing that colonoscopic delivery resulted in a primary cure rate of 80% (8/10 patients) while nasogastric tube delivery resulted in a primary cure rate of 60% (6/10 patients). Due to the small sample size, the study was not sufficiently powered to detect a difference in efficacy between the two methods.[20]

Follow-up data from physicians using OpenBiome capsules demonstrate a 74% cure rate (304/419). This is consistent with two smaller studies observing a cure rate of approximately 70% in smaller patient cohorts.[21,22] Importantly, a randomized clinical trial comparing capsule and colonoscopic FMT found no significant difference in clinical cure rates when the dosage of donor microbiota was controlled.[6]

Overall, comparing efficacy rates across different modalities and studies is challenging due to differences in FMT manufacturing processes and dosing, patient populations, and disease severity. Real-world and clinical trial data suggest that colonoscopic delivery, upper delivery, and capsule delivery have clinical cure rates of at least 70% while the cure rate of enema delivery is substantially lower. When selecting a delivery modality, physicians should consider these relative efficacy rates as well as patient comorbidities that may be contraindications for particular modalities.

Varying definitions of recurrent CDI: Another consideration when interpreting findings from clinical trials and observational studies is the variation in reported definitions of recurrent CDI. Most trials include patients after 3 or more episodes of *C. difficile* infection (patients experienced relapses after at least 2 rounds of antibiotic therapy),however some trials include patients after 2 episodes of CDI (patients experienced relapses after 1 round of antibiotic therapy). Of note, the landmark randomized controlled trial by Van Nood and collegaues[2] mentioned previously included patients who had experienced a relapse of *C. difficile* infection after at least one course of antibiotic therapy.

This definition of recurrent CDI is further complicated by the tests used for diagnosising a case for inclusion, with some studies adopting an enzyme immunoassay (EIA) to detect toxin produced by *C. difficile* bacteria, and other adopting a more sensitive nucleic acid amplificatin test, typically a polymerase chain reaction (PCR) assay, to detect the toxin-producing genes present in *C. difficile* bacteria. The difference in diagnostic methods may lead to either the exclusion of patients whose *C. difficile* infection is not cured (e.g. a false negative by EIA) or more likely, who still have *C. difficile* genes present in their intestinal tract but whose infection has resolved. Thus, cure rates may be artificifically lowered if indications other than *C. difficile* are responsible for patients' chronic diarrhea.

The evidence to-date suggests high clnical cure rates of FMT for CDI. However, there are important points to consider when interpreting this evidence in the context of your patient including the delivery modality, severity of disease and underlying comorbidities such as IBD.

What about fulminant CDI?

Fulminant CDI (previously referred to as severe, complicated CDI) presents a particular challenge characterized by elevated white cell counts, hypotension, or shock. Typically, unlike patients with recurrent CDI, patients with fulminant CDI are not stable on antibiotics. Randomized controlled trials are challenging in such a patient population and therefore there is less robust data on clinical cure rates in this population.

Fulminant CDI is associated with mortality rates of 21% and 43% in those who fail to respond to antibiotic therapy. Colectomy is recommended for fulminant patients but still results in mortality rates close to 50%.[23] Even in patients who are discharged after subtotal colectomy for fulminant disease, long-term outcomes are poor with average survival time of 18 months.[23]

Findings from small study of 48 patients treated with OpenBiome FMT preparations or managed with standard of care found a 77% decrease in odds for mortality (Odds Ratio (OR) 0.23, 95% CI 0.06-0.97, p=.045).[24] In a retrospective review of 430 hospitalizations for fulminant CDI, FMT reduced mortality from 21.3% to 9.1% (P = .015).[25] FMT may therefore offer a potential option for patients who are poor candidates for surgery. However, given the severity of disease and associated poor outcomes, the clinical cure rates are uncertain.

Predictors of treatment non-response

Although the clinical cure rates for FMT in CDI appear good, increasing evidence points to the predictors of treatment non-response. In a 328 patient cohort from the United States, predictors of FMT failure were severe or fulminant CDI, inpatient status during FMT, and previous CDI-related hospitalization. With each additional hospitalization, the odds of failure increased by 43%.[26]

In another cohort from the Unites States, 522 patients underwent FMT for CDI.[27] Systemic antibiotics after FMT, inflammatory bowel disease (IBD), pseudomembranes at FMT, and poor bowel preparation were significantly associated with FMT failure. On multivariate

analysis, IBD (OR 4.34; 95% CI, 1.24-15.15), systemic antibiotics (OR 7.39; 95% CI, 3.02-18.07), and poor bowel preparation (OR 3.84; 95% CI, 1.59-9.28).

Therefore, while FMT has been successful in clinical trials, there is potential for treatment failure or incomplete resolution of patient's symptoms. This is especially relevant if a patient has one of the predictors reviewed above.

