Safety, Tolerability, and Clinical Response After Fecal Transplantation in Children and Young Adults With Ulcerative Colitis

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See ''Medical Stool: The Future of Treatment for Inflammatory Bowel Disease?'' by Davidovics and Sylvester on page 583.

ABSTRACT

Background and Objective: Colonic dysbiosis contributes to the development of colonic inflammation in ulcerative colitis (UC). Fecal microbial transplantation (FMT) is being proposed as a novel treatment for UC because it can eliminate dysbiosis; however, no prospective data exist. We initiated a pilot study to evaluate feasibility and safety of FMT in children with UC.
Methods: Ten children, 7 to 21 years of age, with mild-to-moderate UC (pediatric UC activity index [PUCAI] between 15 and 65) received freshly prepared fecal enemas daily for 5 days. Data on tolerability, adverse events, and disease activity were collected during FMT and weekly for 4 weeks after FMT. Clinical response was defined as decrease in PUCAI by >15, and decrease in PUCAI to <10 was considered clinical remission.
Results: No serious adverse events were noted. Mild (cramping, fullness, flatulence, bloating, diarrhea, and blood in stool) to moderate (fever) adverse events were self-limiting. One subject could not retain fecal enemas. Average tolerated enema volume by remaining 9 subjects was 165 mL/day. After FMT, 7 of the 9 (78%) subjects showed clinical response within 1 week, 6 of the 9 (67%) subjects maintained clinical response at 1 month, and 3 of the 9 (33%) subjects achieved clinical remission at 1 week after FMT. Median PUCAI significantly improved after FMT ($P = 0.03$) compared with the baseline.
Conclusions: Fecal enemas were feasible and tolerated by children with UC. Adverse events were acceptable, self-limiting, and manageable by subjects. FMT indicated efficacy in the treatment of UC.

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Ulcerative colitis (UC) is a chronic, devastating inflammatory bowel disease affecting the colon without a medical cure. UC is characterized by decreased prevalence of protective bacteria and concomitant increase in detrimental bacteria in the colon (1). The colonic microbiome in patients with UC has decreased richness and diversity (2,3) and is dysfunctional (4) (dysbiosis). Colonic inflammation in UC is hypothesized to result from an inappropriate activation of the mucosal innate immune system because of dysbiosis in genetically susceptible individuals.

Medications (aminosalicylic acid preparations, steroids, immunomodulators, and biologics such as anti-tumor necrosis factor-α [TNF-α]) used to treat UC have significant adverse effects. These medical options focus on limiting the colonic inflammation without addressing the dysbiosis itself. Probiotics, for example, VSL#3, have shown some usefulness in the treatment of UC (5); however, not all probiotic formulations contain the same species, their efficacy may be strain specific, and understanding of their mechanism of action in the complex gastrointestinal (GI) microbiome is lacking.

Fecal microbial transplantation (FMT) is being proposed as a novel therapeutic approach specifically to modulate dysbiosis and thereby decrease colonic inflammation in UC. Recent evidence suggests that FMT, the infusion of fecal preparation from a healthy donor into the GI tract of a patient, is capable of altering the gut microbiome of the new host (6,7). Since the first case report nearly 2 decades ago (8), FMT has been used sporadically to treat inflammatory bowel diseases (9), with claims of clinical (10) and endoscopic remission (11). Although abundant data support the possible use of FMT in the treatment of recurrent *Clostridium difficile* infection with a success rate of nearly 90% (7,12,13), limited reports are available on its role in treating UC. No prospective data exist on the applicability of FMT in patients with UC.

Children represent a considerable population affected by UC because approximately 25% of patients are diagnosed during their childhood (younger than 20 years). The psychological turmoil associated with UC appears to be profound in children, who seem less able than older patients to adapt and cope with their disease (14,15). Therefore, as an initial step in understanding the role of FMT in UC, we conducted a phase I clinical trial evaluating feasibility, safety, and tolerability of FMT in children with UC. We also measured the effect of FMT on clinical disease activity in this population to understand its potential efficacy.

