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Fecal transplantation for treatment of inflammatory bowel disease (Protocol)

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TABLE OF CONTENTS

[Intervention Protocol]

Fecal transplantation for treatment of inflammatory bowel disease

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

The objectives of this systematic review are to assess the efficacy and safety of FMT for the treatment of IBD.

BACKGROUND

Description of the condition

Ulcerative colitis (UC), and Crohn's disease (CD), subtypes of inflammatory bowel disease (IBD), are chronic, relapsing diseases of the gastrointestinal (GI) tract that results from the complex interplay between the immune system, microbes and the GI tract in genetically susceptible people (Abraham 2009; Cleynen 2016). UC is characterized by inflammation of the colonic mucosa and can affect variable lengths of the colon (Abraham 2009; Ananthakrishnan 2015). CD can cause transmural inflammation and affect any part of the GI tract from mouth to anus, with a particular predilection for the terminal ileum (Abraham 2009; Ananthakrishnan 2015). The prevalence of UC and CD is increasing in both developing and developed countries (Ahuja 2010; Dahlhamer 2016; Molodecky 2012; Weintraub 2014). IBD is associated with a poor quality of life, a significant economic burden and increased morbidity including the need for hospitalizations and surgical procedures (Abraham 2009; Abraham 2012; Mehta 2016). Most of the current treatment strategies for IBD focus on control of inflammation with medications, including corticosteroids, 5-aminosalicylic acid (5-ASA) preparations, immune-modulating drugs such as azathioprine, 6-mercaptopurine and methotrexate, and biologic therapies such as infliximab, adalimumab, vedolizumab and ustekinumab (Abraham 2009; Vindigni 2016). Unfortunately, these medical therapies have the potential for significant adverse effects. Moreover, while these therapies provide some benefit in many cases (Abraham 2009; Vindigni 2016), there are a significant number of patients who either do not re-

spond to any of these treatment modalities or become refractory over time. Ultimately, some patients may require a colectomy or surgical resection (Vindigni 2016). This supports the need for alternative treatment strategies that target known pathogenic factors to supplement or replace existing treatment strategies that directly target inflammatory cascades or modulate the immune response.

Description of the intervention

There is growing evidence to suggest that 'dysbiosis' is one of the key elements in the pathogenesis of IBD and could be a potential therapeutic target (Assa 2016; Bejaoui 2015; Kostic 2014; Vindigni 2016). Dysbiosis is defined as any alteration in the composition of resident commensal bacteria communities relative to the communities found in healthy individuals (Petersen 2014). In IBD, a decrease in the alpha biodiversity, an increase in certain pathogenic species, and an altered functional core of gut microbiota have been reported (De Preter 2012; Kostic 2014; Vindigni 2016).

Fecal microbiota transplantation (FMT) from healthy donors is one of the interventions used to correct dysbiosis (Cammarota 2017). While FMT is an increasingly studied intervention, most of the published literature on this intervention relates to the treatment of recurrent *Clostridium difficile* (*C. difficile*) infection (rCDI), where its efficacy is reported to be greater than 90% (Austin 2014; Cammarota 2015; Kassam 2013; Kelly 2016; Lee 2016; Leffler 2015; van Nood 2013; Youngster 2014). The Food and Drug Administration (FDA) of the United States considers FMT as a 'biologic product' and a 'drug' under its regulations, and labelled it as an investigational new drug, with exceptions for the treatment for rCDI where the FDA exercises enforcement discretion (FDA 2016; Moore 2014). Even though methods to perform FMT are evolving, a typical FMT procedure involves selection and screening of the donor, collection and preparation of the donor stool for infusion, preparation of the patient to receive the stool infusion and administration of the stool via the upper or lower gastrointestinal tract (Cammarota 2017). There is no universally agreed upon tool for donor screening; however, most studies have adopted a screening strategy similar to that used for a human tissue donor (Austin 2014; Cammarota 2017; Moore 2014; Owens 2013). A donor could be a relative or a non-relative. The donor is screened with an interview and blood and stool studies to rule out chronic diseases and active infectious diseases. After a donor is screened, the stool is collected to be used either immediately for infusion or frozen for later use. At least 30 to 50 g of faeces is typically collected and mixed with normal saline or sterile water in preparation for infusion. The patient is usually prepared with a lavage prior to the infusion. The donor faeces can be administered via colonoscopy, enemas, an upper gastrointestinal delivery route such as duodenal or gastric tubes, or through orally-ingested frozen capsules. All modalities have been studied with overall comparable efficacy, even though the colonic route is thought to be the most efficacious (Cammarota 2017; Lee 2016;van Nood 2013; Youngster 2014). Per published international standards, infection control precautions should be adopted during FMT (Cammarota 2017).

