The risk of inflammatory bowel disease flares after fecal microbiota transplantation: Systematic review and meta-analysis

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ABSTRACT
Several studies have suggested worsening in inflammatory bowel disease (IBD) activity following fecal microbiota transplantation (FMT). We aimed to assess the risk of worsening in IBD activity following FMT. An electronic search was conducted using MEDLINE (1946-June 2016), EMBASE (1954-June 2016) and Cochrane Central Register of Controlled Trials (2016). Studies in which FMT was provided to IBD patients for IBD management or (Clostridium difficile infection) CDI treatment were included. The primary outcome was the rate of worsening in IBD activity. Results: Twenty-nine studies with 514 FMT-treated IBD patients were included. Range of follow up was 4 weeks to 3 y. The pooled rate of IBD worsening was 14.9\% (95\% CI 10–21\%). Heterogeneity was detected: I\textsuperscript{2} D 52.1\%, Cochran Q test D 58.1, p D 0.01. A priori subgroup analyses were performed. Although not significant, the pooled rate of worsening in IBD activity following FMT for CDI (22.7\% (95\% CI: 13–36\%)) was higher compared with FMT for IBD (11.1\% (95\% CI 7–17\%)). Rates of worsening in IBD activity following lower GI FMT delivery revealed a higher rate of worsening in IBD activity (16.5\% (95\% CI: 11–24\%)) compared with upper GI delivery (5.6\% (95\% CI: 2–16\%)). Rates of worsening in high quality studies and randomized controls trials (RCTs) suggested a marginal risk of worsening in IBD activity (4.6\%, (95\% CI: 1.8–11\%). Rates of IBD worsening are overall marginal across high quality RCTS. It is unknown if the FMT itself led to the worsening of IBD in this small fraction or if this represents alternative etiologies.

KEYWORDS
C. difficile; Crohn’s Disease; fecal microbiota transplant; inflammatory bowel disease; ulcerative colitis

Introduction
The gut microbiota has been shown to have a prominent role not only in the maintenance of intestinal homeostasis but also in the modulation of the host immune system.\cite{1} Dysbiosis, or changes in the gut microbiota that result in disease or dysfunction, have been linked to chronic diseases.\cite{2} Fecal microbiota transplantation (FMT) has emerged as a therapeutic modality for the restoration of a disturbed microbiota through the infusion of a fecal suspension from healthy individuals.\cite{3,4} The efficacy of FMT for the management of recurrent Clostridium difficile infection(CDI) has been well described,\cite{5,6} and an emerging body of literature suggests a possible role of FMT in the management of other disorders.\cite{7}

Inflammatory bowel diseases (IBD) are relapsing and remitting inflammatory disorders, comprised of ulcerative colitis (UC) and Crohn’s disease (CD). In genetically susceptible individuals, dysbiosis related to an aberrant immune response to commensal microbial flora has been suggested as a possible causative or contributing factor to the pathogenesis for both UC and CD.\cite{8,9,10} FMT has been recently used as a potential novel therapeutic option in the management of IBD with variable success.\cite{11,12}

The emerging body of literature describes low rates of adverse events following FMT in all populations.\cite{13} However, there have been case reports postulating de novo IBD development after FMT and other studies
reporting IBD flare following FMT in patients with established IBD. Exposure to novel microbiota in participants with altered mucosal integrity may promote a disproportionate host immune response to transplanted microbiota. The host immune response to FMT may result in worsening in IBD disease activity.

Despite the emerging literature, the rate of IBD worsening following FMT is unknown. Thus, we aimed to conduct a systematic review and meta-analysis to determine the rate of worsening in IBD activity following FMT in patients with IBD regardless of indication for FMT.

Methods

Search strategy

An electronic search was conducted using MEDLINE (1950-December 2016), EMBASE (1947-December 2016), and the Cochrane Central Register of Controlled Trials (2016). The search strategy was not limited by language. Abstract data and completed studies were included. Search terms, both free text and medical subject headings (MeSH) included alternatives of fecal microbiota transplantation: feces, stool, fecal flora, and faecal microbiota. The terms were searched individually and in combination with each of the following variation on transplant: transplant, transfusion, implantation, implant, instillation, microbiota, donor, enema, reconstitution, infusion, therapy, and bacteriotherapy. The results were combined with varied terms of inflammatory bowel disease (IBD): Crohn’s disease, Crohn disease, inflammatory bowel disease, colitis, ileitis, regional enteritis, ulcerative colitis, IBD, CD, or UC. Variations of the root word were also searched alone or in combination. A recursive search of bibliographies of all relevant papers was also conducted. Full search strategy is provided in Appendix 1.

Study selection and extraction

Eligibility criteria were determined a priori by the study authors and included the provision of FMT for participants with IBD for any indication via any delivery modality. The study included patients of any age with IBD who underwent FMT. Studies selected included case series, cohort studies, and randomized controlled trials. Exclusion criteria included: studies in animals or in vitro studies and studies where data provided for IBD patients was not reported separately, and studies where the data appeared to be duplicative in other published reports. Only case series with 3 or more patients were included to minimize bias inherently associated with individual case reports and case series. Editorials, prior meta-analyses, and reviews were also excluded (Fig. 1).

