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[Intervention Protocol]

Antibiotics for the induction and maintenance of remission in ulcerative colitis

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A B S T R A C T

Objectives

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

To determine whether antibiotic therapy is safe and effective for the induction and maintenance of remission in ulcerative colitis (UC).

BACKGROUND

Description of the condition

Ulcerative colitis (UC) is a chronic inflammation of the colon, characterised by periods of relapse and remission (Ordas 2012). Symptoms can include persistent diarrhoea, which may often be bloody, problems with defecation, abdominal pain, rectal pain and bleeding, weight loss and fatigue. It starts in the rectum and extends throughout the colon. UC and Crohn's disease (CD) are the two most common inflammatory bowel diseases (IBDs). UC tends to be more common than CD, with an estimated prevalence of 90 to 505 cases per 100,000 people in North America and Northern Europe (Conrad 2014). Whilst prevalence of UC has been historically higher in Western countries, its incidence in industrialised parts of Asia and Latin America is on the rise. The cause of UC is not known but is believed to be associated with certain genetic and environmental factors. The risk of developing UC is higher in Ashkenazi Jews, people with a family history of the disease and those who live in Western countries (da Silva 2014).

Description of the intervention

It has been proposed that there is a link between increased intestinal bacterial concentrations and chronic inflammation (Swidsinksi 2002; Vrakas 2017). Studies have suggested bacterial pathogens, such as *Escherichia coli*, Bacteroides spp, and *Mycobacterium avium,* are linked to the pathogenesis of UC. Antibiotics may influence the course of UC by decreasing the number of bacteria in the gut and altering the composition of the microbiome. Specific antibiotics that have been used for this purpose include ciprofloxacin, metronidazole, rifaximin, anti-tuberculous regimens and antibiotic combinations among others (Nitzan 2016). Oral administration of the antibiotics is the most common route. For induction of remission, antibiotics can be taken from a few days up to a month and for maintenance of remission from a few months to a year.

How the intervention might work

Several antibiotics have been evaluated for the treatment of UC. Reduction of the bacterial load in the intestinal mucosa might reduce the pathological immune response in the intestinal mucosa. Furthermore, antibiotics also act to limit bacterial translocation and reduce the concentration of adherent bacteria to the lumen and mucosa (Scribano 2013). In patients with high levels of *Escherichia coli* in their microbiome, treatment with mesalamine showed a decrease in intestinal inflammation; this further suggests the crucial role the gut microbiome may have in IBD pathophysiology and the potential for treatment with antimicrobial agents (Kostic 2014). There is a possibility that alteration of the mucosal flora may have a therapeutic role in UC by inhibiting the stimulus for pathogenic immune responses (Ott 2004; Swidsinksi 2002).

Why it is important to do this review

Given the possible role of the bacterial load in the pathogenesis of UC, it is reasonable to postulate that antibiotic therapy might be effective for either induction or maintenance of remission in UC. However, several potential problems exist with this approach. First, use of broad-spectrum antibiotics is a very generalised strategy that may aggravate the aforementioned dysbiosis. Second, the resident flora are determined by both genetic and dietary factors that may be difficult or impossible to modify on a chronic basis; therefore, treatment (if effective) might have to be continued indefinitely. Finally, broad-spectrum antibiotic therapy is associated with important adverse effects, notably an increased risk of *C. diff* (*Clostridioides difficile*, previously known as *Clostridium difficile)* infection. For these reasons, evidence from high-quality randomised controlled trials (RCTs) is necessary before antibiotics are accepted as effective and safe for the treatment of UC.

No current recommendations exist regarding the antibiotic of choice, dose, or duration for treatment of UC. Despite limited supporting evidence, the most recent guidelines published by the World Gastroenterology Organisation support the use of antibiotics in perianal disease, fistulising disease, and bacterial overgrowth secondary to stricturing disease (Bernstein 2016). A previous meta-analysis on this topic (Rahimi 2007) suggested that adjunctive antibacterial therapy is effective for induction of clinical remission in UC. However, recently published international guidelines do not recommend the routine use of antibiotics for induction and maintenance of remission in the management of UC, since trials of oral or intravenous antibiotics have not demonstrated any consistent benefit compared to conventional therapies, and a possible role is only suggested in case of infection or prior to surgery (Feuerstein 2020; Harbord 2017; Rubin 2019; Singh 2020). This Cochrane Review aims to examine the current evidence from RCTs that investigate the role of antibiotics in the induction and maintenance of remission in UC.

OBJECTIVES

To determine whether antibiotic therapy is safe and effective for the induction and maintenance of remission in ulcerative colitis (UC).