How the intervention might work

The exact mechanism by which FMT might work for inducing remission in IBD is not well established at this time. However, the prevailing hypothesis is that FMT might correct the 'dysbiosis' associated with IBD, leading to a reversal or improvement of the associated inflammation (Moayyedi 2015; Paramsothy 2017; Rossen 2015; Shi 2016; Sun 2016; Vindigni 2016). Knowledge around the use of FMT for treatment of IBD is evolving such that there is no consensus on the volume, timing, route, and frequency of fecal administration necessary to achieve remission (Cammarota 2017; Kelly 2015; Moore 2014). While a single infusion of feces is enough to treat rCDI in most cases (Austin 2014;Cammarota 2015; Kassam 2013), multiple infusions might be required for the induction of remission in IBD as suggested by the recent FOCUS trial from Australia (Paramsothy 2017). Similarly, response to FMT for rCDI may not vary much with the choice of donor (Osman 2016). However, donor selection might have a significant impact on the induction of remission in UC as reported by Moayyedi 2015, where 7 out of 9 patients who went into remission received stool from a single donor.

The short and long term safety of FMT in patients with IBD is not well established (Cammarota 2017; Kelly 2015; Moore 2014). Some studies report relatively minor adverse effects in the immediate post-procedure period such as diarrhea, abdominal bloating, abdominal cramping, and fever (Khoruts 2016; Kunde 2013). In addition, FMT may increase the risk of a flare in IBD patients (Kelly 2014; Khoruts 2016). Concerns remain that faeces may have microorganisms that can be potentially directly pathogenic to the recipient, and that the change in the functional core of bacteria may confer an undesirable and unanticipated outcome (Cammarota 2017; Alang 2015). Animal models of FMT have demonstrated undesired weight changes that accompanied changes in the microbiome (Blanton 2016; Ridaura 2013). Serious adverse events have been reported in individual cases, including mortality (Kelly 2014), septic shock and toxic megacolon (Solari 2014), and aspiration pneumonia (Link 2016).

Why it is important to do this review

As an increasing body of evidence in the basic science literature associates 'dysbiosis' with the pathogenesis of IBD, there have been efforts to correct the dysbiosis and assess if this can improve IBD-associated outcomes (Chassaing 2011; Fuentes 2017; Morgan 2012; Nagao-Kitamoto 2016; Rapozo 2017; Schulberg 2016; Vindigni 2016). Some of the interventions that might tar-

get gut microbiota include the use of probiotics, prebiotics synbiotics, nutrition therapy, and FMT (Vindigni 2016). Most of these interventions have been the subject of Cochrane reviews (Mallon 2007; Naidoo 2011; Singh 2015). However, FMT for treatment of IBD has not been evaluated in a Cochrane review. Moreover, the available non-Cochrane reviews have not included some of the most recent studies (Colman 2014), only assessed a limited number of outcomes (Shi 2016), and meta-analysed cohort studies and randomized trials in the same analysis (Sun 2016). None of the previous reviews systematically assessed the overall quality of the evidence supporting the use of FMT for treatment of IBD with the GRADE (Grades of Recommendations, Assessment, Development, and Evaluation) criteria. Furthermore, additional evidence has recently become available since the publication of previous reviews (Paramsothy 2017). Collectively, these observations make this an appropriate and opportune time to complete a Cochrane systematic review.

