Article

Prebiotics for induction of remission in ulcerative colitis

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Sinopoulou, Vasiliki orcid iconORCID: 0000-0002-2831-9406, Gordon, Morris orcid iconORCID: 0000-0002-1216-5158, Limketkai, Berkeley N, Mullin, Gerard, Aali, Ghazaleh orcid iconORCID: 0000-0001-9325-9123 and Akobeng, Anthony K (2022) Prebiotics for induction of remission in ulcerative colitis. Cochrane Database of Systematic Reviews, 2022 (3). ISSN 1469-493X

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Prebiotics for induction of remission in ulcerative colitis (Protocol).
Cochrane Database of Systematic Reviews 2022, Issue 3. Art. No.: CD015084.
DOI: 10.1002/14651858.CD015084.

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[Intervention Protocol]

Prebiotics for induction of remission in ulcerative colitis

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Editorial group: Cochrane Gut Group.
Publication status and date: New, published in Issue 3, 2022.

Citation: Sinopoulou V, Gordon M, Limketkai BN, Mullin G, Aali G, Akobeng AK.Prebiotics for induction of remission in ulcerative colitis (Protocol). *Cochrane Database of Systematic Reviews* 2022, Issue 3. Art. No.: CD015084. DOI: 10.1002/14651858.CD015084.

ABSTRACT

Objectives

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

To assess the efficacy and safety of prebiotics for the induction of remission in people with active ulcerative colitis.

BACKGROUND

Description of the condition

Ulcerative colitis (UC) is a form of inflammatory bowel disease (IBD), a chronic condition that can alternate between remission and periods of active disease. It is characterised by inflammation of the intestinal mucosa, starting at the rectum and extending proximally; it is limited to the colon (Feuerstein 2014). Symptoms can include bloody diarrhoea, abdominal pain, urgency, and tenesmus; quality of life can be impacted to a significant degree. It can be diagnosed in children and adults alike, and diagnosis is based on individual medical history, clinical assessment of signs and symptoms, and endoscopic or histopathological findings. (Yangyang 2017).

UC global incidence is on the rise, especially in newly industrialised regions, such as Africa, Asia, and South America, where certain areas have reported increases of up to 15% since 1990 (Ng 2017). Even though incidence is stabilising in Western countries, such as Denmark, prevalence remains above 0.3%, representing a high burden for the individual, the people who care for them, and healthcare systems (Vadstrup 2020).

The aetiology of UC is purported to be complex and multifactorial, caused by the interaction of a multitude of environmental, genomic, immunological, and microbial factors. These interactions can lead to dysregulations that manifest as UC (De Souza 2017). More specifically, genetic predisposition, epithelial barrier defects, and a dysregulated immune response are thought to play a role in the development of UC (Kaur 2020).

Ulcerative colitis can be classified as mild, moderate, severe, or fulminant (very severe), which may guide treatment choices (Pabla 2020).

Description of the intervention

Prebiotics are a category of food ingredients considered to have health benefits for the gastrointestinal system (de Vrese 2008). Prebiotics were first defined in 1995 (Gibson 1995); their definition has evolved many times throughout the years (Carlson 2015). The word 'prebiotic' comes from the Greek words 'pre', meaning 'prior to', and 'bios', meaning 'life', relating to their significance as an energy source for the gut microbiome. Prebiotics cannot be hydrolysed or absorbed by humans; instead, they are fermented by microorganisms that inhabit the gut, producing short-chain fatty acids (SCFA), which have multiple effects on the gut and other areas of the body (Markowiak 2017). Prebiotics are mostly subsets of carbohydrates, mainly oligo-saccharides (Roberfroid 2007). The main prebiotic sub-categories are fructans, which include inulin and fructo-oligosaccharide, galacto-oligosaccharides, resistant starch, and glucose-derived oligosaccharides, such as polydextrose, and pectin and its derivatives. Some theories link certain types of prebiotics with the growth of particular bacterial strains; however, the debate is still ongoing (Davani-Davari 2019).

Prebiotics are found in a diverse variety of foods, and a range of supplements. Naturally, they are more commonly found in fruits, vegetables, legumes, and cereals. They can also be chemically synthesised, and used in a variety of food products, such as sports drinks, isotonic beverages, and cereal bars (Carlson 2015).

How the intervention might work

The proposed method of action for prebiotics is through their effect on the growth and activity of intestinal bacteria and probiotics (Bindels 2015).