Summary

C. difficile infection carries high morbidity and mortality with 462,100 cases in the US annually.[28] In the past decade, FMT has developed from a fringe medical practice to the standard of care for recurrent CDI. FMT is recommended by the Infectious Disease Society of America, American College of Gastroenterology, and the British Gastroenterological Society for patients who have failed antibiotic therapy.[29–31]

Overall, the cure rates of FMT from controlled and real-world settings suggests a high efficacy rate of ~80%. Colonoscopic delivery is associated with the highest clinical cure rates. Disease severity, inpatient status, inflammatory bowel disease and post-FMT exposure to antibiotics may impact efficacy and should be considered when evaluating the risk-benefit of FMT for a particular patient.

References

1. Moayyedi P, Yuan Y, Baharith H, Ford AC. Faecal microbiota transplantation for Clostridium difficile-associated diarrhoea: A systematic review of randomised controlled trials. *Med J Aust*. 2017;207(4). doi:10.5694/mja17.00295

2. van Nood E, Vrieze A, Nieuwdorp M, et al. Duodenal Infusion of Donor Feces for Recurrent Clostridium difficile . *N Engl J Med*. 2013;368(5). doi:10.1056/nejmoa1205037

3. Cammarota G, Masucci L, Ianiro G, et al. Randomised clinical trial: Faecal microbiota transplantation by colonoscopy vs. vancomycin for the treatment of recurrent Clostridium difficile infection. *Aliment Pharmacol Ther*. 2015;41(9):835-843. doi:10.1111/apt.13144

4. Hvas CL, Jørgensen SMD, Jørgensen SP, et al. Fecal microbiota transplantation is superior to fidaxomicin for treatment of recurrent clostridium difficile infection. *Gastroenterology*. 2019;156:1324-1332.

5. Jiang ZD, Ajami NJ, Petrosino JF, al. et. Randomised clinical trial: faecal microbiota transplantation for recurrent Clostridum difficile infection: fresh, or frozen, or lyophilised microbiota from a small pool of healthy donors delivered by colonoscopy. *Aliment Pharmacol Ther*. 2017;45:899-908.

6. Kao D, Roach B, Silva M, et al. Effect of Oral Capsule– vs Colonoscopy-Delivered Fecal Microbiota Transplantation on Recurrent *Clostridium difficile* Infection. *JAMA*. 2017;318(20):1985. doi:10.1001/jama.2017.17077

7. Kelly CR, Khoruts A, Staley C, et al. Effect of Fecal Microbiota Transplantation on Recurrence in Multiply Recurrent *Clostridium difficile* Infection. *Ann Intern Med*. 2016;165(9):609. doi:10.7326/M16-0271

8. Allegretti JR, Fischer M, Papa E, et al. Su1738 Fecal Microbiota Transplantation Delivered via Oral Capsules Achieves Microbial Engraftment Similar to Traditional Delivery Modalities: Safety, Efficacy and Engraftment Results From a Multi-Center Cluster Randomized Dose-Finding Study. *Gastroenterology*. Published online 2016. doi:10.1016/S0016-5085(16)31855-8

9. Hota SS, Sales V, Tomlinson G, et al. Oral Vancomycin Followed by Fecal Transplantation Versus Tapering Oral Vancomycin Treatment for Recurrent *Clostridium difficile* Infection: An Open-Label, Randomized Controlled Trial. *Clin Infect Dis*. 2017;64(3):265-271. doi:10.1093/cid/ciw731

10. Lee CH, Steiner T, Petrof EO, et al. Frozen vs Fresh Fecal Microbiota Transplantation and Clinical Resolution of Diarrhea in Patients With Recurrent *Clostridium difficile* Infection. *JAMA*. 2016;315(2):142. doi:10.1001/jama.2015.18098

11. Orenstein R, Dubberke E, Hardi R, et al. Safety and Durability of RBX2660 (Microbiota Suspension) for Recurrent *Clostridium difficile* Infection: Results of the PUNCH CD Study. *Clin Infect Dis*. 2016;62(5):596-602. doi:10.1093/cid/civ938

12. Kelly CR, Yen EF, Grinspan AM, et al. Fecal Microbiota Transplant is Highly Effective in Real-World Practice: Initial Results from the FMT National Registry. *Gastroenterology*. 2020;0(0). doi:10.1053/j.gastro.2020.09.038

13. Grinspan A. FMT for Severe C. difficile Infection: If at First You Do No Harm, the Second Time's a Charm. *Dig Dis Sci*. 2021;66(1). doi:10.1007/s10620-020-06309-z

14. Rupawala AH, Gachette D, Bakhit M, Jimoh L, Kelly CR. Management of Severe and Severe/Complicated Clostridoides difficile Infection Using Sequential Fecal Microbiota Transplant by Retention Enema . *Clin Infect Dis*. Published online 2021. doi:10.1093/cid/ciab041