Two authors (T.Q and T.A) reviewed the title and abstract search with inclusion decisions for each paper made independently based on eligibility criteria. Data extraction for eligible studies was also conducted independently with the use of a standardized, pretested extraction form. Data extraction forms were compared and any discrepancies were resolved through consensus (with J.A).

Information extracted from each study included the characteristics of patients with IBD, including IBD sub-type and disease severity. FMT characteristics extracted included pre-FMT therapy, FMT dose, FMT delivery location, FMT donor (patient-selected vs. healthy-unrelated donor), and the number of FMT transplants received. Outcome measures including resolution of CDI, improvement in IBD activity and worsening in IBD activity was also extracted. In studies where FMT was provided for CDI, relapse of CDI was also extracted. Relapse of CDI, defined as the recurrence of diarrheal symptoms with confirmatory laboratory testing or the re-initiation of antibiotics to treat CDI was differentiated from worsening in IBD activity.

Methodological quality appraisal

Two investigators independently assessed all studies selected for inclusion in the review for methodological quality using 2 tools. The Newcastle-Ottawa Score was used to assess quality and bias in cohort studies. In studies without a control group, the scale was adjusted as described previously. Points were assigned on the basis of cohort selection, including representativeness of the IBD cohort, ascertainment of FMT, and evidence of no prior FMT. Points were also assigned in regards to outcome, namely on demonstration that the outcome was not present at the start of the study, adequacy of follow up and length of follow up. A follow up period of 4 weeks was chosen to assess the occurrence of deterioration in IBD based on previously published case reports and case series describing
the deterioration in IBD following FMT.\textsuperscript{15,16,20} Quality and bias of randomized control trials was assessed using the Jadaad Scale, which assigns points on the basis of randomization, blinding, and adequacy of follow up.

**Statistical methods**

Our primary measure of effect was rate of worsening in IBD activity following FMT. This was defined as any of the following: IBD flare requiring additional medical therapy, need for surgical intervention for management of IBD, or either an endoscopic or clinical assessment describing worsening colitis using validated scores in the absence of an alternative etiology. Alternative etiologies for increase in clinical symptoms including cases of relapse of CDI were excluded. The weighted pooled rates of worsening in IBD activity were calculated with corresponding 95% confidence intervals for overall studies and predetermined subgroups. Predetermined subgroups analysis included FMT indication, site of FMT delivery, IBD subtype, and type of study. Weighted pooled rates were analyzed using a random effects model.\textsuperscript{21} Heterogeneity was assessed using the $I^2$ statistic and the Cochrane Q test. A $I^2 > 50\%$ or Cochrane $Q < 0.10$ was considered an indicator of significant heterogeneity. Classic fail-safe $n$ was used to determine publication bias. Publication bias was assessed using a funnel plot model with further analysis using Duval and Tweedie’s trim and fill analysis.\textsuperscript{22} Statistical analyses were performed using Comprehensive Meta-Analysis (Version 3.0, Biostat, Englewood, NJ)

**Results**

The initial search strategy yielded 1168 publications. Of those, 781 were discharged after review of abstracts suggested that the papers did not clearly meet the inclusion criteria. Subsequently, the full texts of 42 citations were reviewed. Of these, 29 studies met eligibility criteria (Fig. 1). The qualitative analysis included 3 randomized control trials, 21 cohort studies, and 5 case series.

Excluded studies included 5 studies which did not meet pre-determined sample size eligibility.\textsuperscript{16,23-26} Three studies were determined to be potential duplicates of included studies.\textsuperscript{27-29} Two studies were excluded as the outcomes of subjects with IBD were not clearly described,\textsuperscript{30,31} and one commentary was excluded because outcomes were not clearly described.\textsuperscript{32}
Methodological quality of included studies

Quality was assessed using the Newcastle-Ottawa33 and Jadad score34 (Supplementary Tables). Three studies that were included in the analysis were randomized control trials. Quality of these studies was assessed through the Jadad scale. Of these 3 studies, 2 studies scored highly on the Jadad scale on the basis of randomization, appropriate blinding, and clear delineation of withdrawals and dropout.35,36 The remaining study did not clearly delineate dropouts and withdrawals.37

The remaining 21 cohort studies were assessed via the Newcastle-Ottawa scale (NOS). In studies with the absence of a control group, the scale was adjusted. Seventeen studies had a score of 4 or higher on the NOS. The remaining 4 studies had cohorts that did not appear to be clearly representative of the population of IBD patients due to age or other characteristics of the population or did not clearly discern whether the rate of worsening in IBD activity was through objective criteria or present at the onset of the study.38-41

Patient demographics

The included studies involved 514 patients with IBD treated with FMT. Twenty studies described the use of FMT for the management of IBD and 9 studies described the use of FMT for CDI in patients with IBD (Table 1). The majority of studies did not have a comparator group. Of the studies where FMT was used for the management of IBD, 4 studies described comparator groups that were subjects treated with placebo, autologous FMT, or standard therapy for IBD including immunomodulators and/or anti-TNF agents. Among the 9 studies where FMT was provided for the management of CDI, 2 studies described comparator groups of non-immunosuppressed subjects or subjects without IBD.

