Fecal microbiota transplant in patients with *Clostridium difficile* infection: A systematic review

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BACKGROUND: Fecal microbiota transplantation (FMT) restores a diverse bacterial profile to the gastrointestinal tract and may effectively treat patients with *Clostridium difficile* infection (CDI). The objective of this systematic review was to evaluate the effectiveness of FMT in the treatment of CDI.

METHODS: Ovid MEDLINE, EMBASE, Web of Science, and Cochrane database were used. The authors searched studies with 10 or more patients examining the resolution of symptoms after FMT in patients with CDI. Reviews, letters to the editors, and abstracts were excluded. Participants were patients with CDI. Intervention used was FMT. Quality assessment was performed using the Cochrane risk of bias assessment tool. Results were synthesized using a narrative approach.

RESULTS: Retrospective and uncontrolled prospective cohort studies suggest that FMT is a highly effective therapy for recurrent/refractory CDI, with clinical success rates ranging from 83% to 100%, which is similar to rates published by two randomized controlled trials. Fecal microbiota transplantation may be effectively administered via antegrade (upper gastrointestinal) or retrograde (lower gastrointestinal) routes of delivery. Fecal microbiota transplantation rarely results in major adverse events. However, diarrhea, cramping, and bloating commonly occur and are typically self-limited. Most studies were uncontrolled retrospective studies.

CONCLUSION: Fecal microbiota transplantation should be considered in patients with recurrent episodes of mild to moderate CDI who have failed conventional antimicrobial therapy. There is insufficient evidence to recommend FMT for the treatment of severe CDI. (*J Trauma Acute Care Surg.* 2016;81: 756–764. Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.)

LEVEL OF EVIDENCE: Systematic review, level III.

KEY WORDS: *Clostridium difficile*; colitis; fecal transplant.

Diseases of the colon are increasingly associated with the development of a potentially pathogenic biome of intestinal flora. Dysbiosis of the normal intestinal flora from antibiotic use,[1,2] environmental factors,[3] and/or diet[4] has been implicated in the pathogenesis of *Clostridium difficile* infection (CDI). Fecal microbiota transplantation (FMT) effectively restores a diverse bacterial profile to the colon[5–7] and may provide a potential therapeutic option in treating CDI.

Fecal microbiota transplantation was described more than 1,700 years ago to treat poisoning and diarrhea.[8] Arguably the first contemporary clinical fecal transplantation to treat colonic disease was introduced by the surgical scientist Ben Eiseman in 1958.[9] Four patients with life-threatening refractory colitis were treated with fecal enemas, and all patients had a complete clinical response. Fecal microbiota transplantation was slow to gain acceptance, however, until van Nood et al.[10] published a randomized controlled trial (RCT) in 2013 demonstrating remarkable efficacy compared with vancomycin in patients with recurrent CDI. Since this landmark study, multiple studies have been published on the utilization of FMT for CDI.

An understanding of the current role of FMT for patients referred for consideration of surgical resection of the colon for CDI is essential because it is possible that these patients may benefit from FMT and avoid a colectomy. The objective of this review is to provide a systematic review of the efficacy of FMT for patients with CDI.

METHODS

A systematic review was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) guidelines.[11] No protocol was used for this systematic review, and it was not prospectively registered.

Search Strategy

A literature search using Ovid MEDLINE, EMBASE, Web of Science, and Cochrane database was conducted by a librarian (B.H.) for communications that were published between January 1, 2005, and November 1, 2015. The search strategies included the following concepts: "fecal transplant," "Crohn's disease," "ulcerative colitis," "*Clostridium difficile*," and "inflammatory bowel disease." We excluded studies that evaluated the efficacy of FMT to control inflammation in patients with inflammatory bowel disease (IBD) alone. However, we included IBD patients with CDI in our search strategy. Multiple subject headings (including MeSH [Medical Subject

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Headings] terms in MEDLINE and Emtree terms in EMBASE) and text words were used to identify each concept and develop the search strategies.

Study Selection and Quality Assessment

Titles, abstracts, and articles were independently reviewed by two investigators (H.B.M., B.C.C.). Primary studies were included if they included the following: human subjects of any age with CDI, compared FMT with standard care or reported efficacy/effectiveness outcomes of FMT, and had at least 10 patients in the study. Articles were required to be primary literature. Reviews, letters to the editors, and abstracts were excluded.

Quality assessment of the RCTs was performed independently by two authors (B.C.C., J.D.V.) using the Cochrane Risk of Bias Assessment Tool.[12] We did not assess the quality of the cohort studies included in this review because most studies lacked a control group, and even well conducted studies would be rated as having a high risk of bias.

Data Extraction and Outcomes

Study characteristics including study design, number of patients, and indication for FMT were recorded. Patient characteristics including age, sex, diagnosis of IBD (ulcerative colitis or Crohn disease), number of episodes of CDI, concurrent use of antibiotics and/or medications and FMT, and time from onset of symptoms to FMT were recorded. Method of FMT including delivery method, donor relation, stool type, and amount of stool were recorded. Clinical outcomes recorded in patients with CDI included definition of clinical cure, overall rate of clinical cure, recurrence of symptoms, minor and major adverse events, all-cause mortality, and disease-specific mortality.

Data Synthesis and Analysis

Data extracted and quality assessment results were synthesized using a narrative approach.

RESULTS

Our literature search yielded 1,730 abstracts/titles, and after exclusion of duplicates, 1,035 articles remained. We excluded an additional 951 articles after abstract review that did not meet our inclusion criteria and performed full-text reviews of 84 articles; of those, we excluded 55 articles. Twenty-nine studies evaluating FMT for recurrent CDI were included in this review: two RCTs,[10,13] four prospective uncontrolled cohort studies,[14–17] and 23 retrospective studies[8,18–39] (Fig. 1). Publication dates

