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# EFFECTIVENESS OF ANTIBIOTICS AS A TREATMENT OPTION FOR ADULTS WITH ACTIVE CROHN'S DISEASE: A META-ANALYSIS

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**Abstract –** ***Objectives:*** This paper examines the role of antibiotics in treatment of Crohn's Disease by investigating clinical trials done on the matter. We found antibiotic therapy to be effective in inducing remission or favorable clinical response in adults with active disease. The aim of the study is to perform a meta-analysis on the ability of antibiotics to induce remission or a favorable clinical response in Crohn's Disease (CD) patients.
***Materials and Methods:*** A meta-analysis of randomized, double-blind, placebo-controlled trials of antibiotics for treatment of CD in adults was conducted. Odds ratio and probability difference were performed to estimate risk difference. The Number Needed to Treat (NNT) was also calculated for each antibiotic reviewed (rifaximin, metronidazole, clarithromycin, and ciprofloxacin).
***Results:*** Thirty-six clinical trial studies were identified, including 3346 patients. Twelve studies reported remission (defined as a CDAI < 150, or authors' definition) while 24 reported solely a clinical response (defined as a decrease in CDAI or authors' definition) upon completing an antibiotic regimen. Antibiotics greatly improved patients' Crohn's disease activity, with a total response (defined as clinical response plus remission) odds ratio of 1.85 (95% CI: 1.41-2.43), a clinical response odds ratio of 1.87 (95% CI: 1.48-2.37), and a remission odds ratio of 1.90 (95% CI: 1.40-2.57). The Number Needed to Treat for each of the antibiotics used in the clinical trials were 4.17 (Ciprofloxacin), 7.14 (Clarithromycin), 7.14 (Metronidazole), and 9.09 (Rifaximin).
***Conclusions:*** The odds of a Crohn's Disease patient getting better is higher among those who take antibiotics most notably used in treating Inflammatory Bowel Disease than in placebo. This is an important outcome because it not only opens up a new treatment option for those suffering from Crohn's Disease, but it also leads credibility to the theory that Crohn's is caused, at least in part, by bacteria, such as *Mycobacterium avium* subspecies *paratuberculosis* (MAP) and adherent-invasive *Escherichia coli* (AIEC).

**Keywords:** Crohn's disease, Meta-analysis, Antibiotics, Inflammatory bowel disease (IBD), Remission, CDAI.

## INTRODUCTION

Crohn's disease (CD) is an inflammatory bowel disease (IBD), characterized by widespread inflammation of the intestines. The etiology and pathogenesis of this disease is still unknown, but it is suspected to arise from a combination of three complementary factors: genetic susceptibility[1], intestinal bacteria[2], and environmental factors[3], such as smoking[4], Western dieting[5], etc. The role of infectious agents, most notably *Mycobacterium avium* subspecies *para-*

*tuberculosis* (MAP), have long been suspected. MAP is the known agent of the bovine disease known as Johne's Disease (JD) which is very similar to CD[6,7]. Therefore, many research groups believe that CD is caused by MAP[8-11].

Therapeutic interventions in IBD primarily address the mucosal immune system; more specifically, there has been a preoccupation in stymying the inflammatory response by blocking tumor necrosis factor alpha (TNF-α)[12]. Although the biological treatments (adalimumab, infliximab, etc.) remain a staple in dealing with CD, these drugs do not reverse the effects of Crohn's Disease completely. Patients still experience the same old relapse and remission cycles with no end in sight.

If bacteria really do cause CD (at least in part), then it is no wonder that biologics do not cure the disease, as these drugs do not target the microbiome. To this end, the regulation and modification of the microbiome of an individual should be one of the main treatment options that gastroenterologists recommend to their patients. There is, however, a lack of comprehensive evidence-based recommendations on the topic.

There is, though, a wealth of randomized controlled trials (RCTs) on the usage of antibiotics as a treatment option for Crohn's disease[13-16]. The antibiotics used have included rifaximin (RFX)[13], ciprofloxacin (CIP)[14], metronidazole (MET)[15], and clarithromycin (CLR)[16], each given separately[14,15], or in combination with some other treatment[17].

The purpose, therefore, of this meta-analysis is to determine the effectiveness of antibiotics in reducing Crohn's Disease activity (*vs.* placebo or relevant control) in adults aged 18 and up.