Fecal microbiota transplantation characteristics

The exposure of interest in the studies was FMT. FMT was provided through a variety of routes including colonoscopy, retention enema, nasogastric tube, or duodenal infusion via upper endoscopy. A total of 16 studies used the lower GI route for FMT administration. Six studies used instillation of fecal material via the upper GI route (nasogastric tube or upper endoscope). Eleven studies used fresh donor stool and 6 studies used frozen stool. Two studies used a combination of fresh and frozen stools. Eight studies used unrelated screened donors and 10 studies used patient selected screened donors. Complete FMT details are found in Table 2a, b.

Primary outcome

The primary outcome assessed was IBD worsening as assessed through either clinical and or endoscopic assessment, including the development of an IBD flare requiring the use of additional medical or surgical therapies. The extracted studies used a variety of clinical and endoscopic scores, including Ulcerative colitis Mayo Score, Pediatric Ulcerative Colitis Activity Index (PUCAI), Crohn’s Disease Activity Index (CDAI), Ulcerative Colitis Disease Activity Index (UCDAI), Crohn’s Disease Endoscopic Index of Severity (CDEIS), Ulcerative Colitis Endoscopic Index of Severity (UCEIS), Harvey-Bradshaw Index (HBI), Powell-Tuck Index, or the Pediatric Crohn’s Disease Activity Index (PCDAI), along with a clinical assessment to assess deterioration in IBD.

The pooled rate of IBD worsening is based on 29 studies. Given the presumed heterogeneity, a random-effects model was used. The weighted pooled rate of IBD worsening across all studies was 14.9% (95% CI: 10–21%) (Fig. 2). There was statistically significant heterogeneity between studies (I² = 52.1%, Cochran Q test = 58.1, p = 0.01). Despite the heterogeneity, on a 1 study removed analysis the point estimate remained 14.9%.

A priori subgroup analyses were performed. The first analyzed the rate of IBD worsening by indication for FMT (Fig. 3). Of the 10 studies where FMT was provided for the management of CDI in IBD patients, the pooled weighted rate of IBD worsening was 22.7% (95% CI: 13–36%). The subgroup had an I² = 60.3. The remaining 19 studies where FMT was provided for the management of IBD revealed a pooled weighted IBD deterioration of 11.1% (95% CI 7–17%). The subgroup had an I² = 27.2. The total within the 2 groups resulted a Q-value of 47.4, p < 0.01. The total between the 2 groups revealed a Q-value of 10.9, p < 0.01.