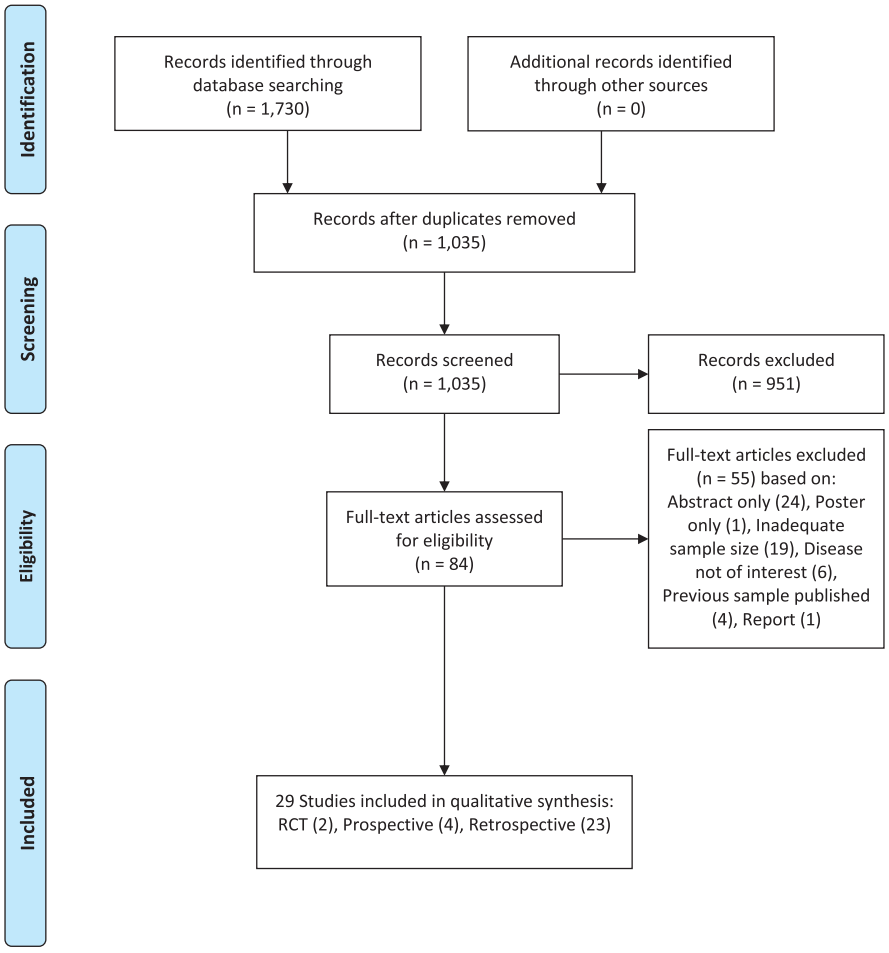

Figure 1. Flow diagram of systematic review of articles included in this review.

TABLE 1. Randomized Controlled Trials Included in Review for Treatment of Recurrent CDI

RCTs	van Nood et al. 2013[10]	Cammarota et al. 2015[13]
Age, y	Mean, 73 (SD, 13)	Median, 71 (range, 29–89)∞
Male sex	8 (50)	8 (40)
CDI definition	Diarrhea* AND positive toxin	Diarrhea* AND positive toxin
Inclusion criteria	(1) ≥18 y	(1) ≥18 y
	(2) Life expectancy >3 mo	(2) Life expectancy >3 mo
	(3) 1 Relapse after antibiotics**	(3) 1 Relapse after antibiotics**
Exclusion criteria	(1) Chemotherapy	(1) Chemotherapy
	(2) HIV infection	(2) HIV infection
	(3) Chronic steroid use	(3) Chronic steroid use
	(4) Pregnancy	(4) Pregnancy
	(5) Other antibiotic use	(5) Other antibiotic use including fidaxomicin
	(6) ICU admission	(6) ICU admission
	(7) Vasopressor therapy	(7) Vasopressor therapy
		(8) Other infectious causes of diarrhea
Primary endpoint	Resolution of CDI-diarrhea without relapse after 10 wk	Resolution of CDI-diarrhea after 10 wk
Trial arms	Arm 1: FMT (nasoduodenal)†	Arm 1: FMT (colonoscopy)‡
	Arm 2: vancomycin§	Arm 2: vancomycin‖
	Arm 3: vancomycin and lavage¶	
No. of recurrences	Median, 3 (range, 1–5)	NR
FMT donor	Nonrelated	Related and nonrelated
Donor stool type	Fresh	Fresh
Amount stool, g	Mean, 141 (SD, 71)	152 (SD, 32)
Time to FMT	NR	NR
Overall cure	Arm 1: n = 15/16, 94%	Arm 1: n = 18/20, 90%
	Arm 2: n = 4/13, 31%	Arm 2: n = 5/19, 26%
	Arm 3: n = 3/13, 23%	
Recurrence	1 (6)	2 (10)
Minor adverse effects	15 (94)	19 (94)
Major adverse effects	0 (0)	0 (0)
Mortality	0 (0)	2 (10)

Listed as n (%) unless indicated otherwise.
*≥3 Loose or watery stools per day for ≥2 consecutive days or ≥8 loose stools in 48 hours.
**≥10 Days of vancomycin at dose of ≥125 mg four times a day or ≥10 days of metronidazole 500 mg three times a day.
†Initial vancomycin (500 mg orally [PO] three times a day for 4 or 5 days) followed by bowel lavage (4L of polyethylene glycol) on last day of antibiotic treatment followed by FMT via nasoduodenal tube.
‡Vancomycin (125 mg by mouth four times a day for 3 days) followed by bowel lavage (4L polyethylene glycol) on last 1 or 2 days followed by FMT via colonoscopy.
§Standard vancomycin regimen (500 mg PO four times a day for 14 days).
‖Vancomycin 125 mg by mouth four times a day for 10 days, followed by pulse regimen (125–500 mg/d every 2–3 days) for at least 3 weeks.
¶Standard vancomycin (500 mg PO four times a day for 14 days) with bowel lavage on Day 4 or 5.
NR, not recorded.

ranged from 2009 to 2015. The number of patients in each study ranged from 10 to 94, with a total sample size of 969 patients.

RCTs of FMT for CDI

In 2013, van Nood et al.[10] evaluated the efficacy of FMT in patients with recurrent CDI defined as diarrhea (≥3 loose or watery stools per day for at least 2 consecutive days or ≥8 loose stools in 48 hours) and a positive *C. difficile* toxin after at least one course of adequate antibiotic therapy (≥10 days of vancomycin at a dose of ≥125 mg four times per day or ≥10 days of metronidazole at a dose of 500 mg three times per day). Importantly, patients were excluded if they were immunocompromised because of recent chemotherapy, HIV infection with a CD4 count of less than 240, or prolonged use of prednisolone at a dose of at least 60 mg/d. In addition, patients were excluded for pregnancy, use of antibiotics other than for treatment of CDI at baseline, admission to an intensive care unit, or need for vasopressor therapy.