OBJECTIVES

The objectives of this systematic review are to assess the efficacy and safety of FMT for the treatment of IBD.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomized controlled trials, observational studies with a comparator arm, and single arm phase I trials (to assess safety). We will include randomized studies irrespective of whether the randomizations were performed at the individual or group level (cluster). For observational studies, we will include only prospective cohort studies, as it is difficult to assess temporality in other observational study designs. For cross-over trials, we will only include data from the first phase of the intervention. We will include randomized trials with multiple arms in a way that the only difference between the intervention and control group is FMT. We will exclude case reports and case series.

Types of participants

Studies will be included if the participants are diagnosed with IBD based on their history, physical examination, and gross endoscopic and histologic evaluations. We will exclude studies where the diagnosis is made without endoscopic or histologic evaluation as these two measures are considered key initial diagnostic studies for IBD (Mowat 2011). There will be no age restrictions for participants, and we will include both paediatric and adult patients. We will only include studies that followed participants for at least six weeks post-FMT (Feakins 2013).We will exclude studies with active enteric infections such as *C. difficile* as these conditions may mimic inflammatory bowel disease.

Types of interventions

We will include studies that evaluate FMT for treatment of IBD. FMT for this review will be defined as, "administration of fecal material containing distal gut microbiota from a healthy individual (donor) to a patient with a disease or condition related to dysbiosis, or an alteration in their normal gut microbiota (Kelly 2015)." Comparator groups will include standard medication, placebo, other control, or no intervention. We will include studies irrespective of the type of stool (liquid or frozen), the volume of stool, routes of administration, frequency (i.e. single versus multiple infusions) and timing of the transplant (at initial diagnosis or to treat a flare). We will exclude studies that used selective microbes rather than the whole stool microbiome from the donor, as this intervention does not fulfil the definition of FMT.

Types of outcome measures

Primary outcomes

The following outcomes will be considered:
1) Induction of clinical remission (as defined by the included studies);
2) Relapse (as defined by the included studies); and
3) Serious adverse events as defined by the authors.
We will measure the primary outcomes as the number of patients achieving clinical remission, relapsing or having serious adverse events, expressed as a proportion of the number of patients randomized.

Secondary outcomes

Secondary outcomes will include:
1) Clinical response (as defined by the included studies);
2) Endoscopic remission (as defined by the included studies);
3) Endoscopic response (as defined by the included studies);
4) Lab measures of inflammation (ESR, CRP, calprotectin) at the time of measurement of the primary outcome;
5) Quality of life (scores) at the time of the measurement of the primary outcome;
6) Any adverse events;
7) Withdrawals due to adverse events; and
8) Change in the alpha diversity in the fecal microbiome in the recipient.

Search methods for identification of studies

Electronic searches

We will search MEDLINE, EMBASE, the Cochrane Library, and the Cochrane IBD Group Specialized Register from inception to date. Please see Appendix 1 for detailed search strategy.

Searching other resources

We will search 'www.clinicaltrials.gov' and 'www.isrctn.com/page/mrct' for ongoing trials. We will search the reference sections of previously published randomized trials and meta-analyses on this topic. We will search the database "Conference Proceedings Citation Index" to search for conference abstracts. We will specifically search abstracts from the last 10 years from major conferences, such as Digestive Disease Week, Infectious Diseases Week, United European Gastroenterology Week , European Crohn's and Colitis Organisation , North American Society of Pediatric Gastroenterology, and the European Society of Pediatric Gastroenterology. Finally, we will contact authors of published and ongoing studies to seek new or additional data when needed.

Data collection and analysis

Selection of studies

Two authors (AI and MN) will do the initial screening to select potentially eligible studies by reviewing titles and abstracts. Any potential discrepancies will be resolved by discussion. After initial screening, selected studies will be further assessed by two authors (AI and MN) by review of full text and a final decision will be made about inclusion or exclusion. Any discrepancies will be resolved by discussion and consensus between two authors (AI and MN). If any conflict about the inclusion of a study persists, a senior author (SA) will be consulted to resolve the conflict.