## MATERIALS AND METHODS

This meta-analysis followed the preferred reporting items for the systematic reviews and meta-analyses (PRISMA) checklist[18].

### Data Source and Search Strategy

A search in the PubMed database up to April 21, 2020, was conducted. The following search terms were used: antibiotics, anti-bacterial, or antimicrobial in conjunction with Crohn's Disease, IBD, or inflammatory bowel disease. The search results were further restricted to double-blind, randomized, placebo-controlled clinical trials. The results were also time restricted so that only studies published between the years 2000 and 2020 (inclusive) were considered. Irrelevant studies were screened out after title and abstract review. Full-text and abstracts of studies that made it past the initial screening were evaluated more closely.

### Selection

Only studies and sources in English were considered. Studies were included if they were randomized, placebo-controlled, double-blinded trials, published between 2000 and 2020 (inclusive), and included the appropriate exposure. Exposure was defined as an adult patient (aged 18 years or older), receiving antibiotic treatment (rifaximin, clarithromycin, metronidazole, and ciprofloxacin) for their active Crohn's Disease. Active Crohn's Disease was defined as a Crohn's Disease Activity Index (CDAI) Score of over 150 (where applicable), or authors' definition. All doses of the antibiotics, as well as their duration, were included. Observational studies, open label studies, and duplicates were screened out. Single studies that reported both remission and clinical response (defined as a reduction in CDAI Score, or authors' definition) but reported distinct patient groups were analyzed as two separate trials.

### Data Extraction

Data was extracted onto a Microsoft Excel spreadsheet. First author, year of publication, study duration (in weeks, or days where applicable), number of participants in treatment and

control groups, treatment parameters (i.e., antibiotic and placebo), and event outcomes in both groups were obtained from each study.

The number of patients who went into remission and the number of patients who had a clinical response were the primary outcomes assessed in this analysis. Remission was defined as a reported CDAI score of less than 150 (where applicable; if CDAI score was not reported, then remission was reported using the authors' definition). Clinical response was defined as a decrease in CDAI score of at least 50 from the beginning to the end of the study duration (where applicable; if CDAI score was not reported, then clinical response was reported using the authors' definition). Total response was defined as the sum of the number of patients who achieved remission and the number of patients who achieved clinical response as defined above (where applicable).

## Risk Difference

Probability difference (PD) was used as the measure of risk differences, as described by Whitehead, 2002[19]. For a trial with NT subjects in the antibiotic treatment group, NC subjects in the control group, and $S_T$ and SC being the number of patients with a clinical response and/or remission, respectively, the ML estimate of the probability difference can be calculated with Equation 1 below:

$$PD = \frac{S_T}{N_T} - \frac{S_C}{N_C} \tag{1}$$

The asymptomatic estimate of the variance of this method was calculated using Equation 2 below:

$$Var_{PD} = \frac{(S_T)\,(F_T)}{(N_T)^3} + \frac{(S_C)\,(F_C)}{(N_C)^3} \tag{2}$$

Where $S_T$ and $S_C$ denote the same as in Equation 1, and $F_T$ and FC denote failure in the treatment and control groups, respectively. Failure was defined as a lack of clinical response from the treatment. Because remission was counted as a type of clinical response, a lack of remission was not counted as failure.

## Relative Odds

Odds ratio (ORs) were calculated using the Mantel-Haenszel method, as described by Whitehead, 200219, using Equation 3 below:

$$OR = \frac{(S_T)\,(F_C)}{(S_C)\,(F_T)} \tag{3}$$

Where $S_T$, $S_C$, $F_T$ and FC denote the same as in Equation 2.

The asymptomatic estimate of the variance of this method was calculated using Equation 4 below:

$$var(OR) = \frac{1}{S_T} + \frac{1}{S_C} + \frac{1}{F_T} + \frac{1}{F_C} \tag{4}$$

Where $S_T$, $S_C$, $F_T$ and FC denote the same as in Equation 3.

### Effect Size Translation

The Number Needed to Treat (NNT)[19] was used as the translation of the effect sizes of each outcome. The NNT is defined as the expected number of people who need to receive the treatment (in this case the studied antibiotic) versus the control for one additional person to respond favorably to the treatment[20]. The NNT was calculated using Equation 5 below:

$$OR = \frac{1}{abs\,(PD)} \tag{5}$$

Where PD denotes the probability difference as calculated in Equation 1, and abs is the absolute value function; the probability difference used was that of the random effects estimate of each antibiotic.