Patients were randomly assigned to one of three treatments: an abbreviated vancomycin regimen (500 mg orally four times per day for 4 or 5 days) followed by bowel lavage and subsequent infusion of donor feces through a nasoduodenal tube (FMT arm), a standard vancomycin regimen (500 mg orally four times per day for 14 days), and a standard vancomycin regimen (500 mg orally four times per day for 14 days) with bowel lavage on Day 4 or 5. The primary endpoint was cure without relapse within 10 weeks after the initiation of therapy, and the secondary endpoint was cure without relapse after 5 weeks. Cure was defined as an absence of diarrhea or persistent diarrhea that could be explained by other causes with three consecutive negative

TABLE 2. Patient Demographics and Study Design of Published Studies of FMT for Recurrent CDI

Study	n	Study Design	Age, y	Male, n (%)	Indication	No. of Recurrent Episodes
Lagier et al., 2015[16]	16	Prospective	84 (66–101)*	2 (12.5)	Ribotype CD027	NR
Fischer et al., 2015[20]	29	Retrospective	65.2 (25–92)*	12 (41)	Severe, complicated	3 (1–12)*
Hirsch et al., 2015[23]	19	Retrospective	61 (26–92)*	6 (31.5)	≥2 Recurrences	4 (2–8)*
Satokari et al., 2015[37]	49	Retrospective	54 (20–88)*	15 (30.6)	≥1 Recurrence	4 (1–12)*
Tvede et al., 2015[38]	55	Retrospective	65.6 (21.1–93.1)**	26 (47.3)	≥2 Recurrences	4 (1–8)*
Kronman et al., 2015[27]	10	Retrospective	5.4 (2.7–10.6)†	4 (40%)	≥3 Recurrences	NR
Zainah et al., 2015[8]	14	Retrospective	73.4 (52–92)*	5 (35.7)	Severe or ≥2 recurrences	NR
Costello et al., 2015[18]	20	Retrospective	69 (43–77)†	NR	≥1 Recurrence	3 (2–4)†
Youngster et al., 2014[17]	20	Prospective	64.5 (11–89)**	11 (55)	≥3 Recurrences	3 (2–6)**
Dutta et al., 2014[15]	27	Prospective	64.5 (18–89)*	5 (18.5)	≥3 Recurrences	NR
Emanuelsson et al., 2014[19]	23	Retrospective	69 (25–99)**	4 (17.4)	≥1 Recurrence	3 (1–5)**
Kelly et al., 2014[26]	80	Retrospective	53 (20–88)*	42 (52%)	Recurrent, severe, refractory, complicated	NR
Lee et al., 2014[28]	94	Retrospective	71.8 (24–95)*	41 (43.6)	≥1 Recurrence	2.1 (1–4)*
Ray et al., 2014[33]	20	Retrospective	62 (27–89)*	4 (20)	≥2 Recurrences or severe	3.2 (1–8)*
Russell et al., 2014[36]	10	Retrospective	9.6 (1–19)*	6 (60)	≥3 Recurrences	3.7 (3–7)*
Patel et al., 2013[31]	31	Retrospective	61.2 ± 19.3	14 (45.2)	≥2 Recurrences	4 (2–7)*
Rubin et al., 2013[35]	74	Retrospective	63 (6–94)**	26 (35)	≥2 Recurrences	NR
Pathak et al., 2013[32]	12	Retrospective	71.9 (37–92)*	4 (33)	≥1 Recurrence	NR
Brandt et al., 2012[14]	77	Prospective	65 (22–87)*	21 (27)	≥2 Recurrences	5 (2–15)*
Jorup-Ronstrom et al., 2012[24]	32	Retrospective	75 (27–94)**	12 (37.5)	≥1 Recurrence	NR
Kelly et al., 2012[25]	26	Retrospective	59 (19–86)*	2 (7.7)	≥3 Recurrences	NR
Mattila et al., 2012[30]	70	Retrospective	73 (22–90)*	28 (40)	≥1 Recurrence	3.5 (1–12)*
Hamilton et al., 2012[22]	43	Retrospective	59 ± 21	12 (27.9)	≥2 Recurrences	5.9 ± 3.3
Garborg et al., 2010[21]	39	Retrospective	75 (53–94)*	19 (47.5)	≥1 Recurrence	NR
Rohlke et al., 2010[34]	19	Retrospective	49 (29–82)*	2 (10.5)	≥3 Recurrences	NR
Yoon and Brandt, 2010[39]	12	Retrospective	66 (30–86)*	3 (25)	≥1 Recurrence	NR
MacConnachie et al., 2009[29]	15	Retrospective	66 (30–86)*	1 (6.7)	≥3 Recurrences	4 (37)**

Values are n (%) or mean ± SD.
*Mean (range).
**Median (range).
†Median (interquartile range).
NR, not recorded.

stool tests for *C. difficile* toxin, and relapse was defined as diarrhea with a positive stool test for *C. difficile* toxin.

This trial was terminated early because most patients in both control groups had high failure rates. Of the 16 patients in the FMT arm, 13 (81%) had resolution of CDI diarrhea after a single infusion. The remaining three patients received a second infusion with feces from a different donor, and two were subsequently cured for an overall cure rate of 94%. Fecal microbiota transplantation was statistically superior in treating recurrent CDI compared with those receiving vancomycin alone (n = 4, 31%; $p < 0.01$) and vancomycin with bowel lavage (n = 3, 23%; $p < 0.01$). Five weeks after the initiation of therapy, there was a recurrence of CDI in 1 (6%) of 16 patients in the FMT arm, 8 (62%) of 13 in the vancomycin-alone group, and 7 (54%) of 13 in the group receiving vancomycin with bowel lavage. Off-protocol FMT was given to 18 patients who had a relapse after initial antibiotic treatment, and 15 patients (83%) were cured.

Diarrhea (94%), cramping (31%), and belching (19%) were common immediately after infusion and resolved within 3 hours without further treatment. No deaths or other adverse events related to study treatment were reported in the FMT arm. This trial was open label, and allocation concealment was not described, but it otherwise had a low risk of bias (Table 1).

More recently, Cammarota et al.[13] performed an open-label RCT and evaluated the efficacy of FMT via colonoscopy in patients with recurrent CDI with similar inclusion/exclusion criteria as van Nood et al.[10] detailed in Table 1. Patients were randomized into two groups: a short regimen of oral vancomycin (125 mg by mouth four times a day for 3 days), followed by bowel cleansing on Day 2 or 3, followed by one or more FMT via colonoscopy (FMT arm) or treatment with oral vancomycin alone 125 mg by mouth four times daily for 10 days, followed by a pulse regimen (125–500 mg/d every 2–3 days) for at least 3 weeks. Patients who developed recurrent CDI after the first fecal infusion were given a second FMT within 1 week. However, after the first two patients with pseudomembranous colitis (PMC) died, this part of the protocol was amended, and all subsequent patients with PMC underwent repeated FMT every 3 days until resolution of colitis.

