

Title: Effectiveness and safety of Fecal Microbiota Transplant in the Treatment of ulcerative colitis: A living systematic review.

OSF: <https://osf.io/6cuad>

DOI:

Authors:

Andrea Correa-Pérez

Affiliation: Clinical Biostatistics Unit. Hospital Universitario Ramón y Cajal (IRYCIS), Madrid, Spain. Faculty of Medicine. Universidad Francisco de Vitoria, Madrid, Spain

Jorge de Vicente Guijarro

Affiliation: Servicio de Medicina Preventiva y Salud Pública, Hospital Universitario Ramón y Cajal (IRYCIS) Madrid, Spain

Andrea Gaetano Gil

Affiliation: Clinical Biostatistics Unit. Hospital Universitario Ramón y Cajal (IRYCIS), Madrid, Spain

Juan Ocaña Jiménez

Affiliation: Servicio de Cirugía General y del Aparato Digestivo. Unidad de Coloproctología. Hospital Universitario Ramón y Cajal, Madrid, Spain

Raquel Luengo González

Affiliation: Department of Nursing and Physiotherapy. University of Alcalá, Madrid, Spain

David Rigau Comas

Affiliation: Iberoamerican Cochrane Centre. C/ Sant Antoni Maria Claret, 167. Pavelló 18, planta 0, 08025 Barcelona, Spain.

Josefina Bendersky

Affiliation: Institut d'Recerca-Servei d'Epidemiologia Clínica i Salut Pública. Hospital de la Santa Creu i Sant Pau. Carrer de Sant Quintí, 89, 08041 Barcelona, Spain

María Ximena Rojas Reyes

Affiliation: Institut d'Recerca-Servei d'Epidemiologia Clínica i Salut Pública. Hospital de la Santa Creu i Sant Pau. Carrer de Sant Quintí, 89, 08041 Barcelona, Spain

María N Plana Farrás

Affiliation: Unidad de Evaluación de Tecnologías Sanitarias, Ramón y Cajal University Hospital (IRYCIS), Madrid, Spain. CIBER Epidemiology and Public Health (CIBERESP)

Corresponding author:

Maria N Plana Farrás.

Email address: nieves.plana@salud.madrid.org

Postal address: Unidad de Evaluación de Tecnologías Sanitarias, Hospital Universitario Ramón y Cajal, IRYCIS, Madrid, España. CIBER de Epidemiología y Salud Pública (CIBERESP).

Funding sources/sponsors:

This work is part of a project that has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No



**Living Evidence Synthesis
Update report**

Hospital Universitario Ramón y Cajal

MSCA-IF-EF-ST #894990 (to María Ximena Rojas). This work is also supported by the Health Technology Assessment Unit of the Hospital Universitario Ramón y Cajal. The funders and institutions did not take any part in the development of this study.

Conflicts of interest: Authors have declared no conflict of interest.

© 2022 Hospital Universitario Ramón y Cajal, Spain/ EU H2020, Living Evidence to Inform Health Decisions Project. All rights reserved.

ABSTRACT:**Objective**

This living systematic review aims to provide a timely, rigorous, and continuously updated summary of the evidence available on the role of fecal microbiota transplant (FMT) for treatment of patients with moderate to severe ulcerative colitis (UC).

Design

Living systematic review.

Database

The Epistemonikos-L.OVE platform was used for evidence identification, screening, and selection. This platform has been validated as a repository for COVID-19 and proved to be a highly comprehensive source of evidence. The main search source for the L.OVE platform is the Epistemonikos database (<https://www.epistemonikos.org>), a comprehensive database that collates information from multiple sources to identify systematic reviews and their included primary studies, including Cochrane Database of Systematic Reviews, MEDLINE, EMBASE, CINAHL, PsycINFO, LILACS, DARE, HTA Database, Campbell database, JBI Database of Systematic Reviews and Implementation Reports, EPPI-Centre Evidence Library.

The team maintaining the Epistemonikos-L.OVE platform devised the literature search, using the following approach: i) Identification of terms relevant to the population and intervention components of the search strategy, using Word2vec technology to the corpus of documents available in Epistemonikos Database; ii) Discussion of search terms with methods experts to identify relevant, irrelevant and missing terms, iii) Creation of a sensitive boolean strategy encompassing all the relevant terms.

The results of the literature searches were automatically incorporated into the L.OVE platform (automated retrieval) and organized in the corresponding L.OVE of “Fecal microbiota transplant for ulcerative colitis”.