METHODS

Criteria for considering studies for this review

Types of studies

Only stydies with a randomised controlled trial (RCT) study design will be considered for inclusion, including cluster RCTs.

Cross-over RCTs will only be included if results are presented seperately for each stage of the trial, or if we can obtain them after contact with the authors.

Types of participants

Participants of any age and with any disease stage or extent will be considered for inclusion.

Participants with active or quiescent UC (as defined by the original studies) will be considered for inclusion.

Types of interventions

All types/classes of antibiotics will be considered, with any route of delivery (i.e. oral, intravenous). Trials that compare antibiotic therapy to a placebo or an active comparator will be considered for inclusion. Antibiotics used as adjunctive therapies or as monotherapy will be considered for inclusion.

Studies on induction of remission must have a minimum duration of at least two weeks to be considered for inclusion. Studies on maintenance of remission must have a minimum duration of at

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least three months to be considered for inclusion. We will exclude studies in which placebo or comparator groups have had recent antibiotic exposure (i.e. within the past six months).

Types of outcome measures

Primary outcomes

For studies on induction of remission, the primary outcome measure will be the proportion of participants who failed to achieve remission, as defined by the original studies.

For studies on maintenance of remission, the primary outcome measure will be the proportion of participants who relapsed, as defined by the included studies.

Secondary outcomes

Efficacy outcomes

1. The proportion of participants who failed to achieve clinical response (as defined by the original studies)
2. The proportion of participants who failed to achieve endoscopic remission (as defined by the original studies)
3. The proportion of participants who failed to achieve histological remission (as defined by the original studies)
4. The proportion of participants who had an endoscopic relapse (as defined by the original studies)
5. Health-related quality of life (as measured by a validated quality-of-life instrument)

Safety outcomes

1. The proportion of participants with any adverse event (AE)
2. The proportion of participants with serious adverse events (SAEs), as defined by the original studies
3. The proportion of participants who withdrew from the study due to adverse events

Search methods for identification of studies

Electronic searches

We will search the following databases for relevant studies.

1. Cochrane Central Register of Controlled Trials (CENTRAL) and Cochrane Database of Systematic Reviews (CDSR) (via Ovid) (Appendix 1)
2. MEDLINE (Ovid, 1946 to present) (Appendix 2)
3. Embase (Ovid, 1974 to present) (Appendix 3)
4. The Cochrane Gut Group Specialized Register (previously The Cochrane IBD Group Specialized Register)
5. ClinicalTrials.gov

Searching other resources

We will search the references listed in relevant studies and review articles for additional citations not identified in the search. Furthermore, we will search the conference proceedings from major meetings (Digestive Disease Week, the European Crohn's and Colitis Organisation congress, and the United European Gastroenterology Week conference) from the last five years, for studies published in abstract form only.

Data collection and analysis

Selection of studies

Two review authors will independently screen the search results for eligible studies based on the inclusion criteria as listed. Any disagreements will be brought to a third author and will be discussed until a consensus is reached.

Data extraction and management

Data will be extracted from included studies by two review authors, independently. Any disagreements over extracted data will be first discussed and then brought to a third review author for resolution if deemed necessary.

Assessment of risk of bias in included studies

Two review authors will independently assess all studies meeting the inclusion criteria for their risk of bias using criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). The following domains will be assessed.

- 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 (such as imbalance in participants' baseline characteristics)

We will judge the studies to be at low, high or unclear risk of bias for each domain assessed, based on the guidance in *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will classify overall risk of bias in the trials as being low if all the bias domains are classified as being at low risk of bias; and we will classify overall risk of bias as high if one or more of the bias domains described in the above paragraphs are classified as being at unclear or high risk of bias.

After data extraction, the two review authors will compare the extracted data and discuss and resolve discrepancies before the data are transferred into the 'Characteristics of included studies' table. For cluster-RCTs, we intend to judge risk of bias as prescribed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011)

Measures of treatment effect

We will use Review Manager 5 to analyse the data on an intention-to-treat (ITT) basis. We will use risk ratios (RRs) for dichotomous outcomes, with 95% confidence intervals (CIs). For continuous outcomes, we will calculate the mean difference (MD) if all studies reported their outcomes using the same scale, and standardised mean difference (SMD) with 95% CIs if the studies used different scales to report their outcomes.

Unit of analysis issues

Cross-over trials will be included if data are available for the first phase of the trial prior to cross-over. To deal with events that may re-occur (e.g. adverse events), we will report on the proportion of participants who experienced at least one event. Separate comparisons will be performed for studies that compared

antibiotics to placebo and for studies that compared antibiotics to other active therapies. We will also perform separate comparisons for each type of antibiotic. If we encounter multiple treatment groups (e.g. for different doses of antibiotics), we will divide the placebo group across the treatment groups, or combine groups to create a single pairwise comparison, as appropriate.