Subgroup analyses were also performed according to IBD subtype. Fourteen studies investigated FMT in patients with UC. The pooled weighted rate of IBD worsening in subjects with UC was 9.8% (95%
| Reference            | Year | Country     | Type of Study | Number of IBD patients | Indication for FMT | Evaluation of Deterioration | Type of IBD       |
|----------------------|------|-------------|---------------|------------------------|-------------------|-----------------------------|-------------------|
| Fischer et al.  | 2016 | USA         | Cohort Study  | 67                     | Clostridum difficile Infection | Clinical Assessment, Endoscopic Assessment, and HBI and UCCS | Mixed              |
| Khortus et al.     | 2016 | USA         | Cohort Study  | 43                     | Clostridum difficile Infection | Clinical Assessment         | Mixed              |
| Agrawal et al.     | 2016 | Multinational | Cohort Study  | 5                      | Clostridum difficile Infection | Clinical Assessment         | Mixed              |
| Kronman et al.     | 2015 | USA         | Cohort Study  | 3                      | Clostridum difficile Infection | Clinical Assessment         | Mixed              |
| Lee et al.         | 2014 | Canada      | Cohort Study  | 3                      | Clostridum difficile Infection | Clinical Assessment         | Mixed              |
| Kelly et al.       | 2014 | USA         | Case Series   | 3                      | Clostridum difficile Infection | Clinical Assessment         | Mixed              |
| Kelly et al.       | 2014 | USA         | Cohort Study  | 36                     | Clostridum difficile Infection | Clinical Assessment         | Mixed              |
| Russell et al.     | 2016 | USA         | Case Series   | 3                      | Clostridum difficile Infection | Clinical Assessment         | Mixed              |
| Mandalia et al.    | 2016 | USA         | Cohort Study  | 11                     | Clostridum difficile Infection | Clinical Assessment         | Mixed              |
| Paramsothy et al.  | 2016 | Australia   | RCT           | 41                     | Ulcerative Colitis Treatment | UC Mayo Score, UCBS         | Ulcerative Colitis |
| Moayedi et al.     | 2015 | Canada      | RCT           | 38                     | Ulcerative Colitis Treatment | UC Mayo Score, UC Endoscopic Mayo Score, IBDQ, SQED | Ulcerative Colitis |
| Rossen et al.      | 2015 | Netherlands | RCT           | 23                     | Ulcerative Colitis Treatment | SCCAI, UC Endoscopic Mayo Score, Ulcerative Colitis | Ulcerative Colitis |
| Kunde et al.       | 2013 | USA         | Cohort Study  | 9                      | Ulcerative Colitis Treatment | UC Mayo Score               | Ulcerative Colitis |
| Kump et al.        | 2013 | Austria     | Cohort Study  | 6                      | Ulcerative Colitis Treatment | UC Mayo Score               | Ulcerative Colitis |
| Angelberger et al. | 2013 | Austria     | Cohort Study  | 5                      | Ulcerative Colitis Treatment | UC Mayo Score               | Ulcerative Colitis |
| Wei et al.         | 2015 | China       | Cohort Study  | 14                     | IBD Treatment              | CDAI, UC May Score, IBDQ    | Mixed              |
| Damman et al.      | 2014 | NR          | Cohort Study  | 5                      | Ulcerative Colitis Treatment | UC Mayo Score               | Ulcerative Colitis |
| Karolewska-Bochenek et al. | 2015 | NR         | Cohort Study  | 4                      | Ulcerative Colitis Treatment | UC Mayo Score               | Ulcerative Colitis |
| Scaldaferrari et al.| 2015 | NR          | Cohort Study  | 8                      | Ulcerative Colitis Treatment | UC Mayo Score               | Ulcerative Colitis |
| Landy et al.       | 2013 | England     | Cohort Study  | 8                      | Ulcerative Colitis Treatment | UC Mayo Score               | Ulcerative Colitis |
| Borody et al.      | 2012 | Australia   | Case Series   | 62                     | Ulcerative Colitis Treatment | Powel-Tuck Index, Endoscopic Assessment | Ulcerative Colitis |
| Borody et al.      | 2012 | Australia   | Case Series   | 3                      | IBD Treatment              | Clinical and Endoscopic Assessment | Mixed              |
| Vaughn et al.      | 2016 | USA         | Cohort Study  | 19                     | Crohn's Disease Treatment  | HBI, CDEIS                  | Crohn's Disease    |
| Suskind et al.     | 2015 | USA         | Cohort Study  | 9                      | Crohn's Disease Treatment  | CDAI                        | Crohn's Disease    |
| Vermiere et al.    | 2012 | NR          | Cohort Study  | 4                      | Crohn's Disease Treatment  | CDAI, CDEIS, SES-CD         | Crohn's Disease    |
| Cui et al.         | 2015 | China       | Cohort Study  | 30                     | Crohn's Disease Treatment  | HBI                         | Crohn's Disease    |
| Kellermeyer et al. | 2015 | USA         | Case Series   | 4                      | Ulcerative Colitis Treatment | CDAI, UC Mayo Score         | Ulcerative Colitis |
| Chin et al.        | 2015 | USA         | Cohort Study  | 35                     | Clostridum difficile Infection | Clinical Assessment         | Mixed              |
| Chin et al.        | 2016 | USA         | Cohort Study  | 35                     | Clostridum difficile Infection | Clinical Assessment         | Mixed              |
| Reference       | Year | Number of IBD patients | IBD Sub-Type            | Severity of Disease                                                                 | IBD therapies                                                                 | FMT Dosage | FMT Delivery          | Donor                                      | Number of FMTs | Follow Up  |