Data extraction and management

Two authors (AI and MN) will independently extract data to a pre-tested Microsoft Excel sheet. We will extract information on the characteristics of included studies such as study authors, date of publication, journal, site of the study, type of study, age of participants, definition of study population (inclusion/exclusion criteria), details of intervention (type, volume, frequency, route of administration of fecal transplant, source), outcomes (primary and secondary outcomes) and risk of bias. We will extract the raw values of events (numerators) in cases and controls along with a total number of subjects allocated (denominators) to intervention and control groups. For studies using randomized control trial designs, we will extract data on an intention-to-treat basis, which considers the initial allocation of participants to an intervention or control group irrespective of whether or not they received the intervention or completed the follow-up (Gupta 2011).

Assessment of risk of bias in included studies

We will use the Cochrane risk-of-bias tool to assess the risk of bias in included randomized trials (Higgins 2011). Briefly, the risk of bias assessment will be based on six criteria: sequence generation, allocation concealment, masking, incomplete outcome data, publication bias and other bias. Each category will be assessed as 'Low risk', 'High risk' or 'Unclear' risk of bias.

For observational studies, we will use the Ottawa-Newcastle Scale to assess risk of bias (Wells 2017). Briefly, this scale assesses the quality of observational studies based on three criteria i.e. selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies, respectively.

Measures of treatment effect

We expect that the authors of included studies will report a range of clinical, endoscopic, and histologic outcomes in response to treatment with FMT. The most important of these outcomes are 'induction of clinical remission' and 'clinical relapse' which are the primary outcomes of our systematic review. We will use the definitions of clinical remission and clinical relapse as defined by the included studies (e.g. Mayo score for UC studies and the Crohn's disease activity index for CD studies). If the primary outcome reported in the trial was a combination of clinical and endoscopic or histologic assessment, we will try to include clinical remission or relapse data only, if available. If disaggregated data are not available, we will correspond with the authors to obtain clinical remission or relapse data. If these data are not available from the authors of the original studies, we will include the data for the combined outcome. All analyses from randomized trials will be conducted on an intention-to-treat analysis basis.

We will consider the primary outcome at 8 weeks and 12 weeks post-FMT. In the case of studies with multiple administrations of faeces, we will measure the primary outcomes at 8 weeks and 12 weeks after the last administration. If a study does not report a primary outcome exactly at 8 weeks but between 6 to 10 weeks post-FMT, it will be included as an outcome at 8 weeks. Similarly, if a study does not report the primary outcome exactly at 12 weeks but between > 10 weeks and 16 weeks, it will be included as an outcome at 12 weeks post-FMT. We will perform sensitivity analysis if there are a number of studies that do not report outcomes exactly at 8 or 12 weeks.

We will calculate the risk ratio (RR) and corresponding 95% confidence interval (95% CI) for all dichotomous outcomes. We will calculate the mean difference (MD) and corresponding 95% CI for continuous outcomes. For continuous outcomes that use different scales to measure the same underlying construct (e.g. quality

of life scores), we will calculate the standardized mean difference (SMD) and 95% CI. For observational studies with a comparison group, we will calculate the odds ratio (OR) and corresponding 95% CI for dichotomous outcomes. For single arm phase I trials, we will calculate the proportion (p) effect size for dichotomous outcomes.

Unit of analysis issues

If we encounter any cluster-randomized trials that are eligible for inclusion, we will synthesize findings from individual and cluster-randomized trials in a single meta-analysis. We will use the cluster-adjusted values as reported by authors. If the authors do not adjust for cluster design, we will adjust for this by decreasing the effective sample size as per the guidelines outlined in the Cochrane handbook (Higgins 2011). Similarly, for any observational studies using cluster-assignment to conditions, we will use cluster-adjusted values when available; otherwise we will adjust for clustering by decreasing the effective sample size.