There are vast numbers of microbial colonies in the gastrointestinal system that live in symbiosis with their host, meaning that both the microorganisms and the host benefit from co-existing. They can have immunomodulatory effects, prevent infection by venting off pathogens, and produce nutrients, such as SCFA, through prebiotic fermentation (Shokryazdan 2017). As such, prebiotics are the source of energy for these microorganisms, and their mechanism of action is mediated via their effect on them (Sanders 2019).

Intestinal microbiota play a major role in maintaining homeostasis, as key regulators of the proposed gut-brain axis (Cryan 2019). The microbiome is in constant communication with the brain via various metabolic routes, and the function of one affects the other. Imbalances and dysregulation of the gut-brain axis are thought to contribute to the emergence of gastrointestinal conditions and diseases, such as UC (Mukhtar 2019). Prebiotics can potentially benefit people affected by UC, by playing a modulator role (Wilson 2019).

Anticipated comparators to prebiotics can be probiotics and synbiotics. Microbes that are introduced into the body through the diet are known as probiotics. They can be found in raw or fermented fruits and vegetables, fermented dairy, and commercial products known as functional foods, or taken as pharmaceutical preparations (Davani-Davari 2019). Preparations that contain both probiotics and prebiotics are known as synbiotics (Swanson 2020). Probiotics and synbiotics can have favourable effects on the intestinal microbiota by promoting and maintaining a healthy balance of the microbial gut ecosystem (Markowiak 2017).

Why it is important to do this review

People affected by UC, and especially people with active UC, are constantly looking for treatments that can improve their health and quality of life; dietary therapies are an area of great interest (Jamieson 2007). Prebiotics have been the focus for a number of recent randomised controlled trials and systematic reviews for other gastrointestinal conditions, in which the prebiotics were mainly in the form of prepared prebiotic preparations, not as whole foods (Asha 2020; Ford 2018; McFarland 2019). However, the effects of prebiotics on UC remain unclear.

Previous Cochrane Reviews have reported low-certainty evidence for the efficacy of prebiotics on conditions, such as infant eczema and neonate hyperbilirubinaemia (Armanian 2019; Osborn 2013). There is also evidence to suggest that UC, IBD, and other related diseases may benefit from probiotics and dietary interventions (Iheozor-Ejiofor 2020; Kaur 2020; Limketkai 2019; Limketkai 2020; Sharif 2020).

The mention of prebiotics in current UC evidence-based and clinical practice guidelines is scarce. The latest British Society of Gastroenterology IBD guidelines provide a literature overview of prebiotics, probiotics, and synbiotics, without reaching a conclusion about prebiotics specifically (Lamb 2019). In their latest iteration, the European Society for Clinical Nutrition and Metabolism practical IBD guidelines do not include prebiotics as a point of consideration. However, they briefly discuss that "prebiotic

fibres may be useful in maintenance of remission in some patients with UC", but not as part of a formal recommendation (Bischoff 2020).

Prebiotics are very unlikely to replace other therapies as the sole agent to induce remission in UC, as essentially, they are a dietary intervention. Instead, they are more likely to be used with other therapies, such as probiotics and standard pharmacological therapy. This might have led to them being overlooked as a Cochrane Review topic for UC. Thus, we decided to systematically review their effect on the induction of remission in UC. It is important to systematically evaluate the evidence for their effectiveness and safety in UC (Ford 2018; Ooi 2019).

OBJECTIVES

To assess the efficacy and safety of prebiotics for the induction of remission in people with active ulcerative colitis.

METHODS

Criteria for considering studies for this review

Types of studies

We will include all published, unpublished, and ongoing randomised controlled trials (RCT) on prebiotic interventions for people with ulcerative colitis (UC). We will consider cross-over and cluster-RCTs. We will consider studies published as full text or abstract; we will also consider unpublished data.

Types of participants

We will include people of all ages and genders with UC with active disease.

Types of interventions

We will consider any type of standalone or combination prebiotic intervention, except those with synbiotics, as these include live bacteria as well as prebiotics.

Control interventions can be placebo, any other type of intervention, or no intervention. We will consider interventions of any dose and duration.

We will list all intervention and comparator groups in the characteristics of included studies tables.

Types of outcome measures

We will consider both dichotomous and continuous outcomes. If both dichotomous and continuous outcome data are available for the same outcomes, we will analyse and report them separately.