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METHODS

Study Oversight

The study was approved by the Spectrum Health institutional review board. Informed consent was obtained from the participants (subjects/parents and donors) at the time of enrollment. When used to treat a disease, human stool constitutes a drug and a biologic. Therefore, an investigational new drug approval (IND#14993) was obtained from the US Food and Drug Administration to use FMT for treating UC. The study was registered at *www.clinicaltrials.gov* before enrolling any participants.

Study Design

A prospective, open-label, uncontrolled, single-center pilot study was conducted at Helen DeVos Children's Hospital's outpatient gastroenterology facility. Subjects were enrolled between April and December 2012. The study was not advertised. Each subject participated in the study for 6 weeks (Fig. 1). Subjects received FMT as freshly prepared fecal retention enemas.

Study Population

Subjects

Ten children between the ages of 7 to 21 years with mild-to-moderate UC (pediatric UC activity index [PUCAI] between 15 and 65) were enrolled prospectively. Subjects had stable disease activity and medical treatment for UC for 2 months before the enrollment. Subjects' exclusion criteria included fulminant colitis, scheduled for abdominal surgery, pregnancy, concurrent probiotic or antibiotic use, severe anemia (hemoglobin <6 g/dL), graft-versus-host disease, immunocompromised host defined as neutropenia or history of opportunistic infection, major intraabdominal surgery within 3 months before FMT, administration of any investigational drug within 1 month before FMT, and use of anti-TNF-α medications within 2 months before FMT or its expected use within 1 month after FMT. Subjects' ongoing treatment for UC was not changed. None of the subjects had concurrent *C difficile* infection.

Donors

Healthy adults (older than 18 years of age) selected by subjects from their family members or close friends were used as donors. Donor exclusion criteria were guided by our IND, the American Association of Blood Bank Donor History Questionnaire version 1.1, and the recommendations from the American Gastroenterological Association (16). Donor exclusion criteria included positive response on the donor screening questionnaire; history of inflammatory bowel diseases, irritable bowel syndrome, chronic abdominal pain, or GI malignancy; diarrhea, blood in stool or antibiotic use within 1 month before FMT; immunocompromised, defined as taking immunosuppressive medications, history of opportunistic infection within 1 year before FMT, oral thrush, or disseminated lymphadenopathy; and abnormal donor screening tests. Donor screening tests were performed by Spectrum Health Regional Laboratory, which is certified by federal Clinical Laboratory Improvement Amendments. The donor screening laboratory values included blood tests (hepatitis A immunoglobulin [Ig]M, hepatitis B surface Ag, hepatitis B surface Ab, hepatitis B core Ab, hepatitis C Ab, Epstein-Barr virus viral capsid antigen IgM, cytomegalovirus IgM, syphilis IgG, HIV I and II enzyme-linked immunosorbent assay), and stool tests (stool culture for *Salmonella*, *Shigella, Escherichia coli*, *Campylobacter, Yersinia, Vibrio, and Listeria*, *C difficile* toxin polymerase chain reaction, ova and parasite screening, fungal smear).

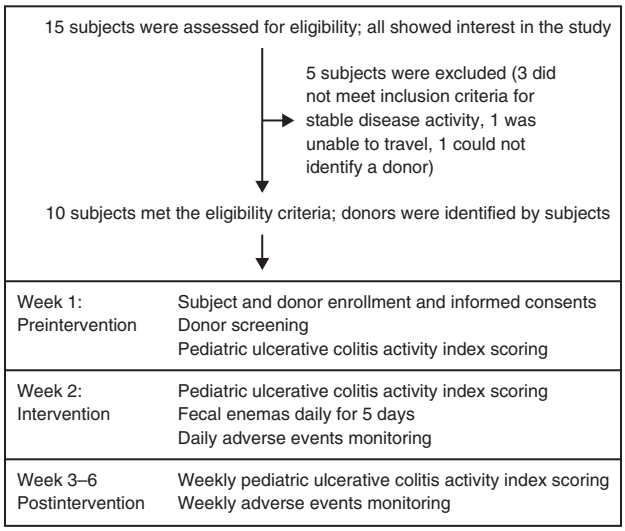

FIGURE 1. Study design and procedures involved in the research.

