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GI ONCOLOGY (R BRESALIER, SECTION EDITOR)

Clinical Review on the Utility of Fecal Microbiota Transplantation in Immunocompromised Patients

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Abstract

Fecal microbiota transplantation (FMT) represents a promising management modality for *Clostridium difficile* infection (CDI). In immunocompromised patients, FMT is utilized for CDI as well as emerging non-CDI indications such as inflammatory bowel disease and graft versus host disease.

Purpose of Review This review aims to shed light on the safety and efficacy of FMT in immunocompromised patients, including patients suffering for human immunodeficiency virus infection, solid organ and hematopoietic stem cell transplant recipients, cancer patients, and patients on immunosuppressive therapies.

Recent Findings Though the body of evidence concerning the use of FMT in immunocompromised is growing, no clinical trials exist to date.

Summary Present literature weighs in favor of FMT in immunocompromised patients, with an acceptable adverse effect profile and minimal risk of infectious adverse events. Further large scale studies and randomized controlled trials to validate the utility of FMT in immunocompromised individuals will be a welcomed endeavor.

Keywords Fecal microbiota transplantation · Immunosuppression · Solid organ transplant · Hematopoietic stem cell transplant · Adverse events · Aspiration · Infection

Introduction

The human gut microbiome is an intricate microcosm, built by more than 1000 bacterial species that collectively carry 150-fold more genetic material than the human genome [1]. Majority of these bacteria are unculturable anaerobes. This microcosm is thought to play a pivotal role in maintaining homeostasis as well as modulating immune response to inflammation and pathogenic gut microbes. Dysbiosis of the gut microbiome in the current era is predominantly a consequence of antibiotic therapy [2]. This stands particularly true in the setting of *Clostridium difficile* infection (CDI). CDI has been plaguing the healthcare system for the last two decades, growing to become the most common cause of nosocomial diarrhea. The increasing incidence of CDI has also ushered in an era of antibiotic failure for CDI therapy, and cure rates with antibiotic therapy have been on a declining trend. The clinical course of patients that do experience *C. difficile* eradication is further impacted adversely by a 20–30% recurrence rate [3]. In terms of costs, a recent meta-analysis reported that CDI imposes a staggering burden of approximately $6.3 billion in total annual costs (range, $1.97–$7.0 billion) [4•]. This translates into a cost $3400–$16000 for primary CDI and $13,700–$18,000 for rCDI per case [5].

Metronidazole, which itself is a risk factor for the development of CDI, remained the first-line therapy of CDI until recently when guidelines recommended vancomycin or fidaxomicin for 10 days for severe or recurrent CDI [6]. Fidaxomicin received FDA approval citing findings of two randomized controlled trials that revealed comparable cure rates of CDI and less recurrence rates than vancomycin [7,

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8]. Pooled intravenous immunoglobulins have been suggested as an alternative non-antimicrobial strategy to treat rCDI, though robust evidence to support their utility is lacking [9, 10]. Bezlotoxumab, a monoclonal antibody against *C. difficile* toxin B, has been approved by the United States Food and Drug Authority (FDA) for prevention of rCDI [11].

Fecal microbiota transplantation (FMT) entails transfusing homogenized fecal matter into patient's gastrointestinal tract. The administration of FMT is not by any means a novel therapeutic strategy. In fact, this practice reportedly dates back at least 1700 years when it was employed by practitioners of traditional Chinese medicine [12, 13]. In the modern era, the earliest use of FMT was documented in 1958 by Eiseman et al., who administered fecal enemas in four patients with pseudomembranous colitis [14]. The curiosity surrounding FMT was reignited in 2003 when a case series consisting of 18 patients was published [15]. Subsequently, by 2016, more than 600 articles concerning the topic of FMT had been published and indexed in PubMed alone. FDA recently issued a regulation guidance concerning the use of FMT, allowing physicians to perform FMT without an investigational new drug (IND) application to treat resistant and recurrent CDI. This led to widespread acceptance of this treatment modality among patients and physicians alike.