The primary endpoint was resolution of diarrhea at 10 weeks, and the secondary endpoint was toxin negative without recurrent CDI at 5 and 10 weeks after the end of the treatments. Cure was defined as the disappearance of diarrhea or

TABLE 3. Characteristics of FMT Procedures in Studies of FMT for Recurrent CDI

Study	Delivery	Donor (Nonrelated, Related)	Stool Type	Amount Stool, g	Concurrent Antibiotics and FMT	Time to FMT
Lagier et al., 2015[16]	NGT	Both	Fresh	30	Yes	NR
Fischer et al., 2015[20]	Colonoscopy	Both	Fresh	50–200	Yes	NR
Hirsch et al., 2015[23]	Capsule	Nonrelated	Frozen	2.3	No	NR
Satokari et al., 2015[37]	Colonoscopy	Both	Both	30	No	42–360
Tvede et al., 2015[38]	Enema	NR	Frozen	NR	No	154.5 d (33–532)*
Kronman et al., 2015[27]	NGT	Both	NR	30	No	250 (90–541)**
Zainah et al., 2015[8]	NGT (93%), colonoscopy (7%)	Both	Fresh	30–50	No	NR
Costello et al., 2015[18]	Colonoscopy (95%), push enteroscopy (5%)	Nonrelated	Frozen	30	No	NR
Youngster et al., 2014[17]	Capsule	Nonrelated	Frozen	48	No	NR
Dutta et al., 2014[15]	Simultaneous enteroscopy and colonoscopy	Both	Fresh	25–30	No	12 mo (2.5–27mo)**
Emanuelsson et al., 2014[19]	Enema	Related	Fresh	50	No	5 mo (1–16 mo)**
Kelly et al., 2014[26]	Colonoscopy	NR	NR	NR	NR	NR
Lee et al., 2014[28]	Enema	NR	NR	NR	Yes	NR
Ray et al., 2014[33]	Colonoscopy	Both	Fresh	NR	No	49.6 (2–192 wk)*
Russell et al., 2014[36]	NGT (20%), colonoscopy (80%)	Related	Fresh	30–40	No	NR
Patel et al., 2013[31]	Colonoscopy	Both	Fresh	115 (18–397)**	No	340 d (18–2205 d)**
Rubin et al., 2013[35]	NGT (85.3%), PEG (5.3%), endoscope (9.4%)	Related	Fresh	30	No	206 d (51–1282 d)
Pathak et al., 2013[32]	Colonoscopy (91.7%), NGT (8.3%)	Both	Fresh	6–8 tbsp	No	NR
Brandt et al., 2012[14]	Colonoscopy	Both	Fresh	6 tbsp	No	11 (1–28 mo)
Jorup-Ronstrom et al., 2012[24]	Rectal catheter (84.4%), colonoscopy (15.6%)	Nonrelated	Fresh	NR	No	NR
Kelly et al., 2012[25]	Colonoscopy	Both	Fresh	6–8 tbsp	No	12.6 (4–84 mo)*
Mattila et al., 2012[30]	Colonoscopy	Both	Fresh	20–30 mL	No	133 (46–360 d)*
Hamilton et al., 2012[22]	Colonoscopy	Both	Both	50	No	NR
Garborg et al., 2010[21]	EGD (95%), colonoscopy (5%)	Both	Fresh	50–100	No	NR
Rohlke et al., 2010[34]	Colonoscopy	Both	Fresh	NR	No	NR
Yoon and Brandt, 2010[39]	Colonoscopy	Both	Fresh	NR	No	NR
MacConnachie et al., 2009[29]	NGT	Nonrelated	Fresh	30	No	NR

*Mean (range).
**Median (range).
NR, not recorded; NGT, nasogastric tube; EGD, esophagogastroduodenoscopy.

persistent diarrhea explained by other causes with two negative stool tests for *C. difficile* toxin. Recurrence was defined as diarrhea (≥3 loose or watery stools per day for ≥2 consecutive days or ≥8 loose stools in 48 hours) unexplainable by other causes, with or without a positive stool toxin within 10 weeks from the end of therapy.

This study was stopped after a 1-year interim analysis demonstrated that 18 (90%) of 20 patients treated with FMT achieved a statistically higher resolution of CDI diarrhea compared with only 5 (26%) of 19 patients in the vancomycin group ($p < 0.0001$). Notably, seven patients in the FMT arm had PMC. The first two patients with PMC failed initial FMT requiring a second FMT within a week but ultimately failed treatment and died of CDI-related clinical complications. However, since modifying the protocol in patients with PMC to receive FMT every 3 days until resolution of colitis, all five subsequent patients with PMC were cured. Among the failures in the vancomycin group, the median time to recurrence was 10 days (range, 4–21 days) and two patients died of CDI-related complications.

Similar to patients treated in the van Nood et al. protocol,[10] the majority of patients in the FMT arm experienced diarrhea (94%) and bloating/cramping (60%) that resolved without intervention within 12 hours. No adverse events were reported in the vancomycin group that could be attributed to vancomycin. Overall, the study was of moderate risk of bias as the study was open label, allocation concealment was not described, and it was unclear if there was an additional selection bias as patients in the vancomycin group did not undergo colonoscopy to determine how many patients had PMC (Table 1).

Cohort Studies of FMT for CDI

Patient Characteristics

The age of patients ranged from 2 to 101 years old, and 327 (36.4%) patients were male. The number of recurrent episodes of CDI prior to FMT ranged from 1 to 15. Seven studies[14,17,22,23,31,35,36] required at least two episodes, and five studies[15,16,25,27,29] required at least three episodes[15,16,25,27,29]