Methods

To prioritize the fecal microbiota transplantation administration route, comparators and outcomes more relevant for supporting the clinical decisions in the treatment of ulcerative colitis patients, we performed a Delphi process conducted by an expert panel in the field of gastroenterology and colorectal surgery. Given Delphi panel results, we decided to include randomized studies evaluating the efficacy and safety of FMT versus any active treatment in patients with moderate to severe ulcerative colitis. Measures included clinical remission, clinical relapse, endoscopic release, clinical response, free time without corticosteroid treatment, serious adverse events and health related quality of life. Two reviewers independently screened each study for eligibility. We planned to extract data and assess the risk of bias using the ROB-2 tool by duplicate. We also planned to apply the GRADE approach to assess the certainty of the

evidence for each outcome. This is the first update report since our previous baseline evidence synthesis report for this question. Last search date 11/07/2022.

Results

Since the beginning of this living review, searches have retrieved 202 references to the L-OVE platform. 28 were considered potentially eligible and 16 were reviewed in full text. The initial baseline report did not include any randomized clinical trial that evaluated the use of FMT compared to the use of any active treatment in patients with moderate to severe ulcerative colitis. No new randomized clinical trials were included for this update.

Conclusions

No randomized trials evaluating the effect of FMT versus any active treatment in patients with moderate to severe ulcerative colitis have been identified. As of this update, this Living Systematic Review will be withdrawn from the living model, as research on the review (PICO) question is not emerging.

Keywords

Living systematic review; fecal microbiota transplant; living evidence synthesis; ulcerative colitis; bowel inflammatory disease; gut microbiota.

INTRODUCTION

Condition being studied

Ulcerative colitis (UC) is a chronic inflammatory disease that mainly affects the large intestine and rectum, causing ulcers and other damage to the tissue (1). Typical intestinal symptoms of the disease are abdominal pain and bloody diarrhea. Other symptoms associated with the disease are the presence of tenesmus or urgency, weight loss and fever (1). Etiology and pathogenesis are not completely understood. Different studies propose that the disease could be the result of the interaction of different factors: a genetic predisposition, changes in the composition of the intestinal microbiota and an abnormal immune response to environmental exposures, mainly microbial (2-4).

Ulcerative colitis has two incidence peaks: between 15 and 25 years of age, and between 55 and 65 years of age (1,5). The disease alternates symptomatic episodes with periods of clinical remission or mild activity (2). Approximately 15% of patients may experience an aggressive course, of which up to 20% may require hospitalization (6). Despite recent advances in overall disease management and improved therapeutics, patients with inflammatory bowel diseases still experience a substantial disease burden (5).

Why it is important to do this review

Fecal microbiota transplantation (FMT) consists of the instillation of a fecal solution from a healthy donor to the gastrointestinal tract of a diseased recipient. Thus, natural bacteria are transferred in order to replace other pathological microbiota. It can be performed through different techniques such as colonoscopy, enema, upper endoscopy and nasojejunal or nasogastric tube. Fecal microbiota transplantation is an alternative treatment option for patients with multiple recurrences of clostridium difficile infection for whom appropriate antibiotic treatment has failed (7). In theory, every disease associated with the impairment of intestinal microflora might benefit from the therapeutic modulation of the gut microbiota. In this regard, several primary studies and systematic reviews (SRs) have been published over the past 10 years to assess the safety and effectiveness of FMT as a treatment for ulcerative colitis. We performed an initial tiered search strategy, beginning with the identification of SRs included in the Epistemonikos Database (8) for mapping the available evidence about this topic. We identified 16 SRs conducted during 2014 and 2021, that assessed the effect of FMT in inflammatory bowel diseases including ulcerative colitis. Based on these SRs we developed an evidence matrix that revealed 45 primary studies that have been included in the published reviews, but no review has included all of them (9). The most recently published SRs, Zhou 2020 (10) and Liu X 2021 (11), included 5 and 11 studies, respectively. The primary studies included in these SR show a great variability in fecal microbiota transplantation delivery methods, type and dose of microbiota, target population and outcomes of interest.

This systematic review have been developed as part of the Living Evidence to Inform Health Decisions project, which supports health system organizations in the implementation of the living evidence model for the development of evidence synthesis to inform health decisions (12).

METHODS

Protocol and registration

This manuscript complies with the 'Preferred Reporting Items for Systematic reviews and Meta-Analyses' (PRISMA) guidelines [20].

A protocol stating the objectives and methodology of this living evidence synthesis was registered in OSF (<https://doi.org/10.12688/openreseurope.14290.2>). This Living systematic review (LSR) was conducted as part of the Living Evidence to Inform Health Decisions project (12).