Demystifying the Bugs that Cure

Mechanisms behind the efficacy of FMT in treating disease are complex and likely multifactorial. It is generally accepted that FMT leads to normalization of the gut microbiome composition [61]. This idea stems from data generated by studying patients whose gut microbiome had been annihilated by multiple antibiotics leading to dysbiosis and had consequently propelled them in a never-ending cycle of rCDI [16, 17]. In these patients, FMT led to symptom resolution and cure of rCDI. Normalization of the gut flora has been reported to occur as early as within 24 h of FMT. Studies have suggested that patients who receive FMT may have donor-like gut microbiome composition for months to years after transplantation [18, 19]. Though these findings support the normalization theory, they fail to address the mechanism of disease remission induced by FMT in conditions such as inflammatory bowel disease (IBD), where gut dysbiosis, though an emerging recognized entity, is not known to be as profound as is in the setting of CDI [20]. Additionally, it is difficult to ascertain if the changes in microbiome composition induced by FMT are the key factors that abrogate the gut inflammation. Furthermore, microbiota changes reported in IBD patients after FMT have also been reported after treatment with adalimumab, a TNF-targeted therapy, indicating that the alteration in gut microbiota may be a consequence of decreased inflammation rather than engraftment of donor microbiome [21, 22]. Nonetheless, the efficacy of FMT in the setting of CDI is undeniable, and the mechanisms underlying the usefulness of FMT in the setting of CDI have been well studied.

FMT is thought to directly interact with *C. difficile* along with normalization of the gut microbiome, which is normally home to more than 40 trillion bacteria, leading to an augmentation of immune defenses against *C. difficile* [23, 24]. These include production of mucin and antimicrobial peptides as well as gut epithelial regeneration, which reinstates the disrupted mucosal barrier. Additionally, the diverse gut microbiota compete with *C. difficile* for nutrition and colonization, consequently hampering the virulence capability of *C. difficile* [61]. Furthermore, the host immune defenses mounted by the gut microbiome include induction of secondary bile acids that are inhibitory to the germination of *C. difficile.*

Clostridium difficile Infection and the Immunocompromised Patient

The vulnerability of immunocompromised patients to *C. difficile* infection is increased due to a number of factors [25–28]. The role of humoral immunity in prevention of primary and recurrent CDI is well established. In addition to being at a heightened risk for CDI due to impaired humoral immunity, immunocompromised patients often require antibiotic therapy or prophylaxis, and when hospitalized, are more likely to have a prolonged length of stay, both of which further add to the risk of CDI [1]. Furthermore, hypoalbuminemia is a common finding in immunocompromised patients, which is an additional risk factor for CDI [29, 30]. Generally, patients suffering from a human immunodeficiency virus (HIV) infection, cancer patients, transplant recipients, and patients on corticosteroid or other immunomodulatory therapies are categorized as immunocompromised. However, the risk for CDI may vary with the category of immunosuppression one falls under.

Cancer, Cancer Therapy, and Transplantation

Cancer patients are at high risk of developing CDI due to a myriad of factors, ranging from cancer-induced immune impairment to cancer therapy–associated adverse events and immunosuppression [25]. In the USA, CDI is reported to affect patients with solid as well as hematological malignancies at twice the rate for non-cancer patients, with a pooled hospital-onset CDI rate of 15.8 per 10,000 patient days [31]. Hematological malignancies in particular have been identified as an independent risk factor for CDI [32]. Cancer therapy, in particular chemotherapy, is notorious for damaging the intestinal mucosa and altering the gut microbiota. In the peri-transplant period, myeloablative conditioning is a risk factor for CDI, though infectious diarrhea in this period may be mild and difficult to differentiate from conditioning induced

diarrhea. These patients proceed to undergo hematopoietic stem cell transplantation (HSCT) with subsequent immunosuppression [33]. This subset of patients has been reported to have one of the highest rates (10%) of CDI, which commonly occurs in the early post-transplant period [34]. Allogeneic HSCT infers a higher risk than autologous HSCT. The development of graft versus host disease is also an independent risk factor for the development of CDI. However, CDI in HSCT patients has not been shown to impose a significant mortality burden. Solid organ transplant (SOT) patients are also at a heightened risk of CDI and fulminant colitis as a consequence of CDI [35]. The incidence of CDI among SOT patients varies with the organ type (Table 1). Similar to HSCT, the risk of CDI is highest in the early post-transplant period.