|-----------------|------|------------------------|-------------------------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|------------|----------------------|--------------------------------------------|-----------------|------------|
| Paramsothy et al. 2016 | 41   | Ulcerative Colitis     | UC Mayo Score: 4–10, resistant to standard therapies | Not Reported                                                                       | Corticosteroids weaned prior to FMT. Other medications not reported          | Not Reported | Colonoscopy and Enema | Unrelated Screened Donor                  | 41              | 8 weeks    |
| Moayyedi et al. 2015 | 38   | Ulcerative Colitis     | UC Mayo Score ≥ 4; UC Endoscopic Mayo Score ≥ 1 | Concomitant medications for IBD were continued as long as doses were stable: Corticosteroids, 5-ASA, or Immunomodulators | Concomitant medications for IBD were continued as long as doses were stable: Corticosteroids, 5-ASA, or Immunomodulators | 50g of stool | 300mL of drinking water | Enema                                      | 6               | 7 weeks    |
| Rossen et al. 2015 | 23   | Ulcerative Colitis     | SCAI ≥ 4, Endoscopic Mayo Score ≥ 1 | Concomitant medications for IBD were continued as long as doses were stable: Corticosteroids, 5-ASA, or Immunomodulators | Concomitant medications for IBD were continued as long as doses were stable: Corticosteroids, 5-ASA, or Immunomodulators | 60g of stool | 500mL of Normal Saline | NG tube                                    | 2               | 12 weeks   |
| Kunde et al. 2013 | 9    | Ulcerative Colitis     | PUCAI: 15–65            | Concomitant medications for IBD were continued: Corticosteroids, 5-ASA, or Immunomodulators | Concomitant medications for IBD were continued: Corticosteroids, 5-ASA, or Immunomodulators | 100–150g of stool | 200–350mL of Normal Saline | Enema                                      | 5               | 6 weeks    |
| Kump et al. 2013  | 6    | Ulcerative Colitis     | UC Mayo Score: 8–11, Chronic Active UC medically refractory | Concomitant medications for IBD were continued: Corticosteroids, 5-ASA, and 6-MP | Concomitant medications for IBD were continued: S-ASA, Corticosteroids, and 6-MP | 90g of stool | 250mL of sterile Normal Saline | Colonoscopic Unrelated Screened Donor     | 1               | 12 months  |
| Angelberger et al. 2013 | 5   | Ulcerative Colitis     | UC Mayo Score ≥ 6, Medically refractory | Concomitant medications for IBD were continued: S-ASA, Corticosteroids, and 6-MP | Concomitant medications for IBD were continued: S-ASA, Corticosteroids, and 6-MP | 60g of stool | 250mL of Normal Saline | Enema and NG tube Unrelated Screened Donor | 3               | 12 weeks   |
| Wei et al. 2015  | 14   | Ulcerative Colitis     | Crohn’s: CDAI score of >150 and <400; UC: Mayo score 2–10 | Concomitant medications for IBD were continued: S-ASA, Corticosteroids, and 6-MP | Concomitant medications for IBD were continued: S-ASA, Corticosteroids, and 6-MP | 60g of stool | 350mL of Normal Saline | Colonscopy and Enema Patient Selected Screened Donor | 1               | 4 weeks    |
| Cui et al 2015   | 14   | Ulcerative Colitis     | Moderate to Severe UC (S2 and S3) - Montral Classification | Concomitant medications for IBD were continued: S-ASA, Corticosteroids, and 6-MP | Concomitant medications for IBD were continued: S-ASA, Corticosteroids, and 6-MP | 30g of stool | 50mL of Normal Saline | EGD Unrelated Screened Donor Patient Selected Screened Donor | 1–2             | 3 months   |
| Damman et al. 2014 | 5    | Ulcerative Colitis     | UCDAI: 6–9              | Concomitant medications for IBD were continued: S-ASA, Corticosteroids, and 6-MP | Concomitant medications for IBD were continued: S-ASA, Corticosteroids, and 6-MP | Not Reported | Not Reported | Colonscopic Unrelated Screened Donor Patient Selected Screened Donor | 1               | 1 month    |
| Karolevska-Bochenck et al. 2015 | 4    | Ulcerative Colitis     | PUCAI: 15–60            | Not Reported                                                                       | Not Reported                                                                      | Not Reported | Not Reported | EGD Unrelated Screened Donor Patient Selected Screened Donor | 8               | 4 weeks    |
| Scaldaferrri et al. 2015 | 8    | Ulcerative Colitis     | Partial Mayo Score ≥ 4; Endo Score ≥ 1 | 80% continued on Corticosteroids and 5-ASA; 40% continued on Immunomodulators | Not reported                                                                       | Not reported | Not Reported | Colonscopic Patient-Selected Screened Donor | 3               | 12 weeks   |
| Landy et al. 2013 | 8    | Ulcerative Colitis with Pouch PDAI ≥ 7 | Not Reported | Not Reported                                                                       | Flexible-Sigmoidscopy                                                           | Not Reported | Not Reported | Colonscopy and Enema Patient-Selected Screened Donor | 1               | 4 weeks    |
| Borody et al. 2012 | 62   | Ulcerative Colitis     | Active UC by Endoscopic Evaluation | Not Reported                                                                       | Not Reported                                                                       | Not Reported | Not Reported | Daily/Weekly - 34–70 | Not Reported | 33 months  |
| Borody et al. 2011 | 3    | 2 - Indeterminate Colitis | Not Reported | Not Reported                                                                       | Not Reported                                                                       | Not Reported | Not Reported | Colonscopic and Enema Patient-Selected Screened Donor | 3               | 3 years    |