### Statistical Analysis

Statistical analysis was carried out using R Studio, R version 4.0.5 (2021-03-31) – "Shake and Throw", Platform: x86_64-w64-mingw32/x64 (64-bit). All calculations were verified by hand using Microsoft Excel.

## RESULTS

### Search Results

The results of the literature search are summarized in Figure 1. A total of 102 articles were located from PubMed. Based upon abstract and title review, 49 articles were removed for being unrelated to search or duplications of other acceptable studies, or review articles. Another 22 articles were removed for being outside the search parameter (7 were about animals, 7 studied children under the age of 18, and 8 were published prior to the year 2000). Of the remaining 31 studies, 15 of them were open label, non-random trials, so these were removed as well, leaving 16 articles to be studied. Twelve trials were located on ClinicalTrials.gov. Of these, 9 were excluded for using treatment options that were not antibiotics (these trials studied the usage of biologics, stem cell transplantation, etc.). One study did look at antibiotic usage, but in respect to preventing post-operative disease, rather than treatment of active disease. Therefore, of the 12 studies located, only two were used – NCT02240108 and NCT02240121. Eight of the PubMed studies and the two clinical trials reported both clinical remission and clinical response at different times, thus, a total of 36 studies were included in the meta-analysis[13-17, 21-33].

The 36 studies (Table I) evaluated Rifaximin (12 studies; 1622 patients), Ciprofloxacin (8 studies; 285 patients), Metronidazole (6 studies; 381 patients), and Clarithromycin (10 studies; 1058 patients). A total of 3346 patients underwent the clinical trials, with 1714 patients in the treatment group and 1632 patients in the control group. Publication dates ranged from 2001 to 2019.

### Risk Difference

The probability differences for each antibiotic by response type are presented in Figure 2. Random effects model results are presented. The weights for each antibiotic by response type are presented in Table II. Briefly, for Clinical Response, the weights for Rifaximin, Ciprofloxacin, Metronidazole, and Clarithromycin were 33.97%, 8.88%, 47.71%, and 9.44%, respectively. For Remission, these weights were 43.06%, 6.23%, 13.81%, and 36.89%, respectively. Finally, for Total Response, the weight the antibiotics contributed to the overall analysis were 37.78%, 7.77%, 33.49%, and 20.95%, respectively.