HIV and Autoimmune Disorders

The risk of developing CDI has been reported to be twice that of normal population among HIV-infected patients [36]. CDI used to be among the most common causes of bacterial diarrhea among these patients in the pre-HAART era. The risk was higher among patients who had progressed to acquired immunodeficiency syndrome (AIDS) [37]. With the advent of HAART, a decline in the incidence of CDI among AIDS patients was seen. However, the same was not observed in non-AIDS patients. Additionally, patients with IBD have been found to have a threefold higher incidence of CDI than patients without IBD [38]. Most CDI in IBD patients are confirmed within 48 h of hospitalization, which hints towards a nosocomial origin. Exposure to immunosuppressive and immunomodulatory medications as well as metronidazole has been associated with an increased risk of CDI [39]. In addition, frequent hospitalizations and high comorbidity burden are associated with an increased risk of CDI among patients with IBD.

Role of FMT in the Eradication of CDI in the Immunocompromised Patient

Immunocompromised patients have been excluded from randomized controlled trials of FMT due to a theoretically heightened risk of FMT-associated infectious complications. Though this theoretical risk stemmed from a justified thorough process, recent observational studies concerning the safety and efficacy of FMT in immunocompromised patients have not revealed an increased infection risk among this patient population [40•]. Granted that the level of evidence is inferior to randomized clinical trials, it does set the premise to proceed with generating level-one evidence to support the use of FMT particularly in immunocompromised patients. The procedural risk does not seem to be higher than the general population either. Nonetheless, minimizing the risk of infectious complications in immunocompromised patients undergoing FMT is dependent upon appropriate screening of donor samples. Rigorous screening of donor stool for a variety of bacteria, viruses, and parasites has been previously recommended. Our institutional protocol for donor blood and stool screening accounts for a myriad of pathogens that can lead to serious illness or prolonged hospital course (Table 2).

Our literature review yielded a number of case reports, case series, and observational studies published over the last decade which have shed light on the safety and efficacy of FMT in the setting of immunosuppression (Table 3). The patient population in the larger series was mixed, including SOT or HSCT patients, cancer patients, and patients on immunosuppressive therapy due to an autoimmune disease (majorly IBD) as well as patients infected with HIV. The indication for FMT in majority of the patients was rCDI, though some patients received FMT for graft versus host disease (GVHD) as well as IBD. The efficacy and adverse events of FMT currently reported in the setting of immunosuppression are comparable to those of immunocompetent patients. Serious adverse events, though very low in incidence, seem to be related to the increased infection risk delivery modality instead. In the current body of evidence, two aspirations and one incidence of mucosal tear have been reported among immunosuppressed patients undergoing FMT. Two mortalities have been reported due to pneumonia and aspiration related to colonoscopy [43, 75•] (Table 3). This highlights the need for procedural caution with patients at high risk of aspiration. In regard to infectious complications, the findings weigh in favor of FMT. Although transient fever is frequently reported, only one case of confirmed gastroenteritis post-FMT has been reported among the immunocompromised population. Additionally, it is not entirely clear whether this was a consequence of FMT, endoscopic instrumentation, or a contagious spread from healthcare personnel. Hospitalizations after FMT are also minimal and are secondary to commonly reported transient adverse events such as abdominal pain.

A recent meta-analysis identified 44 studies investigating the safety and efficacy of FMT in 303 immunocompromised patients [40•]. Most commonly, patients were deemed to be immunosuppressed due to the use of immunosuppressive therapy. A majority of the patients received fresh FMT via colonoscopy. They identified a pooled

Table 1 Prevalence of *Clostridium difficile* in patients with solid organ transplant according to organ type

Organ	Rate of *Clostridium difficile* infection
Liver	3.5–19.0%
Kidney	3.5–16.0%
Heart	8.0–15.0%
Kidney-pancreas	1.5–7.8%
Small bowel	9.0%
Lung transplant recipients	7.0–31.0%

Table 2 FMT donor screening protocol at MD Anderson Cancer Center

Agent	Material	Acceptance criteria
Hepatitis B core antibody	Blood	Negative
Hepatitis B surface antigen	Blood	Negative
Hepatitis C virus antibody	Blood	Negative
Hepatitis A virus IgM	Blood	Negative
HIV-1 and HIV-2 antibody	Blood	Negative
Anti-HTLV I/II	Blood	Negative
Serologic test for syphilis	Blood	Negative
Clostridium difficile toxin A/B	Stool	Negative
Shigella spp.	Stool	Negative
Salmonella spp.	Stool	Negative
Campylobacter spp.	Stool	Negative
Shiga-toxin producing *Escherichia coli*	Stool	Negative
Methicillin-resistant *Staphylococcus aureus*	Stool	Negative
Vancomycin-resistant *Enterococcus* spp.	Stool	Negative
Carbapenem-resistant *Enterobacteriaceae*	Stool	Negative
Extended spectrum b-lactanase producing *Enterococcus coli*	Stool	Negative
Aeromonas spp.	Stool	Negative
Plesiomonas spp.	Stool	Negative
Yersinia spp.	Stool	Negative
Vibrio spp.	Stool	Negative
Cryptosporidium	Stool	Negative
Entamoeba histolytica	Stool	Negative
Cyclospora	Stool	Negative
Isospora	Stool	Negative
Rotavirus	Stool	Negative
Adenovirus	Stool	Negative
Norovirus	Stool	Negative
Giardia lamblia, EIA	Stool	Negative
Helicobacter pylori EIA	Stool	Negative