Electronic searches

We conducted searches using L·OVE (Living Overview of Evidence) platform (<https://app.iloveevidence.com>). The platform is a repository developed and maintained by Epistemonikos Foundation that uses the Epistemonikos database as the main source of evidence. Epistemonikos corresponds to a comprehensive database of systematic reviews and other types of evidence, maintained by screening multiple information sources to identify systematic reviews and their included primary studies, including Cochrane Database of Systematic Reviews, MEDLINE, EMBASE, CINAHL, PsycINFO, LILACS, DARE, HTA Database, Campbell database, JBI Database of Systematic Reviews and Implementation Reports, EPPI-Centre Evidence Library (8). In order to identify randomized trials and primary studies, not included in systematic reviews, an additional search was performed in MEDLINE. The results of the literature search in all databases were automatically incorporated (automated retrieval) into the L·OVE platform. Additionally, every three months, we manually searched for ongoing studies in the WHO International Clinical Trials Registry Platform and the clinicaltrials.gov. We did not search for grey literature.

A living search in the L·OVE platform to detect systematic reviews and randomized controlled trials was performed. The search was supported by an artificial intelligence algorithm deployed in the L·OVE "Fecal microbiota transplant in ulcerative colitis" providing instant and continuous identification of articles with a high likelihood to be eligible, adding them to the screening tool ("my screening").

Search strategies

Our literature search was devised by the team maintaining the L·OVE platform (<https://app.iloveevidence.com>), using the following approach:

- Identification of terms relevant to the population and intervention components of the search strategy, using Word2vec technology [23] to the corpus of documents available in Epistemonikos Database.
- Discussion of terms with content and methods experts to identify relevant, irrelevant, and missing terms.
- Creation of a sensitive boolean strategy encompassing all the relevant terms (see Appendix 1- Search strategy)

- Iterative analysis of articles missed by the boolean strategy, and refinement of the strategy accordingly.
- Application of validated filters to identify clinical trials in the MEDLINE database.

The searches covered from the inception date to 11/07/2022 when we performed the last screening in the repository for this question: https://app.iloveevidence.com/loves/5b5f2f63c80dd41ff5583f36?question_domain=5b1dcd8ae611de7ae84e8f14&population=5d52970369c00e3de533d807&intervention=5d9f92b83c12ef4de3dc e659&classification=all. No date, language, study design, publication status or language restriction were applied to the searches in the Epistemonikos or to the additional databases.

As part of the living evidence approach, we continuously monitored the evidence for the last five months; searches were continually (each hour) updated, and the screening was performed on a monthly basis.

Types of studies

We planned to include randomized controlled trials (RCT) and systematic reviews (SR). We excluded information from studies evaluating the effects on animal models or in vitro conditions.

Types of participants

We planned to include trials assessing participants with ulcerative colitis, as defined by the authors of the trials. Whenever we find substantial clinical heterogeneity on how the condition was defined, we plan to explore it using a sensitivity analysis.

Type of interventions

The intervention of interest was fecal microbiota transplantation. We did not restrict our criteria to any dosage, duration, timing or route of administration. Our comparison of interest was any treatment, excluding placebo.

Type of outcomes

We did not use the outcomes as inclusion criteria during the selection process. Any article meeting all the criteria except for the outcome criterion was preliminarily included and assessed in full text.

The primary outcome was clinical remission and the secondary outcomes were clinical response, corticosteroid free time, endoscopic remission, quality of life, serious adverse events.

Selection of studies

The results of the literature search in all databases were automatically incorporated into the L.OVE platform (automated retrieval), where they were de-duplicated by an algorithm comparing unique identifiers (database ID, DOI, trial registry ID), and citation details (i.e. author names, journal, year of publication, volume, number, pages, article title and article abstract). We subscribed to the L.OVE of our question to receive monthly alerts with new studies

incorporated. Two researchers independently screened the titles and abstracts yielded by the search against the inclusion criteria. We obtained the full reports for all titles that appeared to meet the inclusion criteria or required further analysis to decide about their inclusion.

We recorded the reasons for excluding trials in any stage of the search and outlined the study selection process in a PRISMA flow diagram adapted for the purpose of this project.

Extraction and management of data

We planned to collect by duplicate the following information: study design, setting, participant characteristics (including disease severity and age) and study eligibility criteria; details about the administered intervention and comparison, including dose and therapeutic scheme, duration, timing and route of administration; the outcomes assessed and the time they were measured; the source of funding of the study; the conflicts of interest disclosed by the investigators; and the variables need for the risk of bias assessment.