15. Figueroa I, Johnson S, Sambol SP, Goldstein EJC, Citron DM, Gerding DN. Relapse versus reinfection: Recurrent clostridium difficile infection following treatment with fidaxomicin or vancomycin. *Clin Infect Dis*. 2012;55(SUPPL.2). doi:10.1093/cid/cis357

16. Dayananda P, Wilcox MH. A Review of Mixed Strain Clostridium difficile Colonization and Infection. *Front Microbiol*. 2019;10(APR). doi:10.3389/fmicb.2019.00692

17. Seekatz AM, Wolfrum E, DeWald CM, et al. Presence of multiple Clostridium difficile strains at primary infection is associated with development of recurrent disease. *Anaerobe*. 2018;53. doi:10.1016/j.anaerobe.2018.05.017

18. Nicholson MR, Mitchell PD, Alexander E, et al. Efficacy of Fecal Microbiota Transplantation for Clostridium difficile Infection in Children. *Clin Gastroenterol Hepatol*. Published online 2019:1-9. doi:10.1016/j.cgh.2019.04.037

19. Osman M, O'Brien K, Stoltzner Z, et al. Safety and Efficacy of Fecal Microbiota Transplantation for Recurrent Clostridium difficile Infection From An International Public Stool Bank: Results From a 2050-Patient Multicenter Cohort. *Open Forum Infect Dis*. 2016;3(suppl_1). doi:10.1093/ofid/ofw172.1668

20. Youngster I, Sauk J, Pindar C, et al. Fecal microbiota transplant for relapsing clostridium difficile infection using a frozen inoculum from unrelated donors: A randomized, open-label, controlled pilot study. *Clin Infect Dis*. 2014;58(11). doi:10.1093/cid/ciu135

21. Hirsch BE, Saraiya N, Poeth K, Schwartz RM, Epstein ME, Honig G. Effectiveness of fecal-derived microbiota transfer using orally administered capsules for recurrent Clostridium difficile infection. *BMC Infect Dis*. 2015;15(1). doi:10.1186/s12879-015-0930-z

22. Youngster I, Russell GH, Pindar C, Ziv-Baran T, Sauk J, Hohmann EL. Oral, Capsulized, Frozen Fecal Microbiota Transplantation for Relapsing Clostridium difficile Infection. *JAMA - J Am Med Assoc*. 2014;312(17). doi:10.1001/jama.2014.13875

23. Bhangu A, Nepogodiev D, Gupta A, Torrance A, Singh P. Systematic review and meta-analysis of outcomes following emergency surgery for *Clostridium difficile*

colitis. *Br J Surg*. 2012;99(11):1501-1513. doi:10.1002/bjs.8868

24. Tixier EN, Verheyen E, Ungaro RC, Grinspan AM. Faecal microbiota transplant decreases mortality in severe and fulminant *Clostridioides difficile* infection in critically ill patients. *Aliment Pharmacol Ther*. 2019;50(10):1094-1099. doi:10.1111/apt.15526

25. Cheng Y-W, Alhaffar D, Saha S, et al. Fecal Microbiota Transplantation Is Safe and Effective in Patients With Clostridioides difficile Infection and Cirrhosis. *Clin Gastroenterol Hepatol*. 2020;0(0). doi:10.1016/j.cgh.2020.06.051

26. Fischer M, Kao D, Mehta SR, et al. Predictors of Early Failure after Fecal Microbiota Transplantation for the Therapy of Clostridium Difficile Infection: A Multicenter Study. *Am J Gastroenterol*. 2016;111(7):1024-1031. doi:10.1038/ajg.2016.180

27. Tariq R, Saha S, Solanky D, Pardi DS, Khanna S. Predictors and Management of Failed Fecal Microbiota Transplantation for Recurrent Clostridioides difficile Infection. *J Clin Gastroenterol*. Published online 2020.

28. Guh AY, Mu Y, Winston LG, et al. Trends in U.S. Burden of clostridioides difficile infection and outcomes. *N Engl J Med*. Published online 2020. doi:10.1056/NEJMoa1910215

29. Mullish BH, Quraishi MN, Segal JP, et al. The use of faecal microbiota transplant as treatment for recurrent or refractory Clostridium difficile infection and other potential indications: Joint British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) guidelines. *Gut*. 2018;67(11). doi:10.1136/gutjnl-2018-316818

30. McDonald LC, Gerding DN, Johnson S, et al. Clinical Practice Guidelines for Clostridium difficile Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). *Clin Infect Dis*. 2018;66(7). doi:10.1093/cid/cix1085

31. Surawicz CM, Brandt LJ, Binion DG, et al. Guidelines for Diagnosis, Treatment, and Prevention of Clostridium difficile Infections. *Am J Gastroenterol*. 2013;108(4):478-498. doi:10.1038/ajg.2013.4

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