IgM, immunoglobulin M; *HIV*, human immunodeficiency virus; *HTLV*, human T-lymphotropic virus; *EIA*, enzyme immunoassay

success rate of 88% and 93% with a single and multiple FMTs, respectively. They additionally reported that patients who had only a single reason for their immune-compromise had a higher rate of FMT success compared with patients who had multiple factors for immunosuppression. Similar to our literature review, the meta-analysis reported two mortalities, both in one series within 30 days of FMT. However, whether or not these mortalities could be attributed to FMT was not entirely clear. Two colectomies were reported (one due to treatment failure of CDI including antibiotics and intravenous immunoglobulins, as well as FMT; the other one due to uncontrolled ulcerative colitis despite eradication of CDI after FMT). In terms of infectious adverse events, five instances of bacteremia or infection and one instance of diverticulitis were found in the currently available literature. No randomized controlled trials were identified.

Though the abovementioned findings negate the theoretically increased risk of infections after FMT among immunocompromised patients, there is an additional concern regarding the safety of FMT among patients with IBD. FMT has been used among patients with IBD for the treatment of CDI on an experimental basis. The current body of evidence reveals a higher rate of FMT failure among this subset of patients who are often on immunosuppressive or immunomodulatory therapy (Table 4). Additionally, the adverse events experienced by patients with IBD differ from other immunocompromised patients, with concern surrounding the fate of IBD. The limited data that has been generated to date reveals IBD flare-ups in a significant fraction of patients following FMT. This holds true for patients with both Crohn's disease (CD) and ulcerative colitis (UC). Furthermore, a significant proportion of patients have been reported to require escalation in their IBD treatment. A relatively less proportion of patients

Table 3 Outcomes of CDI post FMT

Study	Number of patients	Immunosuppression etiology	Lower GI*	Upper GI*	Number of FMT	Clinical remission	FMT failure	Recurrence of CDI	Adverse events
(Ehlermann et al. 2014) [41]	1	SOT	0	1	1	1	0	0	0
(Elopre and Rodriguez et al. 2013) [42]	2	HIV	0	2	1	2	0	0	0
(Fischer et al. 2017) [43]	47	SOT	45	2	[1–6]	39	8	0	Aspiration [1], fever [1]
(Fischer et al. 2013) [44]	12	5 SOT 6 IBD 1 MM	12	0	(1–2)	11	1	0	Nausea, vomiting
(Friedman-Moraco et al. 2014) [45]	2	SOT	1	1	2	2	0	2	N/A
(Hefazi et al. 2017) [46]	23	Malignancy	23	0	1	19	3	2	Diarrhea [8], abdominal pain [3], constipation [2], urgency [2], vomiting [1]
(Kelly et al. 2014) [47]	80	3 HIV 19 SOT 7 malignancy, 36 IBD 15 others	N/A	N/A	(1–2)	70	10	0	Aspiration [1], mucosal tear [1], abdominal pain [3], diarrhea [5], hospitalization due to FMT [1]
(Mandalia et al. 2015) [48]	37	HIV, malignancy, others	N/A	N/A	[1, 2]	35	2	0	IBD flare-up [7]
(Mittal et al. 2015) [49]	1	Malignancy	1	0	2	1	0	1	N/A
(Neemann et al. 2012) [50]	1	Malignancy	0	1	1	1	0	0	N/A
(Ramay et al. 2016) [51]	1	SOT	1	0	2	1	0	1	N/A
(Rupali et al. 2014) [52]	22	1 HIV 11 immunosuppressive therapy 7 SOT 3 HSCT	1	21	1	20	2	3	N/A
(Schneider et al. 2018) [53]	1	SOT	1	0	2	1	0	0	N/A
(Schünemann and Oette et al. 2014) [54]	1	HIV	1	0	2	1	0	0	N/A
(Trubiano et al. 2014) [55]	1	Malignancy	0	1	1	1	0	0	N/A
(Webb et al. 2016) [56]	7	HSCT	1	6	1	3	3	1	Abdominal discomfort, nausea/vomiting [4]
(Youssef and Micheal et al. 2013) [57]	1	IBD	1	0	1	1	0	0	N/A