For studies where there are multiple intervention groups (e.g. factorial design), the data will be included in such a way that the only difference between the two groups is FMT. Co-interventions will be permitted if the co-interventions are uniformly applied to both intervention and control groups. For cross-over trials, data will be included from the first segment of the trial only (before the cross-over occurs). We will consider outcomes at fixed intervals of follow-up (e.g. 8 weeks, 12 weeks) irrespective of how often the same outcome was measured before or after that time interval. We will only consider the effect of the first treatment attempt as defined by the authors. The treatment may include multiple infusions of FMT; however, if a patient receives a standard study treatment (intervention or placebo) more than once, the subsequent attempts will be ignored. Such a scenario might occur if authors decide to treat all the patients allocated to placebo with the study intervention at the end of a randomized study. Adverse events will be considered as reported by authors, and we will assume that each adverse event was an independent event unless the published report indicates otherwise.

Dealing with missing data

Attrition is an important factor that may impact the validity of studies, and differential dropout rates between the two study groups can lead to biased estimates of effect size (Dumville 2006). We will describe missing data, including dropouts and reasons for dropout as reported by authors. We will contact authors if data are missing and no reasons are provided for missing data. When authors report data for completers as well as controlling for dropouts (for example, imputed using regression methods), we will extract the latter. If data are not available for the primary outcome of this review, we will contact the authors for additional information. All data from randomized trials will be analyzed on an intention-to-treat basis. As such patients with missing values for the primary outcomes will be assumed to be treatment failures.

Assessment of heterogeneity

We will assess clinical, methodological and statistical heterogeneity among included studies. Clinical heterogeneity will be assessed by comparing the distribution of important factors such as study participants, dose, and frequency of FMT. Methodological heterogeneity will be assessed by comparing data included in the 'Risk-of-bias' tables. Statistical heterogeneity will be assessed based on visual inspection of forest plots, the I^2 statistic and the P value for the Chi^2 test. If the forest plot is indicative of a heterogeneous effect (opposite direction or prominent difference in magnitude of effect), while I^2 values are greater than 50% and P values for the Chi^2 test are less than 0.1, statistical heterogeneity will be considered to be substantial. We will explore potential explanations for heterogeneity using subgroup analyses as described below.

Assessment of reporting biases

Potential publication bias will be assessed with a funnel plot, and will be assessed based on the symmetry of the funnel plot. We will only construct funnel plots if at least 10 studies are included in the pooled analysis.

Data synthesis

We will combine data from individual trials for meta-analysis when the interventions, patient groups, and outcomes are sufficiently similar (as determined by consensus) using the software Review Manager version 5.3 (RevMan 2014). We plan to conduct separate meta-analyses for patients with UC and CD. For dichotomous variables, we will calculate the pooled RR and corresponding 95% CI . We will combine risk ratios (events per participant) and rate ratios (events per participant-days/months/year) for two reasons: Studies are expected to be completed in a relatively shorter duration, and the primary outcome (induction of remission) is not expected to be a recurrent event. All meta-analyses will be conducted using the log risk ratio, with all reported results transformed back into the risk ratio metric for ease of interpretability.

For continuous outcomes, data will be combined to get a MD and corresponding 95% CI. When different scales are used to measure the same underlying construct, we will calculate the SMD (Hedges' g value) and corresponding 95% CI. We will use a random-effects model to conduct all the meta-analysis. The rationale for using a random-effects model is that we expect that there might be heterogeneity in the effect of FMT due to factors such as dose, frequency or donor source (e.g. single donor or multi-donor), as noted in the results of published studies (Moayyedi 2015; Paramsothy 2017; Rossen 2015).

For observational studies, we will pool the proportion of patients who went into remission and obtain a summary OR with a 95%

CI. For adverse event data from single arm phase I trials, we will conduct a meta-analysis of proportions using STATA (version 14). We will pool the proportion of patients with the outcome (e.g. adverse events) and obtain a summary estimate with a 95% CI. The meta-analyses of proportions will synthesize the logit-transformed proportion effect size and all reported results will be transformed back into the proportion metric for ease of interpretability.