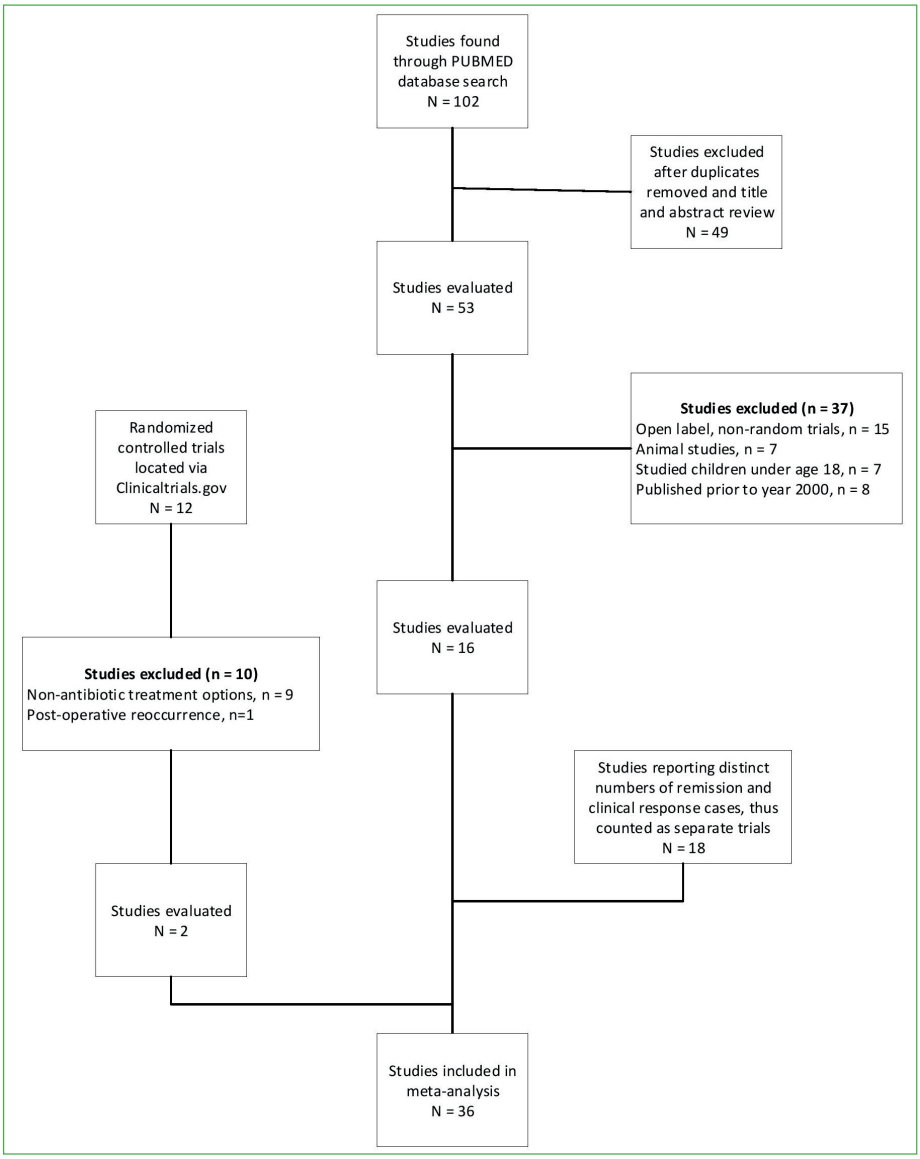


**Figure 1.** Evidence collection and selection.

The funnel plot of the Standard Error *vs.* Risk Difference (Figure 3) indicates there was little bias in the published results.

## Relative Odds

The odds ratio between antibiotic treatment and control was 1.90 (95% CI: 1.40-2.57) for Remission; 1.87 (95% CI: 1.48-2.37) for Clinical Response; and 1.85 (95% CI: 1.41-2.43) for Total Response. Random effects model results are presented. The weights for each antibiotic by response type are presented in Table II. The odds ratios of each antibiotic by response type are presented in Figure 4.

## Number Needed to Treat

The random effects estimate of the probability difference of each antibiotic (*vs.* placebo) was used to calculate the Number Needed to Treat (NNT) (see Equation 5 above). The NNT was based upon the random effects estimate of the total response (remission + clinical response) of a patient to antibiotic usage. The NNT for each antibiotic was 9.09 (Rifaximin), 4.17 (Ciprofloxacin), 7.14 (Metronidazole), and 7.14 (Clarithromycin).