TABLE 4. Outcomes for CDI Patients Following FMT

Study	Clinical Cure Definition	Overall Cure	Recurrence	Minor AE	Major AE	CDI-Associated Mortality
Lagier et al., 2015[16]	NR	NR	16 (37.5)	24 (72)	1 (6.3)*	0 (0)
Fischer et al., 2015[20]	Resolution of diarrhea, no further need of anti-CDI therapy, avoidance of colectomy, discharge from hospital at 30 d	27 (93)	NR	NR	NR	3 (10.3)
Hirsch et al., 2015[23]	Resolution of diarrhea without relapse at 90 d	17 (89)	2 (10.5)	5 (26.3)	0 (0)	0 (0)
Satokari et al., 2015[37]	Resolution of symptoms at 12 wk	25 (96)	4 (8.2)	2 (4.1)	0 (0)	1 (2.0)
Tvede et al., 2015[38]	Resolution of diarrhea without relapse at 30 d	35 (63.6)	20 (36.4)	8 (17.4)	0 (0)	1 (1.8)
Kronman et al., 2015[27]	Resolution of symptoms	9 (90%)	1 (10)	5 (50)	0 (0)	0 (0)
Zainah et al., 2015[8]	<3 Loose bowel movements a day for 2 consecutive days after FMT and no further need for CDI therapy on Day 7	11 (79)	0 (0)	NR	NR	0 (0)
Costello et al., 2015[18]	Resolution of diarrhea and/or absence of toxin in stool polymerase chain reaction after 3 mo	19 (95)	3 (15)	NR	NR	0 (0)
Youngster et al., 2014[17]	Resolution of diarrhea while not receiving antibiotics for CDI without relapse within 8 wk	19 (95)	1 (5%)	6 (30)	0 (0)	0 (0)
Dutta et al., 2014[15]	Resolution of diarrhea and disappearance of stool toxin	27 (100)	NR	8 (29.6)	0 (0)	0 (0)
Emanuelsson et al., 2014[19]	Sustained resolution of symptoms without recurrence at 3 mo	16 (69.6)	2 (8.7)	NR	NR	NR
Kelly et al., 2014[26]	Absence of diarrhea, or marked reduction without need for further CDI therapy at 12 wk	70 (89%)	NR	3 (3.8)	12 (15)**	1 (1.3)
Lee et al., 2014[28]	Clinical resolution at 6 mo	81 (86.2)	NR	9 (10)	0 (0)	0 (0)
Ray et al., 2014[33]	Negative toxin stool at 3 mo	20 (100)	0 (0)	5 (25)	0 (0)	NR
Russell et al., 2014[36]	NR	9 (90)	NR	6 (60)	0 (0)	NR
Patel et al., 2013[31]	Resolution of diarrhea	22 (71)	3 (9.7)	0 (0)	1 (3.0)†	0 (0)
Rubin et al., 2013[35]	Resolution of diarrhea without recurrence at 60 d	59 (79)	16 (21.3)	0 (0)	0 (0)	0 (0)
Pathak et al., 2013[32]	Resolution of diarrhea, fall in white blood cell count, absence of fever and improvement in vitals	12 (100)	1 (8.3)	0 (0)	0 (0)	1 (8.3)
Brandt et al., 2012[14]	Resolution of symptoms without recurrence at 90 d	70 (91)	15 (19.5)	0 (0)	0 (0)	0 (0)
Jorup-Ronstrom et al., 2012[24]	No relapse	22 (69)	2 (9.1)	0 (0)	0 (0)	NR
Kelly et al., 2012[25]	No recurrence of CDI symptoms (diarrhea, fever, abdominal pain)	24 (92%)	2 (7.7)	3 (11.5)	0 (0)	NR
Mattila et al., 2012[30]	Resolution of symptoms at 12 wk	66 (94.3)	4 (5.7)	0 (0)	0 (0)	3 (4.3)
Hamilton et al., 2012[22]	Resolution of diarrhea and negative stool test at 2 mo	41 (95.3)	6 (14.0)	14 (33.3)	0 (0)	NR
Garborg et al., 2010[21]	No further contact with clinic due to CDI symptoms within 80 d	33 (83)	NR	0 (0)	0 (0)	3 (7.7)
Rohlke et al., 2010[34]	No recurrent symptoms	19 (100)	3 (15.8)	NR	NR	NR
Yoon and Brandt, 2010[39]	Absence of diarrhea, cramps, and fever within 3–5 d of FMT	12 (100)	NR	0 (0)	0 (0)	NR
MacConnachie et al., 2009[29]	Resolution of symptoms	11 (73)	1 (6.7)	0 (0)	0 (0)	NR

Values are presented as n (%).
*Acute cardiac insufficiency.
**Fever, diarrhea, encephalopathy, and pancytopenia; abdominal pain post-FMT colonoscopy; IBD flair; cerebrovascular accident; colectomy related to IBD; fall and hip fracture; influenza B and non-CDI diarrhea; catheter line infection; two deaths.
†Microscopic perforation during colonoscopic biopsy that resolved with conservative management.
AE, adverse event; f/u, follow-up; NR, not recorded.

to be included. Eight studies included 66 patients with IBD,[20,22,26,27,31–33,36] one study excluded patients with IBD,[39] and the remaining studies did not specify IBD as a comorbidity. The time from diagnosis of CDI to FMT ranged from 18 days to 16 years, and follow-up ranged from 13 days to 16 years (Table 2).

FMT Procedure

Studies included both related and nonrelated,[8,13–16,20–22,25,27,30–34,37,39] related only,[19,35,36] and nonrelated-only donors[10,17,23,24] (Table 3). Both fresh[8,10,13–16,19–21,24,25,29,31,34,35,39] and frozen[17,18,23] stool donations were used. The CDI cure rate reported for FMT performed with frozen stool was equivalent to that reported for fresh stool, ranging from 90% to 100%.[18,22,37]

The route of administration of FMT differed across studies. These included administration via the upper gastrointestinal tract (nasogastric/nasoduodenal tube,[8,10,16,27,29,35,36] esophagogastroduodenoscopy,[18,21,35] capsules,[17,23] lower gastrointestinal tract (colonoscopy[8,13,14,18,20–22,24–26,31–34,36,37] and rectal catheter/enema[19,24,28]), and simultaneous upper and lower gastrointestinal tracts.[15]

TABLE 5. Summary of Key Findings in the Use of FMT for the Treatment of CDI

- Fecal microbiota transplant should be considered in patients with recurrent episodes of mild to moderate CDI who have failed conventional antimicrobial therapy.
- There is insufficient evidence to recommend FMT for the treatment of severe CDI.
- Fecal microbiota transplant may be effectively administered via antegrade (upper gastrointestinal) or retrograde (lower gastrointestinal) routes of delivery.
- Fecal microbiota transplant rarely results in major adverse events. However, diarrhea, cramping, and bloating commonly occur and are typically self-limited.

The number of FMTs reported ranged from 1 to 10 transplants, and the most common indication for a repeat FMT was failure to resolve CDI with a single FMT or a recurrence of CDI. The amount of fecal supernatant infused during each FMT ranged from 25 to 397 g; the most common amount reported was 30 to 50 g of stool.

Outcomes

The definition of clinical cure was heterogeneous among the studies included and is reported in Table 4. Reported rates of resolution of CDI after a single FMT ranged from 48% to 100%. Success rate improved from 48% to 95% to 83% to 100% on subsequent FMT.[10,13,14,17,18,20–23,26,28,32,34] Overall cure rate was greater than 90% in 18 studies[10,13–15,17,18,20,22,25–27,31–34,36,37,39] and 100% in 7 studies.[15,18,27,32–34,39] In the subpopulation of 66 patients with IBD, FMT successfully treated CDI in 94% of patients (n = 62/66).[22,26,27,31–33,36] Among the failures, one patient was successfully treated with vancomycin,[36] one patient failed a second FMT procedure without follow-up,[31] and the remaining two patients required colectomy.[26] Success rates did not appear to differ significantly depending on route of administration of FMT. Importantly, FMT capsules have success rates of 89% to 90%.[17,23] Recurrence rates ranged from 0% to 36%; most often, this was attributed to the need for additional antibiotics for a non–CDI-related infection.[10,14,22,23,27,29,30,32,34,36–38]

Adverse Events

Minor adverse events were defined as fevers, diarrhea, and abdominal pain that were self-limiting. The frequency of minor adverse was variable but ranged from zero[18,29,32,35,39] to greater than 90% of patients.[10,13] Major adverse events were reported to occur in 0%,[10,13,15,17,18,22,23,28,30,32,35,37,39] 1.8%,[38] 3.2%,[31] 6.3%,[16] and 15%[26] of patients (Table 4). In the subpopulation of patients with IBD, 17% (n = 11/66) experienced an adverse event including an IBD flare (n = 7), bloating/discomfort (n = 1), hip pain (n = 1), pertussis (n = 1), and nausea (n = 1).[22,26,27,31–33,36] Although it is unclear if the IBD flare was the result of the FMT procedure, two patients ultimately required a colectomy.