Donor Fecal Preparation

Donors produced stool samples within 6 hours before the scheduled FMT. Donors were asked to take over-the-counter stool softeners, if necessary, to produce stool samples on schedule. Donor stool was handled as a level 2 biohazard with appropriate universal precautions. On average, each donor produced a 90-g (range 70–113 g) stool sample every day, which was used for FMT. Fecal samples were blended with 250 mL sterile warm (37°C) normal saline for 1 minute using a conventional blender in a designated GI laboratory space. This blended fecal mixture was then filtered through 2 gauze pieces to remove larger sediments. Filtered fecal preparation was then divided into 4 aliquots of 60 mL each and kept in a warm water bath (37°C) until FMT was administered.

Study Intervention

Subjects did not receive any bowel preparation (cleanout or antibiotic pretreatment) before FMT. To help relieve children's anxiety about FMT, we used audiovisual aids to keep them engaged during intervention. Subjects were put in the left lateral decubitus position with elevated hips in a designated private GI clinic room for 90 minutes for FMT intervention. Each subject received FMT as retention enema for 1 hour (60-mL enema every 15 minutes) daily for 5 days. Each 60-mL enema was infused for 5 minutes. Subjects were then asked to rotate 180° (from left lateral to right lateral position and then back to left lateral position) slowly during a 10-minute period. Although 240 mL of fecal solution was prepared for FMT, the final administered dose was dependent on the subject's comfort and willingness to proceed with the next enema, which was assessed after each enema infusion. Subjects were monitored for 30 minutes after FMT for any immediate adverse events and discharged. No antimotility drugs were used to help retain FMT.

Safety Monitoring and Endpoints

An adverse event was defined as any untoward medical occurrence associated with FMT, whether or not related to FMT. A serious adverse event was defined as an adverse event that results in death, is life-threatening, or requires hospitalization. Adverse events were recorded during FMT and until 4 weeks after FMT using an easy-to-understand symptom diary that subjects completed. Intensity and relation of adverse events with FMT was

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described using Common Terminology Criteria for Adverse Events version 3.0 and Toxicity Grading Guidance from Vaccine Clinical Trials (US Food and Drug Administration, September 2007). Intensity of adverse events was classified as mild, moderate, severe, or disabling. Relation of adverse events with FMT was categorized as unrelated or possibly, probably, or definitely related to FMT. Safety reporting was in accordance with the IND requirements per the Code of Federal Regulations, Title 21 (CFR 312.32). A data safety monitoring committee was established that monitored adverse events and halting criteria after every 3 subjects completed the study to assess for patterns and rate of reported or observed complications. Halting criteria was defined as the occurrence of any serious adverse event or if $\geq$3 subjects experienced a similar adverse event of severe intensity that was related to FMT.

Tolerance

Tolerance was defined as ability of subjects to retain a >60-mL enema. This volume was based on the standard mesalamine and hydrocortisone enemas volume used to treat UC. Intolerance was defined as immediate leaking of enema during administration or inability to retain enema for at least 1 hour after administration. No further FMT was performed if the subject showed intolerance for 3 consecutive days.

Clinical Response

Clinical disease activity was measured using PUCAI (17,18), which was calculated at the enrollment, at starting FMT, and weekly for 4 weeks after FMT. We expected a mild-to-moderate improvement in UC symptoms after FMT. Therefore, clinical response was defined as a decrease in PUCAI by >15 points after FMT (17). Clinical remission was defined as decrease in PUCAI to <10. The clinical endpoint was defined as clinical response at 1 month after FMT. The data on PUCAI were collected by using an easy-to-understand symptom questionnaire, which listed symptoms of PUCAI (abdominal pain, rectal bleeding, stool consistency, number of stools, nocturnal stools, and activity limitation). To avoid investigator bias, we did not use clinical recall elicited by investigators. The questionnaire was completed by subjects based on their most recent (within last 2 days) symptoms.

Statistical Analysis

No power calculation or sample size assessment was done for this pilot study. Data on adverse events, tolerability, and disease activity are reported as descriptive analysis. Changes in PUCAI after FMT were compared with baseline using Wilcoxon signed rank test. P value <0.05 was considered statistically significant.