Primary outcomes

- Clinical remission, at end of study, as defined by the authors

Secondary outcomes

- Disease improvement, as defined by the authors (e.g. clinical response, corticosteroid withdrawal, endoscopic remission, histology scores, biochemical markers of inflammation, quality of life scores)
- Escalation of therapy (addition of therapy, surgery)
- Adverse events (number of adverse events and withdrawal due to adverse events, reported separately)

Search methods for identification of studies

Electronic searches

Our information specialist will search the following sources:

- Cochrane Central Register of Controlled Trials (CENTRAL, current issue) in the Cochrane Library
- MEDLINE Ovid SP (1946 to present)
- Embase Ovid SP (1974 to present)
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov; current date)
- World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch; current date)

We will translate the MEDLINE search strategy into the syntax of other resources, and adapt it to the other databases (Appendix 1). We used Cochrane's sensitivity-maximizing version of the MEDLINE RCT search filter for this search strategy (Lefebvre 2021). There will be no limitations on language, date, document type, or publication status for this search.

Searching other resources

As complementary search methods, we will carefully handsearch the reference lists of systematic reviews we deem relevant for potentially relevant studies for our review. In addition, we will scrutinise the references of studies included in our review. We will seek unpublished trials by contacting experts in the field, and we will scan the abstracts submitted to major international congresses from the three years prior to the search, to capture any studies presented but not yet published in full.

We will attempt to obtain translations of papers when necessary.

Data collection and analysis

We will carry out data collection and analysis according to the methods recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021a).

Selection of studies

Two review authors will independently screen the titles and abstracts identified during the literature search, using Covidence (Covidence). We will discard studies that clearly do not meet the inclusion criteria. We will obtain the full report of studies that appear to meet our inclusion criteria, or for which there is insufficient information to make a final decision. Two review authors will independently assess the reports to establish whether the studies meet the inclusion criteria. We will resolve disagreements by discussion, and consult with a third review author if resolution is not possible. We will enter studies rejected at this or subsequent stages in the characteristics of excluded studies tables, and record the main reason for exclusion. We will record the selection process in sufficient detail to complete a PRISMA flow diagram (PRISMA 2020).

Where studies have multiple publications, we will identify and exclude duplicates, and collate the reports of the same study so that each study, rather than each report, is the unit of interest for

the review; in these cases, we will assign a single identifier with multiple references.

Data extraction and management

Two review authors will independently carry out data extraction using data extraction forms, which will initially be piloted with two studies. Disagreements will be resolved by a third author. We will extract relevant data from full-text articles that meet the inclusion criteria including:

- Trial setting: country and number of trial centres;
- Methods: study design, total study duration and date;
- Participant characteristics: age, gender, diagnostic criteria, disease activity (mild, moderate, or severe), concomitant therapies, and total number;
- Eligibility criteria: inclusion and exclusion criteria;
- Intervention and comparator;
- Participant outcomes: outcome definition, unit of measurement, and time of collection;
- Results: number of participants allocated to each group, missing participants, sample size, outcome results;
- Funding source and conflicts of interest;
- Author contact information.

When multiple trial arms are reported in a single trial, we will include only the relevant arms. One review author will manually copy data into Review Manager Web, and another author will double-check the copied data (RevMan Web 2022). In the case of unclear or incomplete information or data, we will contact the study authors to request clarification.

Assessment of risk of bias in included studies

Following data extraction, two review authors will independently assess all studies that meet the inclusion criteria for their risk of bias, using the original Cochrane risk of bias (RoB 1) tool and criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will assess the following domains.

- Sequence generation (selection bias)
- Allocation concealment (selection bias)
- Blinding of participants and personnel (performance bias)
- Blinding of outcome assessment (detection bias)
- Incomplete outcome data (attrition bias)
- Selective reporting (reporting bias)
- Other bias

We will judge the studies to be at low, high, or unclear risk of bias for each domain assessed, based on the original risk of bias guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

After data extraction, the two review authors will compare the extracted data to discuss and resolve discrepancies before they are transferred into the characteristics of included studies table.

We will include all trials in the primary analyses. We plan to perform sensitivity analyses based on risk of bias.

If we find cluster-RCTs, we will assess risk of bias for: recruitment bias; baseline imbalance; loss of clusters; incorrect analysis; and comparability with individually randomised trials, as outlined in section 23.1.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Measures of treatment effect

For dichotomous outcomes, we will express treatment effect as risk ratios (RR) with corresponding 95% confidence intervals (CIs). For continuous outcomes, we will express the treatment effect as mean difference (MD) with 95% CI if studies use the same scales and methods. However, if studies assess the same continuous outcome using different methods, we will estimate the treatment effect using the standardised mean difference (SMD) with 95% CIs. We will present SMDs as standard deviation (SD) units and interpret them as follows: 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 a large effect, as outlined in section 12.6.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021a).