Mortality

The rate of mortality associated with FMT ranged from 0% to 10%[8,10,13,18,20,23,26,28,30–32,35,37,38] (Table 4). Mortality seemed to be associated with patient comorbidities and CDI disease severity at time of FMT as opposed to the risk of the procedure itself; however, the design of the studies was inadequate to fully evaluate this association. Notably, early FMT (defined as receiving FMT within the first week of diagnosis) was associated with reduced mortality at 1 month in patients with *C. difficile* ribotype 027–associated diarrhea (6% vs. 56%), and early FMT was the only independent predictor of survival[16] (Table 5).

DISCUSSION

Altered microbiota and decreased diversity of colonic microflora that normally limits expansion of *C. difficile* has been hypothesized to be a key factor in the development of CDI.[40,41] Currently, standard treatment of CDI is antibiotic therapy; however, recurrence of infection occurs in 15% to 35% of patients within 3 months of initial treatment and is typically caused by regrowth of vegetative *C. difficile* from residual spores that are resistant to antibiotic treatments.[42,43] Fecal microbiota transplantation may restore a normal bacterial profile to the colon and be of therapeutic benefit.[5–7] In this systematic review of the published literature, we provide an update on the efficacy of FMT in the treatment for recurrent/refractory CDI using the most recent data available from 27 large case series and 2 RCTs.

Several retrospective and prospective cohort studies suggest that FMT is a highly effective therapy for CDI with a success rate of 83% to 100%. These results have been confirmed in two recent RCTs. In the landmark trial by van Nood et al.,[10] FMT cured 94% of patients versus 23% of patients receiving vancomycin alone. Similarly, Cammarota et al.[13] reported a 90% success rate in patients receiving FMT compared with 26% of patients receiving vancomycin alone. However, patient selection is critical. In both RCTs, patients with severe disease requiring admission to an intensive care unit and/or vasopressor therapy were excluded. Although case reports suggest that FMT is safe and effective in treating severe CDI, published evidence is very limited, and FMT should not be used outside an institutional review board–approved clinical trial in this setting.[44–47]

Patients with IBD are at an elevated risk for acquiring CDI,[48–52] and concomitant use of immunosuppressive medications in patients with CDI is associated with an increased mortality.[53,54] In the subpopulation of 66 patients with IBD included in this review, the overall CDI cure rate of FMT was 94%. Among the failures, two patients (3%) ultimately required a colectomy. Based on limited evidence, FMT appears to be safe and effective for IBD complicated by CDI.

Although the FMT procedure itself is not yet standardized, findings from this review suggest that upper and lower gastrointestinal routes of administration have similar efficacy, and the preferred method may vary with the clinical condition. In frail or severely ill patients, less invasive methods such as a nasoduodenal tube may be considered to minimize the risk of sedation and perforation associated with endoscopic methods of infusion. In addition, orally administered capsules appear to be effective.[17,23] However, a colonoscopic approach has the advantage of allowing visualization of the colonic mucosa and may be preferred in patients with a clinical suspicion of IBD. Frozen stool suspensions may simplify FMT by providing ready-to-use

suspensions.[18,37] Randomized controlled trials are needed to better define the optimal stool source and processing, volume of stool infused, route of administration, and the number and frequency of transfusions needed for maximal efficacy.

Based on the reviewed data, FMT should be considered in patients with mild- or moderate-severity CDI refractory to antibiotic treatment. Patients with severe CDI, or CDI complicated by systemic compromise, peritonitis, megacolon, or colon perforation, should not be considered for FMT.[20] In general, these patients should be advised to undergo total abdominal colectomy with ileostomy.[55] In select cases of severe CDI that is refractory to medical therapy but not complicated by megacolon, perforation, or peritonitis, creation of a loop ileostomy with antibiotic lavage of the colon may be considered as an alternative to colectomy.[56]

Although this review provides up-to-date data regarding the efficacy of FMT in patients with CDI, we acknowledge that the study data that are presented have limitations. All but two of the studies were cohort studies, performed either retrospectively or as uncontrolled prospective studies. Both RCTs were open label, and the methods of allocation concealment were not described. In addition, there was significant heterogeneity among the studies in patient demographics, inclusion criteria, measurement of disease severity, duration of disease, time from diagnosis to FMT, methods of FMT, and definitions of clinical resolution, which limits comparison across studies and analysis of aggregate data. Furthermore, there are likely numerous negative studies in this area that have not been published, resulting in a publication bias.

In conclusion, strong RCT evidence supports the use of FMT for recurrent/refractory CDI and should be considered if antibiotic treatments have failed. There is insufficient evidence to support the use of FMT in patients with severe/complicated CDI.

AUTHORSHIP

All authors contributed to study design. B.C., H.B.M., D.M.O., B.H., and J.D.V. conducted the literature search. B.C., H.B.M., D.M.O., A.P.M., and B.H. performed data collection. B.C., H.B.M., D.M.O., A.P.M., M.E.G., and J.D.V. contributed to data analysis and interpretation. B.C., H.B.M., D.M.O., A.P.M., M.E.G., and J.D.V. wrote the manuscript, which all authors critically revised.

DISCLOSURE

The authors declare no conflicts of interest.