RESULTS

We received interest from patients from all over the world to participate in this study. Fifteen subjects were assessed for the eligibility to enroll in the study (Fig. 1). We enrolled all of the planned 10 subjects within 9 months of starting the study. The age of subjects ranged from 7 to 20 years (Table 1). Steroid-dependent patients continued to take the medication throughout the study period. Only 1 subject had used anti-TNF-α medications in the past. All had active disease diagnosed by colonoscopy within 6 months before the enrollment. All of the donors were first-degree relatives of subjects, except 1 subject, who identified a family friend as donor. All of the donors had negative/normal screening laboratories (blood and stool tests).

Tolerance

One subject showed intolerance with immediate leaking of enemas for 3 consecutive days. The remaining 9 subjects tolerated enema volumes ranging from 75 to 240 mL (average 165 mL) without leakage. These 9 subjects tolerated FMT well because they were able to retain fecal enemas from 3 to 24 hours (average 10 hours).

Adverse Events

Subject-reported symptoms and their relations with FMT are described in Table 2. No serious adverse events were noted. As

TABLE 1. Subject demographic and disease characteristics

Subject	Age, y	Sex	Disease duration, y	Present medications*	Last medications*	Disease extent†	Disease activity before FMT†	Disease activity 4 weeks after FMT‡,§	Donor: age, y/sex
1	18	M	8	5-ASA	5-ASA, 6-MP, probiotics	Pancolitis	30	15	56/F
2	17	M	7	5-ASA, 6-MP	5-ASA	Proctitis	35	0	51/M
3	20	F	1	5-ASA, 6-MP, Steroids	5-ASA, steroids	Pancolitis	50	40	18/M
4	15	M	1.5	5-ASA, 6-MP	5-ASA, steroids	Proctitis	40	55	43/M
5	19	F	3	5-ASA	5-ASA	Extensive	30	10	48/F
6	14	F	5	None	5-ASA, 6-MP, steroids, methotrexate, anti-TNF-α	Pancolitis	50	50	44/M
7	18	M	0.6	5-ASA, steroids	5-ASA, steroids	Pancolitis	55	—	20/M
8	8	M	5	None	None	Pancolitis	35	0	33/F
9	16	M	1	5-ASA, steroids	6-MP, steroids, probiotics	Left-sided	50	25	47/M
10	7	F	3	6-MP	5-ASA, steroids	Pancolitis	20	0	36/F

* Medications: 5-ASA = 5-aminosalicylic acid preparations (oral or enema); 6-MP = 6-mercaptopurine; anti-TNF-α = antitumor necrosis factor-α; steroids = hydrocortisone (oral or enema).

† Disease extent: extensive = involving left and transverse colon; left-sided = involving rectum and sigmoid or descending colon; pancolitis = involving the entire colon; proctitis = involving rectum.

‡ Disease activity: measured by pediatric ulcerative colitis activity index.

§ Subject no. 7 showed intolerance to FMT (immediate leaking of enemas) and was not included in post-FMT disease activity evaluation.

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TABLE 2. Subject-reported symptoms, their intensity, and relation with FMT

Reported symptoms*	Intensity	No. subjects			Related to FMT
		Overall	During FMT	During follow-up	
Bloating/flatulence	Mild to moderate	9	7	4	Possible
Abdominal pain/cramping	Mild	6	5	6	Possible
Diarrhea	Mild to moderate	6	4	5	Possible
Blood in stool	Mild	3	2	3	Possible
Fatigue	Mild to moderate	3	1	2	Possible
Fever	Mild to moderate	2	2	0	Probable

FMT = fecal microbial transplantation.
* Only symptoms that could be related to fecal microbial transplantation are listed in the table.

expected, fecal enemas were associated with mild left-sided abdominal fullness. One subject reported a moderate degree of fever and chills 3 hours after FMT, which spontaneously resolved during the next 6 hours for 2 consecutive FMT days. No signs of sepsis were reported. For the remaining 3 FMT days, the use of antipyretic (acetaminophen) and antihistaminic (diphenhydramine) medications immediately after FMT prevented the development of fever. Another subject had single episode of low-grade fever (without chills or signs of sepsis) after FMT; no intervention was necessary. Owing to the temporal relation of fever with FMT and use of medications to control this symptom, fever was classified as ''probably'' related to FMT.