Unit of analysis issues

The participant will be the unit of analysis. For studies comparing more than two intervention groups, we will make multiple pair-wise comparisons between all possible pairs of intervention groups. To avoid double counting, we will divide shared intervention groups evenly among the comparisons. For dichotomous outcomes, we will divide both the number of events and the total number of participants. For continuous outcomes, we will divide the total number of participants, and leave the means and standard deviations unchanged.

We will include cross-over studies if data are separately reported before and after cross over; we will only use data from the first phase for our analysis. If we find cluster-RCTs, we will use study data only if the authors used appropriate statistical methods to take the clustering effect into account.

Dealing with missing data

We will contact authors when there are missing data, or studies have not reported data in sufficient detail. If studies report standard errors, we will attempt to estimate missing standard deviations, using relevant statistical tools and calculators (Higgins 2021b). We will judge studies that fail to report measures of variance as being at high risk of selective reporting bias.

Assessment of heterogeneity

We will scrutinise studies to ensure that they are clinically homogeneous in terms of participants, intervention, comparator, and outcome. To test for statistical heterogeneity, we will use a Chi^2 test. A P value of less than 0.1 will give an indication of the presence of heterogeneity. We will quantified and represent inconsistency with the I^2 statistic. We will interpret the thresholds as follows (Higgins 2021a):

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%; may represent substantial heterogeneity;
- 75% to 100%: may represent considerable heterogeneity.

Assessment of reporting biases

We will minimise most reporting biases by using an inclusive search strategy. We will investigate publication bias using a funnel plot if there are 10 or more studies. We will determine the magnitude of publication bias by visually inspecting the asymmetry of the funnel plot. In addition, we will test funnel plot asymmetry by undertaking a linear regression of the intervention effect estimate against its standard error, weighted by the inverse of the variance of the intervention effect estimate (Egger 1997).

Data synthesis

To summarise the study characteristics, we will undertake a narrative synthesis of all included studies. This will include key summary data of characteristics of participants within included studies. If there are two or more studies that assessed similar populations, interventions, and outcomes, we will undertake a meta-analysis. We will synthesise data using the random-effects model in Review Manager Web (RevMan Web 2022). We will combine effect estimates of studies that report data in a similar way in the meta-analysis. We will pool RRs for dichotomous outcomes and MDs or SMDs for continuous outcomes with 95% CIs.

When meta-analysis of effect estimates is not possible, we will summarise effect estimates (e.g. range and distribution of observed effects), combine P values (e.g. evidence that there is an effect in at least one study), or vote count, based on the direction of effect (e.g. is there any evidence of an effect? (Higgins 2021a)).

Subgroup analysis and investigation of heterogeneity

If there is heterogeneity, we will investigate possible causes, and address them using methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021a). If, despite this, substantial heterogeneity remains that cannot be explained or addressed, we will not undertake a full meta-analysis.

We will undertake subgroup analyses of potential effect modifiers if there are 10 studies or more (Deeks 2021). If enough data are available, we will perform subgroup analyses by age, sex or gender (if enough separate data are provided by the primary studies, we will report and analyse these factors separately), disease activity, long-term (≥ 4 weeks) or short-term (< 4 weeks) study duration, and prebiotic type.

Sensitivity analysis

When possible, we will undertake sensitivity analyses for the primary outcome of clinical remission, to assess whether the findings of the review are robust to the decisions made during the review process.

- we will include studies at low risk of bias across all risk of bias items
- we will include studies that have no risk of bias items rated as high risk
- when data analyses include studies with reported and estimated standard deviations, we will exclude studies with estimated standard deviations to assess whether this affects the findings of the review
- to explore heterogeneity, we will investigate whether the choice of model (fixed-effect versus random-effects) impacts the results
- we will also exclude cluster-RCTs to assess their impact on the results.

Summary of findings and assessment of the certainty of the evidence

Two reviewers will independently assess the certainty of the evidence; disagreement will be resolved by consulting and reaching consensus with a third author (Schünemann 2021). We will present the main results in a summary of findings table. We will export each comparison and all outcomes to GRADEpro GDT software to assess the certainty of the evidence (GRADEpro GDT). We will create summary of findings tables for all comparisons and we will include all outcomes (one primary and three secondary). Based on risk of bias, inconsistency, imprecision, indirectness, and publication bias, we will rate the certainty of the evidence for each outcome as high, moderate, low, or very low. These ratings have been defined as follows.