GI, gastrointestinal; *FMT*, fecal microbiota transplantation; *SOT*, solid organ transplantation; *HIV*, human immunodeficiency virus; *IBD*, inflammatory bowel disease; *MM*, multiple myeloma; *N/A*, not applicable; *HSCT*, hematopoietic stem cell transplantation

*Upper GI approach: endoscopy, capsule, and nasogastric or nasoduodenal tube; Lower GI approach: colonoscopy and enema

Table 4 Outcomes of IBD and CDI post-FMT in IBD patients

Study	Number of patients	Clinical response	IBD flare-up	Required IBD treatment escalation	Required surgical intervention for IBD
(Chin et al. 2017) [58]	35	34	NR	19	2
(Fischer et al. 2016) [59]	67	53	1	20	3
(Khanna et al. 2015) [60]	38	22	0	10	0
(Khoruts et al. 2016) [61]	43	32	11	11	3
(Meighani et al. 2017) [62]	20	15	0	0	0
(Newman et al. 2017) [63]	56	48	19	28	5
(Tariq et al. 2018) [64]	145	116	52	42	0
(Tabbaa et al. 2018) [65]	21	14	6	0	1
(Jain et al. 2015) [66]	11	10	1	0	2

FMT, fecal microbiota transplantation; *IBD*, inflammatory bowel disease; *NR*, not reported

have required surgical intervention for IBD management post-FMT. Whether FMT led to either treatment escalation or requirement for a surgical intervention among these patients is not entirely clear. There is an association between IBD and gut microbiome dysbiosis [61]. Hence, assuming that FMT did not play any role in the alteration of IBD course among these patients cannot be suggested. Since FMT is currently being experimentally administered for the treatment of IBD in many active clinical trials, the issue of autoimmune disease flare-up warrants further investigation.

Other Gastrointestinal Disorders as Indications of FMT Beyond CDI in the Context of Immunocompromised Condition

IBD as an Indication for FMT

Although FMT is commonly discussed in the context of rCDI, its use in conditions such as GVHD and IBD has been investigated, the latter being more comprehensively studied in RCTs than the former. One RCT randomized 75 patients with active UC to 50 mL of retention enema once a week for 6 weeks from anonymous stool donors or placebo enema [76]. They defined remission as a reduction in Mayo score and endoscopic Mayo score to < 3 and 0, respectively. Although the trial was terminated early due to futility and it was deemed that the primary endpoint is unlikely to be achieved at the 50% recruitment point, patients that were already enrolled in the trial were allowed to complete their allocated treatment. A total of 70 patients completed therapy. The safety profile of FMT is worth highlighting, where only two patients experienced adverse events necessitating antibiotic therapy (rectal abscess and colonic inflammation) with subsequent resolution without life-threatening consequences. A similar trend in terms of the efficacy of FMT in IBD was reported in a second early terminated RCT by Rossen et al. who randomized 50 patients with UC to either donor stool or autologous FMT via nasoduodenal tube performed twice 3 weeks apart [77]. They also failed to reach the primary endpoint of disease remission which was defined as a reduction in Mayo score at 12 weeks. However, contrary to the previously mentioned RCT, the adverse effect profile reported by Rossen et al. in both treatment arms surpassed 50%, though no serious adverse events were reported. Of note, fever was reported in two of the 23 patients who received donor FMT, whereas none of the patients in the autologous FMT group developed fever. A subsequent RCT by Paramsothy et al. which enrolled 85 patients with active UC resistant to standard therapies randomized to either a single FMT followed by five FMT enemas per week for 8 weeks from multiple donors or placebo was able to demonstrate the utility of FMT beyond a favorable safety profile [78]. Overall, 27% of patients in the FMT arm were able to achieve steroid-free remission or endoscopic remission compared with 8% in the placebo arm. Close to this time, a meta-analysis of 25 studies enrolling 243 UC patients revealed a 40.5% of clinical remission rate and a 66% clinical response rate [79]. Though the efficacy of FMT in UC was suboptimal, the safety profile was yet again solidified as adverse effects were mild and self-limiting in the majority.