(continued on next page)
Table 2a. (Continued)

| Reference        | Year | IBD patients | IBD Sub-Type          | Severity of Disease                          | IBD therapies                                                                 | FMT Dosage        | FMT Delivery   | Donor                      | Number of FMTs | Follow Up |
|------------------|------|--------------|-----------------------|-----------------------------------------------|-------------------------------------------------------------------------------|------------------|---------------|--------------------------|----------------|-----------|
| Vaughn et al.    | 2016 | 19           | Crohn’s Disease       | HBI ≥ 5; Failed Standard therapy with Mesalamine ≥ 2 weeks, Thiopurines > 3 weeks, anti-TNF > 12 weeks, or were steroid dependant | Corticosteroids, Immunosuppressant, and 5-ASA were continued                  | 50g of stool     | Colonoscopic  | Unrelated Screened Donor | 1              | 26 weeks |
| Suskind et al.   | 2015 | 9            | Crohn’s Disease       | PCDAI: 10–29; Immunomodulators and 5-ASA therapies continued | 30g of stool 100–200mL of Normal Saline                                         | NG tube          | Patient-Selected Screened Donor | 1              | 12 weeks |
| Vermiere et al.  | 2012 | 4            | Crohn’s Disease       | Median CDAI: 284 (224–338); Refractory to treatment with corticosteroids, immunomodulators, and anti-TNF | Not Reported                                                               | 200g of stool  mixture | NG tube       | Unrelated Screened Donor  | 3              | 8 weeks   |
| Cui et al.       | 2015 | 30           | Crohn’s Disease       | HBI≥7, Medically Refractory; Mesalamine continued. Other therapies weaned/discontinued prior to FMT | Not Reported                                                               | EGD              | Unrelated Screened Donor or Patient Selected Screened Donor | 1              | 6 months |
| Kellemeyer et al. | 2015 | 4            | Ulcerative Colitis    | PUCAI<10 and UC Mayo Score: 0–1, on Immunotherapy | Mesalamine continued                                                        | 50g of stool 200mL of Normal Saline                                             | Colonscopy and Enema | Patient 1: 30 Patient 2: 25 Patient 3: 22 | >5 weeks |

Note: Abbreviations: Harvey-Bradshaw Index (HBI), Ulcerative Colitis Clinical Score (UCCS), Inflammatory bowel disease (IBD), Fecal Microbiota Transplantation (FMT), CDAI: Crohn’s Disease Activity Index (CDAI), Ulcerative Colitis Disease Activity Index (UCDAI), Pediatric Ulcerative Colitis activity index (PUCAI), Simple Clinical Colitis Activity Index (SCCAI).
### Table 2b. Characteristics of FMT studies for the management of Clostridium difficile Infection in patients with IBD. Abbreviations: Harvey-Bradshaw Index (HBI), Ulcerative Colitis Clinical Score (UCCS), Inflammatory bowel disease (IBD), Fecal Microbiota Transplantation (FMT).

| Reference | Year | Number of IBD patients | IBD Sub-Type | Severity of Disease | FMT Dosage | FMT Delivery | FMT state | Donor | Number of FMTs | Follow Up |
|-----------|------|------------------------|--------------|---------------------|------------|--------------|-----------|-------|----------------|-----------|
| Fischer et al. | 2016 | 67 | 35 - Crohn's Disease, 31 - Ulcerative Colitis | HBI>4; UCCS>1, Endoscopic/Clinical Evidence of Active Disease 7 (10.4%) - No Disease, 51 (76%) - Endoscopic evidence of disease - 29 (43.2%) - Mild, 16 (23.6%) - Moderate, 15 (22.4%) - Severe | Not Reported | Colonoscopic/Sigmoidoscopy | Fresh | Unrelated Screened Donor or Patient Selected Screened Donors | 1 | 3 months |
| Khortus et al. | 2016 | 43 | 22 - Crohn's Disease, 21 - Ulcerative Colitis, 1 - Indeterminate Colitis | Not Reported | 50g of stool in 250ml of Normal Saline | Colonoscopic of Normal Saline | Fresh and Frozen | Unrelated Screened Donor or Patient Selected Screened Donors | 1–3 | 2 months |
| Agrawal et al. | 2016 | 5 | 3 - Crohn's Disease, 2 - Ulcerative Colitis | Not Reported | 60–100g of Normal Saline | Not Specifically Reported in IBD patients | Not Reported Specifically | Unrelated Screened Donor or Patient Selected Screened Donors | Unreported for IBD patients specifically | 12 weeks |
| Kronman et al. | 2015 | 3 | 1 - Crohn's Disease, 1 - Ulcerative Colitis, 1 - Indeterminate Colitis | Not Reported | 30g | Nasogastric Tube | Fresh | Patient Selected Screened Donors | 1 | 44 days |
| Lee et al. | 2014 | 3 | Mixed - Not Reported | Not Reported | 150g | Enema | Not Reported Specifically | Unrelated Screened Donors | Unreported for IBD patients specifically | 6 months |
| Kelly et al. | 2012 | 3 | Mixed - Not Reported | Not Reported | 6–8 tablespoons of fresh stool | Colonoscopic | Fresh | Patient Selected Screened Donors | 1 | 10.7 months |
| Kelly et al. | 2014 | 36 | Mixed - Not Reported | Not Reported | 1L of Sterile Water | Variable among sites | Not Reported Specifically | Variable among sites | 1 FMT - 31 subjects > 1 FMT - 3 subjects | 11 months |
| Russell et al. | 2014 | 3 | 2 - Crohn's Disease, 1 - Ulcerative Colitis | Not Reported | 30–40g of stool | Colonoscopic | Fresh | Patient Selected Screened Donors | 1 | 10 months |
| Mandalia et al. | 2016 | 11 | Mixed - Not Reported | Not Reported | 250mL of sterile NS | Colonoscopic/Enema | Not Reported | Unrelated Healthy Screened Donor or Patient Selected Screened Donors | 1–3 | 12 weeks |
| Chin et al. | 2016 | 35 | 13 - Crohn's Disease, 22 - Ulcerative Colitis, 2 - Ulcerative Colitis with Pouch | Not Reported | 50g of stool | 27 - Capsule, 5 - NG | Frozen | Unrelated Screened Donors | 1 | 6 months |
Subgroup analyses were also performed according to FMT delivery location. Sixteen studies used lower GI delivery. The pooled weighted rate of IBD worsening in this group was 16.5% (95% CI: 11–24%). The subgroup had an $I^2 = 24.3$. Six studies used upper GI delivery, and the rate of IBD worsening in this group was 5.6% (95% CI: 2–16%). The subgroup had an $I^2 = 0$. In the 3 studies including a mixed population, the pooled rate of IBD worsening was 32.5% (95% CI: 8.6–71%). This subgroup had an $I^2 = 66.1$. The total within the groups resulted in a Q value of 28.5, $p = 28$. The total between the 3 groups resulted in a Q value of 29.9, $p < 0.01$.