REFERENCES

1. Leffler DA, Lamont JT. *Clostridium difficile* infection. *N Engl J Med*. 2015; 372(16):1539–1548.
2. Scribano ML, Prantera C. Antibiotics and inflammatory bowel diseases. *Dig Dis*. 2013;31(3–4):379–384.
3. Ananthakrishnan AN. Environmental risk factors for inflammatory bowel diseases: a review. *Dig Dis Sci*. 2015;60(2):290–298.
4. Albenberg LG, Wu GD. Diet and the intestinal microbiome: associations, functions, and implications for health and disease. *Gastroenterology*. 2014; 146(6):1564–1572.
5. Broecker F, Kube M, Klumpp J, Schuppler M, Biedermann L, Hecht J, Hombach M, Keller PM, Rogler G, Moelling K. Analysis of the intestinal microbiome of a recovered *Clostridium difficile* patient after fecal transplantation. *Digestion*. 2013;88(4):243–251.
6. Seekatz AM, Aas J, Gessert CE, Rubin TA, Saman DM, Bakken JS, Young VB. Recovery of the gut microbiome following fecal microbiota transplantation. *MBio*. 2014;5(3):e00893–14.
7. Weingarden AR, Chen C, Bobr A, Yao D, Lu Y, Nelson VM, Sadowsky MJ, Khoruts A. Microbiota transplantation restores normal fecal bile acid composition in recurrent *Clostridium difficile* infection. *Am J Physiol Gastrointest Liver Physiol*. 2014;306(4):G310–G319.
8. Zainah H, Hassan M, Shiekh-Sroujieh L, Hassan S, Alangaden G, Ramesh M. Intestinal microbiota transplantation, a simple and effective treatment for severe and refractory *Clostridium difficile* infection. *Dig Dis Sci*. 2015; 60(1):181–185.
9. Eiseman B, Silen W, Bascom GS, Kauvar AJ. Fecal enema as an adjunct in the treatment of pseudomembranous enterocolitis. *Surgery*. 1958;44(5): 854–859.
10. van Nood E, Vrieze A, Nieuwdorp M, Fuentes S, Zoetendal EG, de Vos WM, Visser CE, Kuijper EJ, Bartelsman JF, Tijssen JG, Speelman P, Dijkgraaf MG, Keller JJ. Duodenal infusion of donor feces for recurrent *Clostridium difficile*. *N Engl J Med*. 2013;368(5):407–415.
11. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg*. 2010;8(5):336–341.
12. Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.handbook.cochrane.org. Accessed January 26, 2016.
13. Cammarota G, Masucci L, Ianiro G, Bibbo S, Dinoi G, Costamagna G, Sanguinetti M, Gasbarrini A. 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.
14. Brandt LJ, Aroniadis OC, Mellow M, Kanatzar A, Kelly C, Park T, Stollman N, Rohlke F, Surawicz C. Long-term follow-up of colonoscopic fecal microbiota transplant for recurrent *Clostridium difficile* infection. *Am J Gastroenterol*. 2012;107(7):1079–1087.
15. Dutta SK, Girotra M, Garg S, Dutta A, von Rosenvinge EC, Maddox C, Maddox C, Song Y, Bartlett JG, Vinayek R, Fricke WF. Efficacy of combined jejunal and colonic fecal microbiota transplantation for recurrent *Clostridium difficile* Infection. *Clin Gastroenterol Hepatol*. 2014;12(9): 1572–1576.
16. Lagier JC, Delord M, Million M, Parola P, Stein A, Brouqui P, Raoult D. Dramatic reduction in *Clostridium difficile* ribotype 027–associated mortality with early fecal transplantation by the nasogastric route: a preliminary report. *Eur J Clin Microbiol Infect Dis*. 2015;34(8):1597–1601.
17. 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*. 2014;312(17):1772–1778.
18. Costello SP, Conlon MA, Vuaran MS, Roberts-Thomson IC, Andrews JM. Faecal microbiota transplant for recurrent *Clostridium difficile* infection using long-term frozen stool is effective: clinical efficacy and bacterial viability data. *Aliment Pharmacol Ther*. 2015;42(8):1011–1018.
19. Emanuelsson F, Claesson BE, Ljungström L, Tvede M, Ung KA. Faecal microbiota transplantation and bacteriotherapy for recurrent *Clostridium difficile* infection: a retrospective evaluation of 31 patients. *Scand J Infect Dis*. 2014;46(2):89–97.
20. Fischer M, Sipe BW, Rogers NA, Cook GK, Robb BW, Vuppalanchi R, Rex DK. Faecal microbiota transplantation plus selected use of vancomycin for severe-complicated *Clostridium difficile* infection: description of a protocol with high success rate. *Aliment Pharmacol Ther*. 2015;42(4):470–476.
21. Garborg K, Waagsbo B, Stallemo A, Matre J, Sundoy A. Results of faecal donor instillation therapy for recurrent *Clostridium difficile*–associated diarrhoea. *Scand J Infect Dis*. 2010;42(11–12):857–861.
22. Hamilton MJ, Weingarden AR, Sadowsky MJ, Khoruts A. Standardized frozen preparation for transplantation of fecal microbiota for recurrent *Clostridium difficile* infection. *Am J Gastroenterol*. 2012;107(5):761–767.
23. 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;15:191.