- High: further research is very unlikely to change our confidence in the estimate of effect.
- Moderate: further research is likely to have an important impact on our confidence in the estimate of effect, and may change the estimate.
- Low: further research is very likely to have an important impact on our confidence in the estimate of effect, and is likely to change the estimate.
- Very low: any estimate of effect is very uncertain.

We will justify all decisions to downgrade the certainty of the evidence using footnotes, and we will make comments to aid the reader's understanding of the review where necessary.

ACKNOWLEDGEMENTS

Dr. Farhad Shokraneh (Information Specialist) designed the search strategies for this review.

Cochrane Gut supported the authors in the development of this protocol.

The following people conducted the editorial process for this article:

Sign-off Editor: Paul Moayyedi (McMaster University)
Managing Editor: Teo Quay (McMaster University)
Information Specialist: Yuhong (Cathy) Yuan (McMaster University)
Copy Editor: Victoria Pennick
Peer-reviewers: Omar Cauli (University of Valencia; clinical/content review); Brock Williams (The University of British Columbia; clinical/content review)

The peer reviewers provided comments on this protocol, but were not otherwise involved in the editorial process or decision making for this article.

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APPENDICES

Appendix 1. MEDLINE search strategy

1 Colitis, Ulcerative/ or Inflammatory Bowel Diseases/ or (Idiopathic Proctocolitis or Ulcerative Colitis or Colitis Gravis).ti,ab.

2 Oligosaccharides/ or Prebiotics/ or exp Dietary Fiber/ or Resistant Starch/ or Gum Arabic/ or Inulin/ or Lactoferrin/ or Lactulose/ or (Dietary Fiber? or Dietary Fibre? or Fructooligosaccharide* or Oligofructose or Oligofructan or FOS or FOSS or Galactooligosaccharide* or Gum Arabic or Gum Acacia or Acacia Gum or Hi-Maize or Inulin* or Lactoferrin* or Lactotransferrin* or Lactulose* or Oligosaccharide* or Pre? Biotic* or Polydextrose or Resistant Starch or Roughage? or Wheat Bran? or Idolax or "Raftilose P95" or "RP G28" or "HAM RS2" or Duphalac or Normase or Amivalex).ti,ab.

3 ((Randomized Controlled Trial or Controlled Clinical Trial).pt. or (Randomi?ed or Placebo or Randomly or Trial or Groups).ab. or Drug Therapy.fs.) not (exp Animals/ not Humans.sh.)

4 and/1-3

CONTRIBUTIONS OF AUTHORS

VS: developed; produced the first draft; contributed to writing and editing; made an intellectual contribution to; approved the final version prior to submission; is a guarantor of the protocol

MG: conceived the review question; secured funding; developed, contributed to writing and editing, made an intellectual contribution to, advised on, approved the final version prior to submission; is a guarantor of the protocol

BL: made an intellectual contribution to; approved the final version prior to submission

GM: made an intellectual contribution to; approved the final version prior to submission

GA: provided substantial comments regarding intellectual content; approved the final version prior to submission

AA: made an intellectual contribution to; advised on; approved the final version of the protocol prior to submission

DECLARATIONS OF INTEREST

VS: has declared that they have no conflict of interest

MG: since January 2019, I have received travel fees to attend international scientific and training meetings from two Pharma companies. These grants included no honoraria, inducement, advisory role, or any other relationship, and were restricted to the travel and meeting-related costs of attending such meetings. This was DDW May 2019 from companies including Biogaia (2019) and Tillots (2019). Neither of these companies have had any involvement in any works completed by me, and I have never had any payments for any other activities for them, as confirmed below. From this date onwards, I have made a personal undertaking to take no further funds from any pharmaceutical or formula company in any form, for travel or other related activities. This is to lift the limitations such funding has on my ability to act as a first and corresponding author on reviews, in line with the Cochrane policies on such matters, and is reported in line with these policies. These current declarations will expire in May 2022 and this statement updated regularly to reflect this.

AA: has declared that they have no conflict of interest

BL: has declared that they have no conflict of interest

GA: has declared that they have no conflict of interest

GM: has declared that they have no conflict of interest

AKA: has declared that they have no conflict of interest

SOURCES OF SUPPORT

Internal sources

- National Institute for Health Research, UK

  NIHR funded project (Project:NIHR132748) - a programme of high priority Cochrane systematic Reviews to investigate the management of Inflammatory Bowel Disease during and after the COVID-19 pandemic: Optimal biologic and immunomodulator therapies, diet therapies, telehealth and education interventions

External sources

- None, Other

  None