Disabling hematochezia was seen in the third week after FMT (not shown in Table 2) in 1 subject (subject no. 4). Because this subject showed initial clinical response to FMT and there was a lack of immediate temporal relation with FMT, the symptom was likely because of an UC flare and unlikely from the FMT intervention. This subject responded well to corticosteroid enema therapy. Other reported symptoms that were not related to FMT included cervical lymphadenopathy (after an upper respiratory infection during follow-up period in 1 subject); lower back pain (from positioning while performing FMT in 1 subject); headache, nausea, or vomiting (baseline symptoms from concurrent medication use in 3 subjects). All of the adverse events related to FMT were self-limiting, did not require intervention from health care providers (except fever), and the majority of them were similar to subjects' baseline symptoms of UC.

Clinical Response

The subject who showed intolerance to FMT was not included in the clinical response evaluation. After FMT, 7 of the 9 (78%) subjects showed clinical response within 1 week. Six of the 9 subjects (67%) maintained clinical response at 1 month. Three of the 9 (33%) subjects achieved clinical remission at 1 week after FMT and were able to maintain it by 4 weeks after FMT (Fig. 2). Median PUCAI score significantly decreased after FMT ($P = 0.03$) compared with baseline. The decision to cease medications for UC for the subjects who achieved clinical remission after the study completion was left to their respective gastroenterologists.

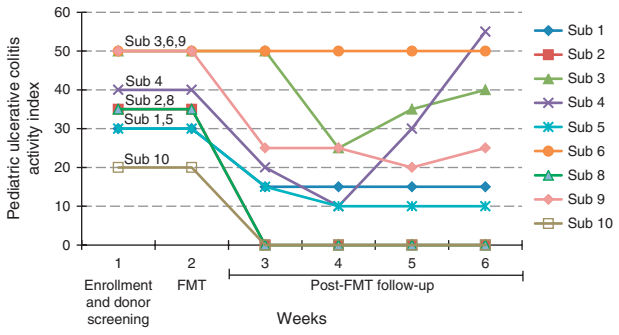

FIGURE 2. Clinical response to fecal microbial transplantation (FMT). Fecal enemas were provided in the second week of the study. Clinical disease activity was determined using pediatric ulcerative colitis activity index. Changes in disease activity can be seen after FMT (weeks 3–6). Subject no. 7 was not included in this analysis because of intolerance to fecal enemas.

DISCUSSION

The results of this study demonstrate that performing FMT as fecal enemas is feasible; they are well tolerated and safe in children with UC. The study also indicates the potential efficacy of FMT in treating UC. We report, for the first time, that when used to mitigate a human condition, human stool constitutes a biologic, and IND approval should be obtained to perform FMT.

As reported previously (10), because of the chronic process of colonic inflammation, multiple FMT sessions may be needed to see a clinical response in UC. As such, we performed 5 FMT treatments compared with 1 (or 2) treatments required for recurrent *C difficile* infection (7). Multiple studies have used various bowel sterilizing preparations (antibiotics and bowel cleanout) before FMT (19,20) to help donor microbiota establish in the new host. We did not use any bowel preparation to avoid confounding of the changes in clinical response and also to avoid further discomfort to children. Upper and lower GI routes have been used to administer FMT; however, because of the vulnerable nature of our study population, we chose enema as the safest route to instill FMT. In this exploratory study, for the safety of the subjects, we excluded children with severe UC (PUCAI >65) and immunocompromised subjects (eg, taking concurrent anti-TNF-α). We did this to limit the theoretical risk of sepsis from possible translocation of new bacteria through inflamed mucosa during FMT, although no such risk has been reported yet (7,21). Further long-term follow-up studies are required to determine safety and to exclude the possibility of inadvertent transmission of disease-causing pathogens through FMT.