**TABLE 1. SUMMARY OF RANDOMIZED, CONTROLLED, DOUBLE-BLIND TRIALS INCLUDED.**

| Study | Follow-up duration (wks.) | Response Type | Antibiotic Usage (success) | Antibiotic Usage (total) | Control (success) | Control (total) |
|---|---|---|---|---|---|---|
| **Rifaximin** | | | | | | |
| Prantera et al[21], 2006 | 12 | Clinical Response | 30 | 52 | 11 | 27 |
| Prantera et al[21,] 2006 | 12 | Clinical Disease Remission | 22 | 52 | 9 | 27 |
| Biancone et al1[3], 2008 | 1 | Clinical Response | 6 | 7 | 2 | 7 |
| Prantera et al[22], 2012 | 12 | Clinical Response | 176 | 301 | 52 | 101 |
| Prantera et al[22], 2012 | 12 | Clinical Disease Remission | 164 | 301 | 43 | 101 |
| Jigaranu et al[23], 2014 | 12 | Clinical Disease Remission | 65 | 83 | 34 | 83 |
| Bausch Health Americas, Inc[24], 2019[a] | 16 | Clinical Disease Remission | 17 | 35 | 12 | 45 |
| Bausch Health Americas, Inc[24], 2019[a] | 16 | Clinical Response | 10 | 35 | 10 | 45 |
| Bausch Health Americas, Inc[24], 2019[a] | 52 | Clinical Response | 9 | 35 | 15 | 45 |
| Bausch Health Americas, Inc[25], 2019[b] | 16 | Clinical Disease Remission | 12 | 40 | 15 | 40 |
| Bausch Health Americas, Inc[25], 2019[b] | 16 | Clinical Response | 16 | 40 | 16 | 40 |
| Bausch Health Americas, Inc[25], 2019[b] | 52 | Clinical Response | 11 | 40 | 10 | 40 |
| | | Total | 538 | 1021 | 229 | 601 |
| **Ciprofloxacin** | | | | | | |
| West et al[14], 2004 | 6 | Clinical Response | 1 | 3 | 10 | 21 |
| West et al[14], 2004 | 8 | Clinical Response | 10 | 18 | 1 | 6 |
| West et al[14], 2004 | 12 | Clinical Response | 10 | 18 | 1 | 6 |
| West et al[14], 2004 | 18 | Clinical Response | 8 | 13 | 3 | 11 |
| Thia et al[26], 2009 | 10 | Clinical Response | 4 | 10 | 1 | 8 |
| Dewint et al[27], 2013 | 12 | Clinical Disease Remission | 22 | 39 | 12 | 37 |
| Dewint et al[27], 2013 | 12 | Clinical Response | 24 | 39 | 17 | 37 |
| Herfarth et al[28], 2013 | 26 | Clinical Response | 6 | 9 | 5 | 10 |
| | | Total | 85 | 149 | 50 | 136 |
| **Metronidazole** | | | | | | |
| Steinhart et al[29], 2002 | 8 | Clinical Disease Remission | 21 | 64 | 25 | 66 |
| Castiglione et al[30], 2003 | 1.5 | Clinical Disease Remission | 8 | 15 | 6 | 14 |
| D'haens et al[31], 2008 | 12 | Clinical Response | 18 | 32 | 9 | 29 |
| Maeda et al[15], 2010 | 4 | Clinical Response | 10 | 27 | 4 | 34 |
| Manosa et al[17], 2013 | 26 | Clinical Response | 18 | 25 | 14 | 25 |
| Manosa et al[17], 2013 | 52 | Clinical Response | 16 | 25 | 11 | 25 |
| | | Total | 91 | 188 | 69 | 193 |

*CONTINUED*

**TABLE 1 *CONTINUED*. SUMMARY OF RANDOMIZED, CONTROLLED, DOUBLE-BLIND TRIALS INCLUDED.**

| Study | Follow-up duration (wks.) | Response Type | Antibiotic Usage (success) | Antibiotic Usage (total) | Control (success) | Control (total) |
|---|---|---|---|---|---|---|
| **Clarithromycin** | | | | | | |
| Goodgame et al[32], 2001 | 3 | Clinical Response | 10 | 18 | 5 | 18 |
| Goodgame et al[32], 2001 | 6 | Clinical Response | 8 | 15 | 7 | 17 |
| Goodgame et al[32], 2001 | 9 | Clinical Response | 9 | 14 | 6 | 16 |
| Goodgame et al[32], 2001 | 12 | Clinical Response | 7 | 13 | 8 | 13 |
| Selby et al[33], 2007 | 16 | Clinical Disease Remission | 67 | 122 | 35 | 189 |
| Selby et al[33], 2007 | 52 | Clinical Disease Remission | 41 | 65 | 61 | 166 |
| Selby et al[33], 2007 | 104 | Clinical Disease Remission | 31 | 47 | 71 | 148 |
| Selby et al[33], 2007 | 156 | Clinical Disease Remission | 14 | 24 | 88 | 91 |
| Leiper et al[16], 2008 | 4 | Clinical Response | 10 | 19 | 3 | 22 |
| Leiper et al[16], 2008 | 12 | Clinical Response | 5 | 19 | 6 | 22 |
| | | Total | 202 | 356 | 290 | 702 |
| | | Grand Total | 916 | 1714 | 638 | 1632 |