The utility of FMT in treating CD is comparatively less studied, with the evidence majorly comprising of observational studies, though RCTs are underway. Cui et al., in 2015, reported 86.7% clinical improvement and 76.7% clinical remission rate 1 month after FMT [80]. One significant finding in their study was a significant weight gain 3 months post-FMT. Though this was attributed to improvement in nutritional status among patients with FMT, it may also be a reflection of the donor's BMI, though this claim cannot be validated from their cohort. A meta-analysis of 11 CD studies from 2017 reported 50% remission rate [81]. The favorable safety profile was reiterated in this meta-analysis where most adverse events were found to be transient gastrointestinal complaints.

Put together, though the efficacy of FMT in IBD at this point of time is questionable, the safety profile seems to be persistently limited to mild, transient, and self-limiting gastrointestinal symptoms. In 2017, He et al. reported in a study comprised of 25 patients with CD complicated by an intra-abdominal mass that sequential FMTs were able to induce radiological improvement of the inflammatory mass in 71.4% of cases [82]. The current body of evidence mounds in favor of further studies concerning the utility of FMT in the spectrum of IBD, even in cases with complicated CD (Table 5).

GVHD as an Indication for FMT

A growing body of evidence has attributed GVHD, at least in partly to be a consequence of gut microbiome disruption [83]. This is in line with the reported influence of gut microbiome on intestinal inflammation and immunity. With this context in mind, the rationale for utilizing FMT in the setting of GVHD seems plausible. However, the evidence to support the effectiveness of FMT in treating GVHD is very limited and to this date is comprised of only case series (Table 6). The first series was reported by Kakihana et al. comprising of four patients with acute GVHD after HSCT for underlying acute myeloid leukemia (AML) [84]. Patients received the first FMT at a median of 92 days after HSCT and were on methylprednisolone therapy as ≥ 1 mg/kg. FMT was administered through a nasoduodenal tube with a median feces volume of 126 g. Two sessions of FMT were completed in all four cases. Within days of FMT, three patients demonstrated complete response to FMT, whereas partial response was reported in the fourth case. Importantly, steroid dose post-FMT was successfully reduced by more than half. This was followed by three subsequent series, with the largest one comprised of eight patients who had failed methylprednisolone therapy at ≥ 2 mg/kg [85, 86•, 87]. FMT entailed infusion of 40–50 mL of frozen stool suspended in 200 mL of warm normal saline delivered through a nasoduodenal tube. Though this was a smaller suspension dose than the 500 mL suspension previously reported in a series of seven patients, their findings corroborated with the previous series, leading to symptomatic relief in all patients as well as a reconstitution of the gut microbiome, though 2/8 patients in the series by Qi et al. failed to respond to FMT. Additionally, one patient experienced relapse of diarrhea 11 days post-FMT. Notably, patients who received FMT had longer progression-free survival compared to patients who were not treated with FMT in the same series of eight patients. None of the case series reported any serious adverse events associated with FMT.

Efficacy and Complication Based on Route of FMT Administration in Immunocompromised Patients

A recent meta-analysis aimed at studying the safety and efficacy of FMT in immunocompromised patients also reported treatment efficacy based on the delivery route [40•]. The overall success rate for FMT in CDI patients reached 87% with a single FMT and up to 93% with repeat FMTs. However, a wide range of treatment success rate was reported according to the delivery modality of FMT (i.e., endoscopy, enema, capsule, and nasogastric or nasoduodenal tube). Moreover, since randomized controlled trials analyzing the superiority of one approach over another are lacking, the questionable quality of the current body of evidence should be highlighted, and caution should be practiced for interpretation. In terms of adverse

Table 5 IBD as an indication for FMT

Study	Number of patients	Colonoscopy flexible sigmoidoscopy or enema	EGD or NG tube	Number of FMT	Clinical response	FMT failure	Required IBD treatment escalation	Required surgical intervention for IBD	Adverse events
(Uygun et al. 2017) [67]	30	30	0	1–2	21	9	0	0	Fever [4]
(Nishida et al. 2017) [68]	41	41	0	1	34	7	0	0	N/A
(Jacob et al. 2017) [69]	20	20	0	1	10	10	3	1	Fever [1]; chills [1]; fatigue/malaise [4]; abdominal pain [3]; anorexia [1]; diarrhea [2]; constipation [1]
(Vaughn et al. 2016) [70]	19	19	0	1	11	7	7	1	N/A
(Damman et al. 2015) [71]	7	7	0	1	1	6	0	0	Microperforation [1]
(Cui Li et al. 2015) [72]	14	14	0	2	8	6	0	0	Fever [2]
(Kump et al. 2013) [73]	6	6	0	1	2	4	2	3	Fever [1]
(Cui Li et al. 2015) [74]	30	0	30	1	26	4	0	0	Fever [2]