24. Jorup-Ronstrom C, Hakanson A, Sandell S, Edvinsson O, Midtvedt T, Persson AK, Norin E. Fecal transplant against relapsing *Clostridium difficile*–associated diarrhea in 32 patients. *Scand J Gastroenterol*. 2012; 47(5):548–552.
25. Kelly CR, de Leon L, Jasutkar N. Fecal microbiota transplantation for relapsing *Clostridium difficile* infection in 26 patients: methodology and results. *J Clin Gastroenterol*. 2012;46(2):145–149.
26. Kelly CR, Ihunnah C, Fischer M, Khoruts A, Surawicz C, Afzali A, Aroniadis O, Barto A, Borody T, Giovanelli A, Gordon S, Gluck M, Hohmann EL, Kao D, Kao JY, McQuillen DP, Mellow M, Rank KM, Rao K, Ray A, Schwartz MA, Singh N, Stollman N, Suskind DL, Vindigni SM, Youngster I, Brandt L. Fecal microbiota transplant for treatment of *Clostridium difficile* infection in immunocompromised patients. *Am J Gastroenterol*. 2014;109(7):1065–1071.
27. Kronman MP, Nielson HJ, Adler AL, Giefer MJ, Wahbeh G, Singh N, Zerr DM, Suskind DL. Fecal microbiota transplantation via nasogastric tube for recurrent *Clostridium difficile* infection in pediatric patients. *J Pediatr Gastroenterol Nutr*. 2015;60(1):23–26.
28. Lee CH, Belanger JE, Kassam Z, Smieja M, Higgins D, Broukhanski G, Kim PT. The outcome and long-term follow-up of 94 patients with recurrent and refractory *Clostridium difficile* infection using single to multiple fecal microbiota transplantation via retention enema. *Eur J Clin Microbiol Infect Dis*. 2014;33(8):1425–1428.
29. MacConnachie AA, Fox R, Kennedy DR, Seaton RA. Faecal transplant for recurrent *Clostridium difficile*–associated diarrhoea: a UK case series. *QJM*. 2009;102(11):781–784.
30. Mattila E, Uusitalo-Seppala R, Wuorela M, Lehtola L, Nurmi H, Ristikankare M, Moilanen V, Salminen K, Seppälä M, Mattila PS, Anttila VJ, Arkkila P. Fecal transplantation, through colonoscopy, is effective therapy for recurrent *Clostridium difficile* infection. *Gastroenterology*. 2012;142(3):490–496.
31. Patel NC, Griesbach CL, DiBaise JK, Orenstein R. Fecal microbiota transplant for recurrent *Clostridium difficile* infection: Mayo Clinic in Arizona experience. *Mayo Clin Proc*. 2013;88(8):799–805.
32. Pathak R, Enuh HA, Patel A, Wickremesinghe P. Treatment of relapsing *Clostridium difficile* infection using fecal microbiota transplantation. *Clin Exp Gastroenterol*. 2013;7:1–6.
33. Ray A, Smith R, Breaux J. Fecal microbiota transplantation for *Clostridium difficile* infection: the Ochsner experience. *Ochsner J*. 2014;14(4):538–544.
34. Rohlke F, Surawicz CM, Stollman N. Fecal flora reconstitution for recurrent *Clostridium difficile* infection: results and methodology. *J Clin Gastroenterol*. 2010;44(8):567–570.
35. Rubin TA, Gessert CE, Aas J, Bakken JS. Fecal microbiome transplantation for recurrent *Clostridium difficile* infection: report on a case series. *Anaerobe*. 2013;19:22–26.
36. Russell GH, Kaplan JL, Youngster I, Baril-Dore M, Schindelar L, Hohmann E, Winter HS. Fecal transplant for recurrent *Clostridium difficile* infection in children with and without inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*. 2014;58(5):588–592.
37. Satokari R, Mattila E, Kainulainen V, Arkkila PE. Simple faecal preparation and efficacy of frozen inoculum in faecal microbiota transplantation for recurrent *Clostridium difficile* infection—an observational cohort study. *Aliment Pharmacol Ther*. 2015;41(1):46–53.
38. Tvede M, Tinggaard M, Helms M. Rectal bacteriotherapy for recurrent *Clostridium difficile*–associated diarrhoea: results from a case series of 55 patients in Denmark 2000–2012. *Clin Microbiol Infect*. 2015;21(1): 48–53.
39. Yoon SS, Brandt LJ. Treatment of refractory/recurrent *C. difficile*–associated disease by donated stool transplanted via colonoscopy: a case series of 12 patients. *J Clin Gastroenterol*. 2010;44(8):562–566.
40. Wilson KH. The microecology of *Clostridium difficile*. *Clin Infect Dis*. 1993; 16(Suppl 4):S214–S218.
41. Chang JY, Antonopoulos DA, Kalra A, Tonelli A, Khalife WT, Schmidt TM, Young VB. Decreased diversity of the fecal microbiome in recurrent *Clostridium difficile*–associated diarrhea. *J Infect Dis*. 2008;197(3):435–438.
42. McFarland LV, Elmer GW, Surawicz CM. Breaking the cycle: treatment strategies for 163 cases of recurrent *Clostridium difficile* disease. *Am J Gastroenterol*. 2002;97(7):1769–1775.
43. Kyne L, Kelly CP. Recurrent *Clostridium difficile* diarrhoea. *Gut*. 2001; 49(1):152–153.
44. You DM, Franzos MA, Holman RP. Successful treatment of fulminant *Clostridium difficile* infection with fecal bacteriotherapy. *Ann Intern Med*. 2008;148(8):632–633.
45. Neemann K, Eichele DD, Smith PW, Bociek R, Akhtari M, Freifeld A. Fecal microbiota transplantation for fulminant *Clostridium difficile* infection in an allogeneic stem cell transplant patient. *Transpl Infect Dis*. 2012;14(6):E161–E165.
46. Trubiano JA, Gardiner B, Kwong JC, Ward P, Testro AG, Charles PG. Faecal microbiota transplantation for severe *Clostridium difficile* infection in the intensive care unit. *Eur J Gastroenterol Hepatol*. 2013;25(2):255–257.
47. Weingarden AR, Hamilton MJ, Sadowsky MJ, Khoruts A. Resolution of severe *Clostridium difficile* infection following sequential fecal microbiota transplantation. *J Clin Gastroenterol*. 2013;47(8):735–737.
48. Ananthakrishnan AN, Issa M, Binion DG. *Clostridium difficile* and inflammatory bowel disease. *Gastroenterol Clin North Am*. 2009;38(4): 711–728.
49. Ananthakrishnan AN, McGinley EL, Binion DG. Excess hospitalisation burden associated with *Clostridium difficile* in patients with inflammatory bowel disease. *Gut*. 2008;57(2):205–210.
50. Nguyen GC, Kaplan GG, Harris ML, Brant SR. A national survey of the prevalence and impact of *Clostridium difficile* infection among hospitalized inflammatory bowel disease patients. *Am J Gastroenterol*. 2008;103(6): 1443–1450.
51. Issa M, Vijayapal A, Graham MB, Beaulieu DB, Otterson MF, Lundeen S, Skaros S, Weber LR, Komorowski RA, Knox JF, Emmons J, Bajaj JS, Binion DG. Impact of *Clostridium difficile* on inflammatory bowel disease. *Clin Gastroenterol Hepatol*. 2007;5(3):345–351.
52. Rodemann JF, Dubberke ER, Reske KA, Seo DH, Stone CD. Incidence of *Clostridium difficile* infection in inflammatory bowel disease. *Clin Gastroenterol Hepatol*. 2007;5(3):339–344.
53. Das R, Feuerstadt P, Brandt LJ. Glucocorticoids are associated with increased risk of short-term mortality in hospitalized patients with *Clostridium difficile*–associated disease. *Am J Gastroenterol*. 2010;105(9):2040–2049.
54. Ben-Horin S, Margalit M, Bossuyt P, Maul J, Shapira Y, Bojic D, Chermesh I, Al-Rifai A, Schoepfer A, Bosani M, Allez M, Lakatos PL, Bossa F, Eser A, Stefanelli T, Carbonnel F, Katsanos K, Checchin D, Miera IS, Chowers Y, Moran GW, European Crohn's and Colitis Organization (ECCO). Combination immunomodulator and antibiotic treatment in patients with inflammatory bowel disease and *Clostridium difficile* infection. *Clin Gastroenterol Hepatol*. 2009;7(9):981–987.
55. Steele SR, McCormick J, Melton GB, Paquette I, Rivadeneira DE, Stewart D, Buie WD, Rafferty J. Practice parameters for the management of *Clostridium difficile* infection. *Dis Colon Rectum*. 2015;58(1):10–24.
56. Neal MD, Alverdy JC, Hall DE, Simmons RL, Zuckerbraun BS. Diverting loop ileostomy and colonic lavage: an alternative to total abdominal colectomy for the treatment of severe, complicated *Clostridium difficile* associated disease. *Ann Surg*. 2011;254(3):423–427; discussion 7–9.