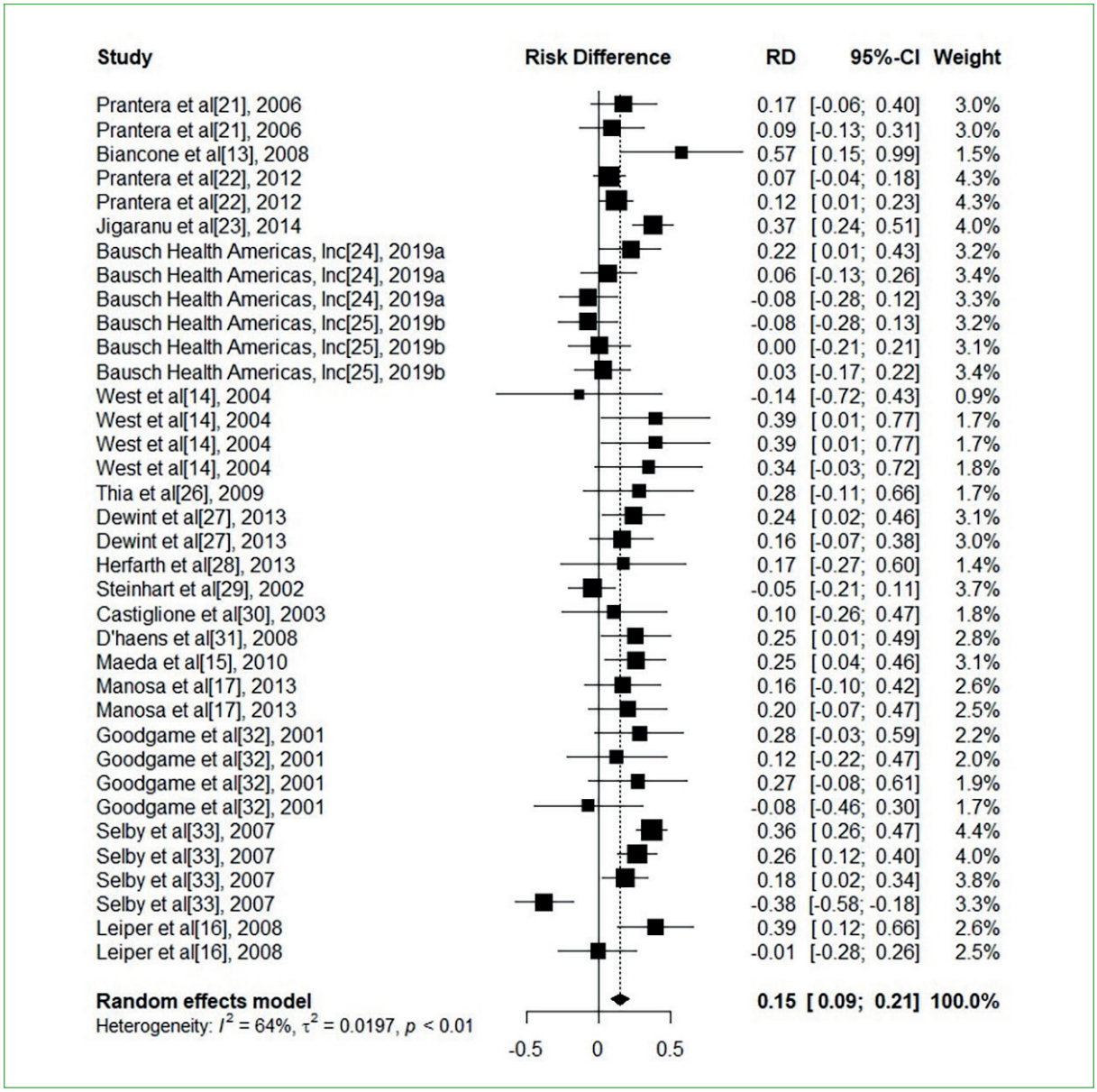


**Figure 2.** Difference of the 'risk' of response to antibiotics by adult patients with active Crohn's Disease and those treated with control. Risk difference is indicated by the numbers on the x-axis. Weight: the percentage contribution of an individual study to the overall estimation. The vertical dashed line indicates the overall point estimate, in this case the random effects estimate. The solid horizontal lines show the 95% confidence interval (CI). The size of the black box and diamond is proportional to the corresponding weight.

## DISCUSSION

The underlying causes of Crohn's Disease are still, as of yet, unknown, but it is suspected that bacteria play an important role in disease development/maintenance[2]. Various agents have been identified as being the likely pathogen, including adherent invasive *E. coli*, and *Mycobacterium avium* subspecies *paratuberculosis* (MAP)[6]. The veracity, though, of these claims constantly falls under intense scrutiny as each bacterium has its own set of support from research, as well as those that contradict them.

Despite this lack of consensus, it is agreed, though, that the microbiome is, in some way or form, associated with the disease[2]. As such, the manipulation of this area ought to be considered in treating the disease, the main way being via antibiotics.