We planned to resolve disagreements by discussion, and one arbiter adjudicated unresolved disagreements.

Living evidence synthesis and statistical analysis considerations

To maintain the living evidence process for this review, two reviewer (AC and AG) was in charge for assessing eligibility of the evidence identified by searches and retrieved to the L.OVE of this question and applied the selection criteria presented above in a monthly basis. If a potentially eligible study was found, another reviewer (MNP) confirmed its eligibility by reading the full text. Results of evidence surveillance were collected and kept as part of the study records. Information on PRISMA was updated accordingly.

Criteria for selecting studies was revised every month. We did not introduced changes during the LE processes. All new eligible studies underwent to data extraction process.

Revisit of parameters

During the evidence monitoring process we re-assessed the research question and PICO components every month. As a result, up to 11/07/2022 we did not identify any relevant change in our PICO parameters.

Communication and publication of review updates

This review evidence monitoring status is reported monthly on the LE-IHD project website (<https://livingevidenceframework.com/en/lesr/>)

RESULTS

Results of the search

Since the beginning of this living review, searches have retrieved 202 references to the L-OVE platform. We considered 28 as potentially eligible and 16 were reviewed in full text.

The initial baseline report included 0 randomized clinical trial that evaluated the use of FMT compared to the use of any active treatment in adult patients with moderate or severe ulcerative colitis. For this update 0 new randomized clinical trials were included. Results presented in this report include the total of studies identified from the initial baseline synthesis up to 11/07/2022.

DISCUSSION

This living systematic review have not found RCTs evaluating the use of FMT compared to the use of any active treatment in adults patients with ulcerative colitis. Its results show that there is no evidence to conclude if there is any difference between the intervention and control groups.

This review is part of a larger project set up to put such an approach into practice. This project aims to produce multiple parallel living systematic reviews relevant to inform decisions, following the higher standards of quality in evidence synthesis production [21]. We believe that our methods are well suited to handle the evidence that is to come, including evidence on the role of FMT in ulcerative colitis. We concluded to stop monitoring the evidence on our research question because of research about the review PICO question is no emerging.

NOTES

Acknowledgements

The members of the Epistemonikos Foundation have made it possible to build the systems and compile the information needed by this project. Epistemonikos is a collaborative effort, based on the ongoing volunteer work of over a thousand contributors since 2012. Laura Trujillo, Master program student, who supported the screening of identified studies every month.

Roles and contributions

AC, RL and MNP drafted the manuscript, and all other authors contributed to it. The corresponding author is the guarantor and declares that all authors meet authorship criteria and that no other authors meeting the criteria have been omitted.

Competing interests

All authors declare no financial relationships with any organization that might have a real or perceived interest in this work. There are no other relationships or activities that might have influenced the submitted work.

Funding

Epistemonikos Foundation is providing training, support and tools at no cost for all the members of the organizations participating in the Living Evidence to Inform Health Decisions Project that has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No MSCA-IF-EF-ST #894990 (to María Ximena Rojas).

PROSPERO registration OSF registration

CRD42021257579 (29/10/2021).

<https://open-research-europe.ec.europa.eu/articles/2-17>.

Ethics

As researchers will not access information that could lead to the identification of an individual participant, obtaining ethical approval was waived.

Data sharing

All data related to the project will be available. Epistemonikos Foundation will grant access to data.

REFERENCES

1. Calkins BM, Mendeloff AI: Epidemiology of inflammatory bowel disease. *Epidemiol Rev.* 1986; 8(1): 60–91. PubMed Abstract | Publisher Full Text
2. Podolsky DK: Inflammatory bowel disease. *N Engl J Med.* 2002; 347(6): 417–29. PubMed Abstract | Publisher Full Text
3. Ungaro R, Mehandru S, Allen PB, et al.: Ulcerative Colitis. *Lancet.* 2017; 389(10080):1756–70. PubMed Abstract | Publisher Full Text | Free Full Text
4. Kirsner JB: Historical origins of current IBD concepts. *World J Gastroenterol.* 2001; 7(2):175–184. PubMed Abstract | Publisher Full Text | Free Full Text
5. Windsor JW, Kaplan GG: Evolving Epidemiology of IBD. *Curr Gastroenterol Rep.* 2019; 21(8):40. PubMed Abstract | Publisher Full Text
6. Fumery M, Singh S, Dulai PS, et al.: Natural history of adult ulcerative colitis in population-based cohorts: a systematic review. *Clin Gastroenterol Hepatol.* 2018; 16(3): 343–356.e3. PubMedAbstract | Publisher Full Text | Free Full Text
7. Johnson S, Lavergne V, Skinner AM, et al.: Clinical Practice Guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021