Limited data are available on the adverse events related to FMT. A recent study (7) evaluating the role of FMT in treating recurrent *C difficile* infection reported adverse events, which, similar to our study, were predominantly GI symptoms. The symptoms were short-lived, acceptable to subjects, and manageable. Symptoms (other than fever) reported by our study population were similar to the symptoms of UC, and thus could not be definitely attributed to FMT. Similar to our study, development of fever after FMT without signs of sepsis or positive blood culture has been reported in patients with UC (22). This indicates that FMT may mount a temporary systemic immune response without bacteremia and it can be prevented using antipyretic and antihistaminic medications.

Selection of 240-mL volume for FMT was based on earlier studies (10,20,23), which used colonoscopic or enema routes of

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FMT infusion. Administrating FMT for 1 hour with changing positions helped subjects retain large volume enemas for a longer time. The FMT enema was tolerated (>60 mL) even by the youngest subjects; however, the subject who showed intolerance was an adult. This indicates that intolerance to fecal enemas may not be dependent on age or size of the subject. The determinants of intolerance may include severity of distal colonic disease, experience with enemas, and anxiety associated with the enema.

A dramatic response to FMT seen within 1 week was not maintained by all of the subjects. We speculate that differences in the clinical response seen in our study population can be the result of severity, duration or the extent of the disease, and because of the differences in the ability to retain larger FMT volumes for longer periods. Whether patients with UC need a longer duration of FMT or multiple scheduled FMT infusions to maintain a clinical response is unknown and needs further exploration. A recent systematic review of case reports on the use of FMT in the management of inflammatory bowel diseases indicated that 76% of subjects experienced improvement in symptoms and 63% achieved clinical remission after FMT (9). In this review, 18 patients had UC without concurrent *C difficile* infection and 13 of these 18 (72%) patients showed clinical response after FMT. This is similar to clinical response seen in our population.

As expected with any single-center, uncontrolled study, we cannot exclude investigator or participant bias; however, every attempt was made to collect the data objectively (eg, use of symptom questionnaire) without bias by investigators. Because of financial limitations, fecal and mucosal microbial community profiling was not performed. This profiling would have been critical to determine whether the mechanism of action in FMT in the treatment of UC is similar to its use in recurrent *C difficile* infection (eg, reestablishing the normal microbiota (6) and increasing fecal bacteria diversity) (7). Colonoscopic disease activity or stool inflammatory markers (to support reported disease activity) was also not measured because of financial limitations and should be a part of future studies. Whether there are any implications in using adult donors for pediatric patients is unknown and should be addressed in future studies. We did not use age-matched or pediatric donors for this study because we believed it was unethical to ask a child to produce a stool on demand or to take a medication for that reason. This short-term pilot study is limited by its small sample size; therefore, studies with a larger sample size and longer follow-up period will be required to determine true efficacy of FMT in patients with UC.

Use of FMT in UC may not be as simple as its use in recurrent *C difficile* infection. To better understand how FMT can be used to treat UC, many unanswered questions need to be addressed. We must further investigate standardization of FMT preparation, ideal donor selection, ideal route of administration, and optimal duration or scheduling of FMT to induce and maintain a clinical response. Most important, the effects of FMT on the colonic microbiome and mucosal inflammation in UC need to be explored.

CONCLUSIONS

FMT in the form of fecal enema is feasible and well tolerated by children and young adults with UC. Adverse events of FMT are mild to moderate, acceptable by subjects, self-limiting, and manageable. This unique biologic is potentially efficacious in treating UC.