Dealing with missing data

An ITT analysis will be used for dichotomous outcomes, whereby participants with missing treatment outcomes will be assumed to be treatment failures. Sensitivity analyses will be performed to assess the impact of this assumption on the effect estimate.

Assessment of heterogeneity

We will assess heterogeneity using the Chi^2 test (a P value of 0.10 will be considered statistically significant) and the I^2 statistic. We will consider an I^2 statistic of 75% or greater to indicate high heterogeneity among study data, between 75% and 50% to indicate moderate heterogeneity, and 25% or less to indicate low heterogeneity (Higgins 2003). Sensitivity analysis will be conducted to explore possible explanations for heterogeneity.

Assessment of reporting biases

We will initially compare outcomes listed in the study protocols to those reported in the published manuscripts. If we do not have access to a study protocol, we will compare the outcomes listed in the methods section of the published manuscript to what was reported in the results section. If any pooled analyses include 10 or more studies, we will investigate potential publication bias using funnel plots (Egger 1997).

Data synthesis

Data from individual trials will be combined for meta-analysis when the interventions, participant groups and outcomes are similar, as deemed by author consensus. A fixed-effect model will be used to pool data unless significant heterogeneity exists between the studies. A random-effects model will be used if heterogeneity exists (i.e. where the I^2 value is 50% to 75%). We will not pool data for meta-analysis where there is a high degree of heterogeneity (i.e. an I^2 value of 75% or greater).

Subgroup analysis and investigation of heterogeneity

If enough data are available, we plan to perform subgroup analyses of the primary outcomes for the following factors.

1. Age of participants (children versus adults)
2. Different antibiotic doses/choices
3. Duration of the intervention
4. Gender (female versus male)
5. Route of delivery (oral versus intravenous)

Sensitivity analysis

Where possible, we will undertake a sensitivity analysis for the primary outcome of 'failure to achieve remission' for induction studies and 'relapse' for maintenance studies, to assess whether the findings of the review are robust to the decisions made during the review process. In particular, we will exclude from the analyses studies at high or unclear risk of selection bias (due to the method of allocation concealment) and performance bias. Where data analyses include studies with reported and estimated standard deviations, we will exclude those with estimated standard deviations to assess whether this affects the findings of the review. We will investigate whether the choice of model (fixed-effect versus random-effects) may have affected the results.

GRADE and 'Summary of findings' table

We will present the main results in a 'Summary of findings' table. Each comparison and primary outcome will be exported to GRADEpro GDT software (developed by the GRADE Working Group) for quality assessment. Data permitting, we intend to present four 'Summary of findings' tables. Other comparisons will be graded and presented in additional tables. Based on risk of bias, inconsistency, imprecision, indirectness and publication bias, we will grade the quality of the evidence for each outcome as high, moderate, low, or very low. These ratings have been defined as follows.

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

We will justify all decisions to downgrade the quality of the evidence using footnotes, and we will make comments to aid readers' understanding of the review where necessary. The outcomes we plan to include in the tables are both primary outcomes and withdrawal of participants due to adverse events.

ACKNOWLEDGEMENTS

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APPENDICES

Appendix 1. Cochrane CENTRAL and CDSR search strategy (Ovid)

1. exp ulcerative colitis/

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2. Inflammatory Bowel Diseases/

3. (colitis or proctocolitis or proctosigmoiditis or proctitis or rectosigmoiditis or rectocolitis or colorectitis or coloproctitis or UC).tw,kw.

4. inflammatory bowel disease*.tw,kw.

5. IBD.tw,kw.

6. or/1-5

7. exp Anti-Bacterial Agents/

8. exp *Anti-Infective Agents/

9. (antibiotic* or anti-biotic* or antibacterial* or anti-bacterial*).tw,kw.

10. (antimicrobial* or anti-microbial* or antiseptic* or anti-septic*).tw,kw.

11. (bactericid* or bacteriocid*).tw,kw.

12. Bacteriostatic.tw,kw.

13. (ciprofloxacin or metronidazole or levamisole or ornidazole or fusidin or rifaximin or vancomycin or fusidic acid or nitazoxanide or teicoplanin or rifampicin or bacitracin or fidaxomicin or amoxicillin or azithromycin or cephalosporin* or cephalexin or clarithromycin or clindamycin or doxycycline or erythromycin or flouroquinolone* or levofloxacin or macrolide* or nitrofurantoin or penicillin or tetracycline or trimethoprim).mp.