- Focused Update Guidelines on Management of Clostridioides difficile Infection in Adults. Clin Infect Dis. 2021; 73(5): e1029–e1044. PubMed Abstract | Publisher Full Text
8. Rada G, Pérez D, Araya-Quintanilla F, et al.: Epistemonikos: a comprehensive database of systematic reviews for health decision-making. BMC Med Res Methodol. 2020; 20(1):286. PubMed Abstract | Publisher Full Text | Free Full Text
9. Plana MN: FMT in Ulcerative Colitis. 2021; Cited: October 10, 2021. Reference Source
10. Zhao HL, Chen SZ, Xu HM, et al.: Efficacy and safety of fecal microbiota transplantation for treating patients with ulcerative colitis: A systematic review and meta-analysis. J Dig Dis. 2020; 21(10): 534–548. PubMed Abstract | Publisher Full Text
11. Liu X, Li Y, Wu K, et al.: Fecal Microbiota Transplantation as Therapy for Treatment of Active Ulcerative Colitis: A Systematic Review and Meta-Analysis. Gastroenterol Res Pract. 2021; 2021: 6612970. PubMed Abstract | Publisher Full Text | Free Full Text
12. Rojas-Reyes MX, Urrutia Chuchí G, Rada G, et al.: Implementing living evidence to inform health decisions: A strategy for building capacity in health sector (Protocol) [version 1; peerreview: 2 approved with reservations]. Open Research Europe. 2021; 1: 114. Publisher Full Text
13. Bendersky J: Fecal microbiota transplantation for treatment of moderate to severe ulcerative colitis: living systematic review (Protocol). 2021. <http://www.doi.org/10.17605/OSF.IO/NRZF6>
14. Okoli C, Pawlowski SD: The Delphi method as a research tool: an example, design considerations and applications. Inform Manage. 2004; 42(1): 15–29. Publisher Full Text
15. Living Overview of Evidence (L.OVE platform) disponible en. Reference Source
16. Verdugo-Paiva F, Vergara C, Ávila C, et al.: COVID-19 L-OVE REPOSITORY IS HIGHLY COMPREHENSIVE AND CAN BE USED AS A SINGLE SOURCE FOR COVID-19 STUDIES. medRxiv. Preprint. Publisher Full Text
17. Rada G, Pérez D, Araya-Quintanilla F, et al.: Epistemonikos: a comprehensive database of systematic reviews for health decision-making. BMC Med Res Methodol. 2020; 20(1):286. PubMed Abstract | Publisher Full Text | Free Full Text
18. Page MJ, McKenzie JE, Bossuyt PM, et al.: The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021; 372: n71. PubMed Abstract | Publisher Full Text | Free Full Text
19. Sterne JAC, Savović J, Page MJ, et al.: RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019; 366: l4898. PubMed Abstract | Publisher Full Text
20. Guyatt G, Oxman AD, Akl EA, et al.: GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011; 64(4): 383–394. PubMed Abstract | Publisher Full Text

Appendix 1

The main search source will be Epistemonikos database (<https://www.epistemonikos.org>), a comprehensive database of systematic reviews and other types of evidence, maintained by screening multiple information sources to identify systematic reviews and their included primary studies, including Cochrane Database of Systematic Reviews, MEDLINE, EMBASE, CINAHL, PsycINFO, LILACS, DARE, HTA Database, Campbell database, JBI Database of Systematic Reviews and Implementation Reports, EPPI-Centre Evidence Library (6).

For this project, additional search was performed on MEDLINE in order to identify randomized trials/primary studies not included in reviews.

Boolean search strategy**Epistemonikos**

```
(((((fecal* OR stool* OR microbi*) AND (transplant* OR bacteriotherapy*)))) AND (((ulcerative* AND colitis*)) AND (((inflammatory AND bowel) OR IBD OR IBDs) OR (crohn*) OR (ulcerative* AND colitis*))))
```

Medline. PUBMED

```
(((((fecal* OR stool* OR microbi*) AND (transplant* OR bacteriotherapy*)))) AND (((ulcerative* AND colitis*)) AND (((inflammatory AND bowel) OR IBD OR IBDs) OR (crohn*) OR (ulcerative* AND colitis*)))) AND ((randomi* OR RCT OR placebo* OR trial OR "controlled-trial" OR randomly*))
```