A subgroup analysis of the pooled rate of IBD worsening in the randomized controlled trials revealed a pooled rate of worsening at 4.6% (CI: 1.8–11%). The subgroup had an $I^2 = 0$. Among the cohort studies the rate of IBD worsening was 18.7% (CI: 11.6–24.4%). The subgroup had an $I^2 = 38.7$.

### Bias analysis

To assess for publication bias a funnel plot was drawn (Fig. 4). This did show evidence of asymmetry. Therefore Duval and Tweedie’s trim and fill analysis was done revealing an addition of 12 studies to the right of the funnel.
the mean. Classic fail-safe revealed a $p < 0.01$ and 899 studies were needed to bring the $p$ value $> 0.05$.

**Discussion**

The therapeutic use of fecal microbiota transplantation to alter the intestinal microbiome has been used for the successful management of CDI and is being explored for the management of IBD. A unique issue to the use of FMT in IBD patients is the risk of worsening in IBD activity. Despite the emerging data on FMT in IBD patients, the rate of worsening in IBD activity following FMT has yet to be elucidated. In our study, the overall risk of worsening in IBD across all studies was determined to be 14.3% (95% CI 11–19%). Although the rate of IBD worsening following FMT appears elevated when including observational trials, sub-group analyses of comparative studies suggest only a marginal risk of worsening in IBD activity following FMT. The rate of worsening in IBD activity was measured at 14.9%, when restricting the analysis to only include randomized controlled trials, the rate of worsening in IBD activity was found to be 4.6% without evidence of significant heterogeneity (natural history of flares). The results of the sub-group analysis suggest that the FMT appears to be a relatively safe therapeutic modality when limiting the results to higher quality studies.

A priori sub-group analyses demonstrated that the rate of worsening in IBD activity following FMT for CDI was higher compared with the rate of worsening in IBD activity following FMT for the management of IBD. This difference, however, was found not to be significant in the analysis. There are several plausible explanations for this phenomenon. First, subjects with CDI and IBD represent a population with a baseline increased disease activity and are likely different from subjects with IBD alone. Second, changes in the natural course of IBD may occur following CDI. Third, alterations in the mucosal immune response following CDI may result in worsening IBD severity. Lastly, interruptions and delays in the provision of biologic and other immunomodulator agents for IBD therapy in the setting of an active infection may worsen disease course. These hypotheses are supported by previous studies suggesting poorer outcomes in IBD patients following CDI. A higher mortality and colectomy rate have previously been described in IBD patients with CDI compared with subjects with IBD alone as well as those with CDI alone. Moreover, in a retrospective study, antecedent CDI was linked to escalation in medical therapy a year following infection. A broad definition of worsening in IBD activity was used in the meta-analysis to capture deterioration in any form, including the need for increased medical therapy or surgical intervention. The discrepancy in the pooled rate of IBD worsening by indication may also be explained by the possible disincentive of escalating medical therapies in patients enrolled in FMT for IBD trials to assess response to FMT and limit confounding of additional agents. In contrast, in studies where FMT was provided for the management of CDI, the early use of immunosuppressive therapies was described. Nevertheless, by using a broad definition of worsening in IBD activity, any degree of deterioration across a multitude of studies is captured in the analysis.