14. or/7-13

15. 6 and 14

Appendix 2. MEDLINE search strategy (Ovid)

1. exp ulcerative colitis/

2. Inflammatory Bowel Diseases/

3. (colitis or proctocolitis or proctosigmoiditis or proctitis or rectosigmoiditis or rectocolitis or colorectitis or coloproctitis or UC).tw,kw.

4. inflammatory bowel disease*.tw,kw.

5. IBD.tw,kw.

6. or/1-5

7. exp Anti-Bacterial Agents/

8. exp *Anti-Infective Agents/

9. (antibiotic* or anti-biotic* or antibacterial* or anti-bacterial*).tw,kw.

10. (antimicrobial* or anti-microbial* or antiseptic* or anti-septic*).tw,kw.

11. (bactericid* or bacteriocid*).tw,kw.

12. Bacteriostatic.tw,kw.

13. (ciprofloxacin or metronidazole or levamisole or ornidazole or fusidin or rifaximin or vancomycin or fusidic acid or nitazoxanide or teicoplanin or rifampicin or bacitracin or fidaxomicin or amoxicillin or azithromycin or cephalosporin* or cephalexin or clarithromycin or clindamycin or doxycycline or erythromycin or flouroquinolone* or levofloxacin or macrolide* or nitrofurantoin or penicillin or tetracycline or trimethoprim).mp.

14. or/7-13

15. 6 and 14

16. randomized controlled trial.pt.

17. controlled clinical trial.pt.

18. random*.mp.

19. placebo.ab.

20. trial.ab.

21. groups.ab.

22. drug therapy.fs.

23. or/16-22

24. exp animals/ not humans.sh.

25. 23 not 24

26. 15 and 25

Note: Lines 16-25. RCT filter, used the "Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision); Ovid format". We made the following minor revision: we used "random*" instead of "randomized.ab" or "randomly.ab." to capture word variations such as "randomised, randomization, random".

Appendix 3. Embase search strategy (Ovid)

1. exp ulcerative colitis/
2. inflammatory bowel disease/
3. (colitis or proctocolitis or proctosigmoiditis or proctitis or rectosigmoiditis or rectocolitis or colorectitis or coloproctitis or UC).tw,kw.
4. inflammatory bowel disease*.tw,kw.
5. IBD.tw,kw.
6. or/1-5
7. exp antibiotic agent/
8. exp *antiinfective agent/
9. (antibiotic* or anti-biotic* or antibacterial* or anti-bacterial*).tw,kw.
10. (antimicrobial* or anti-microbial* or antiseptic* or anti-septic*).tw,kw.
11. (bactericid* or bacteriocid*).tw,kw.
12. Bacteriostatic.tw,kw.
13. (ciprofloxacin or metronidazole or levamisole or ornidazole or fusidin or rifaximin or vancomycin or fusidic acid or nitazoxanide or teicoplanin or rifampicin or bacitracin or fidaxomicin or amoxicillin or azithromycin or cephalosporin* or cephalexin or clarithromycin or clindamycin or doxycycline or erythromycin or flouroquinolone* or levofloxacin or macrolide* or nitrofurantoin or penicillin or tetracycline or trimethoprim).mp.
14. or/7-13
15. 6 and 14
16. random:.tw.
17. placebo:.mp.
18. double-blind:.tw.
19. or/16-18
20. exp animal/ not human/
21. 19 not 20
22. 15 and 21

Note: Lines #16-19, RCT filter, used the Hedge Best balance of sensitivity and specificity filter. https://hiru.mcmaster.ca/hiru/HIRU_Hedges_EMBASE_Strategies.aspx

H I S T O R Y

Protocol first published: Issue 9, 2020

C O N T R I B U T I O N S   O F   A U T H O R S

MG: Conceived the review topic, contributed to all sections of the protocol and the peer review process

VS: Contributed to all sections of the protocol and the peer review process

CGC: Contributed feedback on draft versions of the protocol and peer review process

AKA: Contributed in the resolution of disagreements and offered general guidance

D E C L A R A T I O N S   O F   I N T E R E S T

MG: Since October 2017, I have received travel fees to attend international scientific and training meetings from 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. These include:

World Congress of Gastroenterology October 2017

DDW May 2018

Advances in IBD December 2018

DDW May 2019

The companies include: Biogaia (2017-19), Ferring (2018), Allergan (2017), synergy (bankrupt - 2018) and Tillots (2017-19).

None of these companies have had any involvement in any works completed by me and I have never had any payments for any other activites for them, as confirmed below.

From these 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 over the next 3 years and this statement updated regularly to reflect this.

VS: none

CGC: none

AKA: none