EGD, esophagogastroduodenoscopy; *NG*, nasogastric; *FMT*, fecal microbiota transplantation; *IBD*, inflammatory bowel disease; *N/A*, not applicable

Table 6 GVHD as an indication for FMT

Study	Number of patients	Colonoscopy flexible sigmoidoscopy or enema	EGD or NG tube	Number of FMT	Clinical remission	FMT failure	Recurrence	Adverse events
(Qi et al. 2018) [86]	8	N/A	8	1–2	6	2	1	N/A
(Kakihana et al. 2016) [84]	4	N/A	4	1–2	4 (1 partial responder)	0	0	Abdominal pain [4]; pharyngolaryngeal pain [2]; diarrhea [2]
(Spindelboeck et al. 2017) [85]	3	3		1–6	3 (1 partial responder)	0	0	N/A
(van Lier et al. 2017) [87]	7	N/A	7	N/A	3	4	0	N/A

EGD, esophagogastroduodenoscopy; *NG*, nasogastric; *FMT*, fecal microbiota transplantation; *N/A*, not applicable

events, our literature review revealed that studies which utilized the colonoscopic FMT approach reported some increase in adverse events compared with an upper gastrointestinal approach (Table 3). However, this could be a biased observation, particularly since studies with larger sample size more often employed a colonoscopic approach. Further large-scale studies will be beneficial to further delineate the adverse event profile of FMT according to the route of administration.

Oral ingestion of FMT capsules was reported by Hirsch et al. in four patients with lymphoma, AML, and renal cell carcinoma, as well as one patient on immunosuppressant therapy [88]. Abdominal pain was the only reported adverse event. Treatment failure was documented in one patient with non-Hodgkin's lymphoma, who experienced recurrence within 4 weeks.

Future Directions

The indications for FMT are increasing exponentially, with a plethora of experimental studies published and in the process of publication. With a growing population of cancer patients as well as patients on biologics or other immunosuppressive therapy, it is crucial to adapt an inclusive strategy for such patients in clinical research regarding FMT while maintaining room for justifiable concerns regarding an altered adverse effect profile. The current body of evidence mounts in favor of utilizing FMT in immunocompromised patients. However, a major issue surrounding FMT is the regulation of fecal samples. More stringent requirement for donor screening should be considered to serve immunocompromised patients. Although definitive guidelines are lacking, fecal specimen preparation with extra precaution is desired for better safety.

We were unable to find any reports on the safety profile of FMT in patients with neutropenia. This should be a focus of prospective research studies since it is a frequent predicament, particularly in cancer patients.

Bacteriotherapy represents an alternative to FMT, which entails transferring a synthetic bacterial mixture which carries the advantage of minimizing pathogenic microbial inoculation and antimicrobial resistance genes. This technique was reported in 1989 by Tvede et al. who successfully treated CDI with a mixture of anaerobic and aerobic bacteria [89]. Another group of investigators isolated 33 nonpathogenic strains from donor feces, creating a mixture that was administered for CDI treatment in two patients [23]. Both patients experienced sustained long-term response to this strategy.

The American Gastroenterology Association (AGA) and several other societies have devised a national FMT registry to track 4000 patients over a time period of 10 years after their FMT procedure, aiming to enable understanding of long-term safety and efficacy of FMT [90•]. Though this is a tremendous step forward in the right direction, disparities remain, particularly surrounding immunocompromised patient populations. In particular, no standardized screening protocols exist that are tailored for immunocompromised patients, neither is there ample evidence regarding identifying factors associated with treatment failure in this patient population.

The future of FMT is promising, and the manufacturing of pharmacologically produced formulations will pave a way for clinical trials to obtain FDA approval. Immunocompromised patients represent a special patient population, and designing a randomized controlled trial that addresses the safety and efficacy of FMT among these individuals will surely be a welcoming step forward.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:
- Of importance

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