In comparing the rate of worsening in IBD activity by FMT delivery location, the rates of IBD worsening appear to be greater when FMT was delivered through the lower gastrointestinal route in comparison to administration via nasogastric tube (NG) or upper endoscopy. The environment of the upper GI tract is not conducive to the survival of microbiota, including anaerobic colonies. Of note, studies using delivery of FMT using the upper gastrointestinal route tend to utilize lower volumes of donor stool in comparison to delivery via the lower gastrointestinal route. Conceivably, limited exposure of the host immune system to the novel microbiota in the colon is associated with a lower likelihood of worsening in IBD disease activity. This rate is driven mainly by uncontrolled observation studies. Additionally, this finding is in opposition to the RCT data, all using a lower GI delivery route, which reveal a much lower rate of IBD worsening.
RCT data additionally revealed, specifically those using lower GI administration, achieved improvement in IBD disease activity. Moayeddi and colleagues used the lower route of FMT delivery in the randomized trial for the management of UC and reported a significant difference in clinical remission rates (24% in the FMT group compared with 5% in the placebo group). Similarly, Paramsothy et al. used both colonoscopic infusion and enemas and reported a significant difference in the rates of clinical remission measured at 27% in the FMT group compared with 8% in the placebo group. In contrast, Rossen and colleagues used a nasoduodenal infusion of fecal microbiota and did not report a significant difference in remission rates between the treatment and control arms: 30.4% in the FMT group compared with 20.0% in the FMT-autologous group. Thus, of the randomized controlled trials using FMT for the management of UC, significant differences in remission rates were only observed in the studies where FMT was delivered via the lower gastrointestinal route. Again, in these studies the rate of IBD worsening was very low. This helps demonstrate the possible benefits of FMT as a novel therapeutic for IBD, even through the lower route, outweigh the risks of possible or IBD worsening.

Additional etiologies of the small number of patients who experience worsening of IBD should be acknowledged. These include the natural disease progression of IBD, worsening disease activity precipitated by infection, and interruptions in the provision of IBD therapies. There are questions regarding donor dependent variations of FMT’s therapeutic potential. Highlighting the variable effect of donor stool, Moayeddi and colleagues were able to describe the effect of a particular donor in inducing remission in patients with UC. Theoretically, as certain donors can induce remission, other donors may induce worsening in IBD activity.

Our study does have multiple strengths. Using a broad search strategy encompassing multiple databases, multiple studies were captured that used FMT in IBD patients to assess safety concerns. By including all patients, we hoped to describe the pooled rate of worsening in IBD activity across all studies, which used FMT in IBD patients. Lastly, to our knowledge, this is the first analysis to provide a detailed systematic review and meta-analysis on the rate of worsening in IBD following alteration of the host microbiota.

There are some limitations to this study however. There was a wide range of study designs, indications for FMT, assessment tools used for the evaluation of disease activity, and methods of FMT delivery in the studies included in the meta-analysis. As expected, the analyses revealed a significant degree of heterogeneity. Despite this heterogeneity, the overall quality of studies included in the analysis was good as assessed through the Jadaad score for randomized controlled trials and the Newcastle-Ottawa scale for cohort studies (Supplementary Tables). Additionally, among the studies analyzed, only 4 studies used a comparator group against the use of FMT. The remaining studies had the absence of a comparator group limiting the interpretation regarding risk of worsening in disease activity. Thus, despite the extensive literature on the use of FMT in IBD patients, there are a limited number of randomized controlled trials and comparative studies.

A standardized assessment strategy for worsening of IBD activity should be using in future studies investing FMT in IBD patients. Ideally, endoscopic evaluation before and after FMT would provide a definitive assessment of worsening in IBD activity. However, at a minimum, use of validated clinical scales such as the partial UC Mayo score or the Harvey-Bradshaw Index (HBI) would also aid in quantifying the degree of worsening in IBD activity following FMT, regardless of indication.

Across all studies IBD worsening was observed. However, when restricting analysis only to randomized control trials, the rate of IBD worsening was marginal reconfirming the safety of FMT as a novel therapeutic modality. Considering the results of our meta-analysis, the potential risk of IBD worsening does not seem to outweigh the potential benefits of FMT. However, this does still raise the question, should patients with IBD who are under going FMT receive pretreatment compared with subjects without IBD? Several investigators have implemented the pre-emptive use of anti-inflammatory agents following FMT in IBD patients, though this requires further study. Lastly, the need for well-controlled, randomized, prospective studies to further investigate the source of IBD deterioration following FMT are needed to better understand this phenomenon.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.
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Appendix I: Search Strategy

Databases were searched using the following alternatives of fecal microbiota transplantation; “faecal,” “microbiota,” “microflora,” “feces,” “faeces,” “stool,” “fecal flora,” and “faecal flora;” individually with each of the following variations on transplant: “transplant,” “transfusion,” “implantation,” “implant,” “instillation,” “microbiota,” “donor,” “enema,” “reconstitution,” “infusion,” “therapy,” and “bacteriotherapy,” as earlier identified in previous studies. These terms were searched alone and in combination. The results were combined with varied IBD terms (“Crohn disease,” “Crohn’s disease,” “inflammatory bowel disease,” “colitis,” “ileitis,” “regional enteritis,” “ulcerative colitis,” “IBD,” “CD,” or “UC”) and combined by the Boolean term “AND.” This strategy was used both as Medical Subject Headings (MeSH) terms if available and as free text.