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REFERENCES

1. Gophna U, Sommerfeld K, Gophna S, et al. Differences between tissue-associated intestinal microfloras of patients with Crohn's disease and ulcerative colitis. *J Clin Microbiol* 2006;44:4136–41.
2. Michail S, Durbin M, Turner D, et al. Alterations in the gut microbiome of children with severe ulcerative colitis. *Inflamm Bowel Dis* 2011;18:1799–808.
3. Peterson DA, Frank DN, Pace NR, et al. Metagenomic approaches for defining the pathogenesis of inflammatory bowel diseases. *Cell Host Microbe* 2008;3:417–27.
4. Morgan XC, Tickle TL, Sokol H, et al. Dysfunction of the intestinal microbiome in inflammatory bowel disease and treatment. *Genome Biol* 2012;13:R79.
5. Tursi A, Brandimarte G, Papa A, et al. Treatment of relapsing mild-to-moderate ulcerative colitis with the probiotic VSL#3 as adjunctive to a standard pharmaceutical treatment: a double-blind, randomized, placebo-controlled study. *Am J Gastroenterol* 2010;105:2218–27.
6. Khoruts A, Dicksved J, Jansson JK, et al. Changes in the composition of the human fecal microbiome after bacteriotherapy for recurrent Clostridium difficile-associated diarrhea. *J Clin Gastroenterol* 2010;44:354–60.
7. Van Nood E, Vrieze A, Nieuwdorp M, et al. Duodenal infusion of donor feces for recurrent Clostridium difficile. *N Engl J Med* 2013;368:407–15.
8. Bennet JD, Brinkman M. Treatment of ulcerative colitis by implantation of normal colonic flora. *Lancet* 1989;1:164.
9. Anderson JL, Edney RJ, Whelan K. Systematic review: faecal microbiota transplantation in the management of inflammatory bowel disease. *Aliment Pharmacol Ther* 2012;36:503–16.
10. Borody TJ, Warren EF, Leis S, et al. Treatment of ulcerative colitis using fecal bacteriotherapy. *J Clin Gastroenterol* 2003;37:42–7.
11. Borody TJ, Campbell J. Fecal microbiota transplantation: techniques, applications, and issues. *Gastroenterol Clin North Am* 2012;41:781–803.
12. van Nood E, Speelman P, Kuijper EJ, et al. Struggling with recurrent Clostridium difficile infections: is donor faeces the solution? *Euro Surveill* 2009;14:pii.19316.
13. Guo B, Harstall C, Louie T, et al. Systematic review: faecal transplantation for the treatment of Clostridium difficile-associated disease. *Aliment Pharmacol Ther* 2012;35:865–75.
14. Rubin DT, Siegel CA, Kane SV, et al. Impact of ulcerative colitis from patients' and physicians' perspectives: results from the UC: NORMAL survey. *Inflamm Bowel Dis* 2009;15:581–8.
15. Rubin DT, Dubinsky MC, Panaccione R, et al. The impact of ulcerative colitis on patients' lives compared to other chronic diseases: a patient survey. *Dig Dis Sci* 2010;55:1044–52.
16. Bakken JS, Borody T, Brandt LJ, et al. Treating Clostridium difficile infection with fecal microbiota transplantation. *Clin Gastroenterol Hepatol* 2011;9:1044–9.
17. Turner D, Otley AR, Mack D, et al. Development, validation, and evaluation of a pediatric ulcerative colitis activity index: a prospective multicenter study. *Gastroenterology* 2007;133:423–32.
18. Turner D, Seow CH, Greenberg GR, et al. A systematic prospective comparison of noninvasive disease activity indices in ulcerative colitis. *Clin Gastroenterol Hepatol* 2009;7:1081–8.
19. Hamilton MJ, Weingarden AR, Sadowsky MJ, et al. Standardized frozen preparation for transplantation of fecal microbiota for recurrent Clostridium difficile infection. *Am J Gastroenterol* 2012;107:761–7.
20. Grehan MJ, Borody TJ, Leis SM, et al. Durable alteration of the colonic microbiota by the administration of donor fecal flora. *J Clin Gastroenterol* 2010;44:551–61.
21. Kyne L. Clostridium difficile—beyond antibiotics. *N Engl J Med* 2010; 362:264–5.
22. S. Angelberger CL, C. Gratzer, P. Papay, C. Primas, A. Eser, A. Mikulits, C. Dejaco, G. Novacek, H. Vogelsang, W. Reinisch. Fecal transplantation in patients with moderately to severely chronic active ulcerative colitis (UC). *ECCO Conf Abstr* 2012:P374.
23. Rohlke F, Surawicz CM, Stollman N. Fecal flora reconstitution for recurrent Clostridium difficile infection: results and methodology. *J Clin Gastroenterol* 2010;44:567–70.

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