The overall quality of the evidence supporting the primary outcomes and selected secondary outcomes will be assessed using the Grades of Recommendations, Assessment, Development and Evaluation (GRADE) criteria (Guyatt 2011). This method of evidence evaluation takes into consideration the impact of type of studies (i.e. randomized versus observational) and risk of bias, indirectness, inconsistency (i.e. unexplained heterogeneity), imprecision, and potential publication bias and rates the overall quality of the evidence as 'high', 'moderate', 'low' and or 'very low'. We will present the results of the GRADE evaluation in a 'Summary of Findings' table for all primary outcomes and selected secondary outcomes (e.g. clinical response, endoscopic remission,etc.).

Subgroup analysis and investigation of heterogeneity

We plan the following a priori subgroup analyses:

1) Route of administration: upper gastrointestinal tract (i.e. nasogastric, nasoduodenal, nasojejunal, gastric tube, capsulated) versus colonic (i.e. rectal or beyond);

2) Frequency of administration: single versus multiple;

3) Type of Donor: single donor versus multiple donors; self-identified donor versus stool repository; fresh sample versus frozen sample; and

4) Age of participants: pediatric population (< 18 years of age) versus adult (≥18 years of age).

Sensitivity analysis

The following sensitivity analysis will be performed:

1) Definition of clinical remission: studies that used clinical criteria only to define clinical remission or relapse versus studies that used a combination of clinical and endoscopic or histologic criteria to define remission or relapse and disaggregated data are not available; and

2) Choice of statistical model: random versus fixed-effect models for primary outcomes.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Search Strategies

MEDLINE

1. Exp Inflammatory bowel disease/
2. Crohn*.mp.
3. Ulcerative colitis.mp
4. IBD.mp.
5. Inflammatory bowel disease*.mp.
6. Or/1-5
7. Fecal microbiota transplant*.mp.
8. Faecal microbiota transplant*.mp.
9. fecal microbiome transplant*.mp.
10. Stool transplant*.mp.
11. FMT.mp.
12. Fecal transfusion*.mp.
13. Fecal bacteriotherap*.mp.
14. Or/7-13
15. 6 and 14

EMBASE

1. Exp Inflammatory bowel disease/
2. Crohn*.mp.
3. Ulcerative colitis*.mp

4. IBD.mp.
5. Inflammatory bowel disease*.mp.
6. Or/1-5
7. Fecal microbiota transplant*.mp.
8. Faecal microbiota transplant*.mp.
9. fecal microbiome transplant*.mp.
10. Stool transplant*.mp.
11. FMT.mp.
12. Fecal transfusion*.mp.
13. Fecal bacteriotherap*.mp.
14. Or/7-13
15. 6 and 14

Cochrane CENTRAL

#1 MeSH: [Inflammatory bowel disease] explode all trees
#2 Crohn
#3 Ulcerative colitis
#4 IBD
#5 #1 or #2 or #3 or #4
#6 MeSH: [Fecal transplant] explode all trees
#7 Fecal microbiota transplant*
#8 Faecal microbiota transplant*
#9 Fecal microbiome transplant*
#10 Stool transplant*
#11 FMT
#12 Fecal transfusion*
#13 Fecal bacteriotherap*
#14 Fecal bacteriotherap*
#15 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14
#16 #5 and #15

Clinical Trials. Gov

1. Fecal transplantation and Inflammatory Bowel Disease
2. Fecal transplant and Inflammatory Bowel Disease
3. Fecal microbiota transplant and Inflammatory Bowel Disease

CONTRIBUTIONS OF AUTHORS

AI and SA conceptualised the idea of the study. AI, MN, and SA wrote the manuscript. ETS assisted with formulating the methods for the protocol. SA, OG, JZ, DMBB and ETS helped with revisions and provided overall supervision for completion of the manuscript.

DECLARATIONS OF INTEREST

Aamer Imdad: None known

Maribeth R Nicholson: None known

Sari Acra: None known

Oscar Gomez-Duarte: receives funding from the NIH for research on enteric pathogens. In addition to his employment at the University at Buffalo, he offers lectures at the University of Santander for which he receive honoraria. Dr Gomez-Duarte is a member of the Revista Colombiana de Anestesiologia Editorial board which compensates him for time as an editor.

Emily E Tanner-Smith: None known

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