**TABLE 2. WEIGHT OF EACH ANTIBIOTIC BY RESPONSE TYPE AND RISK ESTIMATE·**

| Response Type | Antibiotic | RD Weight (%) | OR Weight (%) |
|---|---|---|---|
| Clinical Disease Remission | Rifaximin | 43.06 | 44.1 |
| | Ciprofloxacin | 6.23 | 4.88 |
| | Metronidazole | 13.81 | 10.19 |
| | Clarithromycin | 36.89 | 40.83 |
| Clinical Response | Rifaximin | 33.97 | 48.92 |
| | Ciprofloxacin | 8.88 | 11.78 |
| | Metronidazole | 47.71 | 14.05 |
| | Clarithromycin | 9.44 | 25.25 |
| Total Response | Rifaximin | 37.78 | 46.39 |
| | Ciprofloxacin | 7.77 | 8.16 |
| | Metronidazole | 33.49 | 12.02 |
| | Clarithromycin | 20.95 | 33.42 |

This study makes a compelling case for the usage of antibiotics as a first-line treatment against Crohn's Disease.

First, a comparative analysis of antibiotic usage against active Crohn's Disease was performed (*vs.* control), using probability difference. Second, the odds ratio was calculated, revealing that antibiotic usage had greater odds of success against active disease than control.

Lastly, with the use of these analytical approaches, as well as the calculation of the NNT, it was shown that antibiotics are an effective treatment against active Crohn's Disease in adult patients.

In our study, all 36 qualified trials were included. Among these 36 studies, 1714 people were enrolled in the treatment group and 1632 in the control group. The median sample size of both the control and treatment groups were 27 people; the median follow-up duration

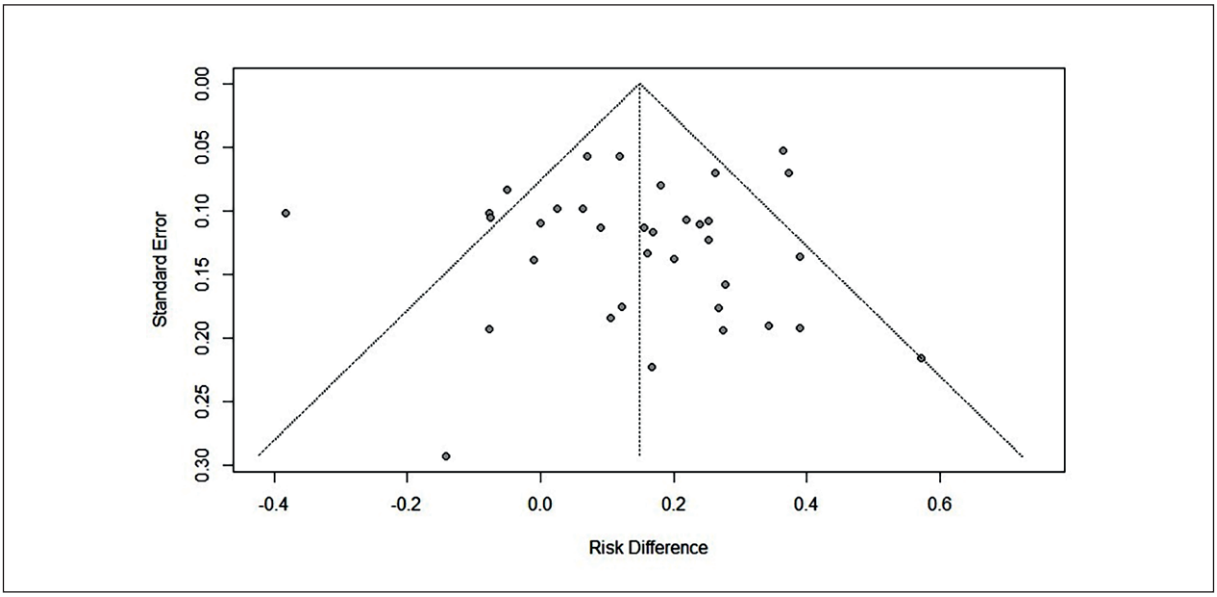


**Figure 3.** Relationship between the estimated effect of antibiotic usage on active Crohn's Disease risk difference and the corresponding standard error of the estimate. The dashed vertical line indicates the overall risk difference found, and the diagonal lines indicate the expected 95% confidence intervals associated with the mean RD for clinical trials with various numbers of study subjects.

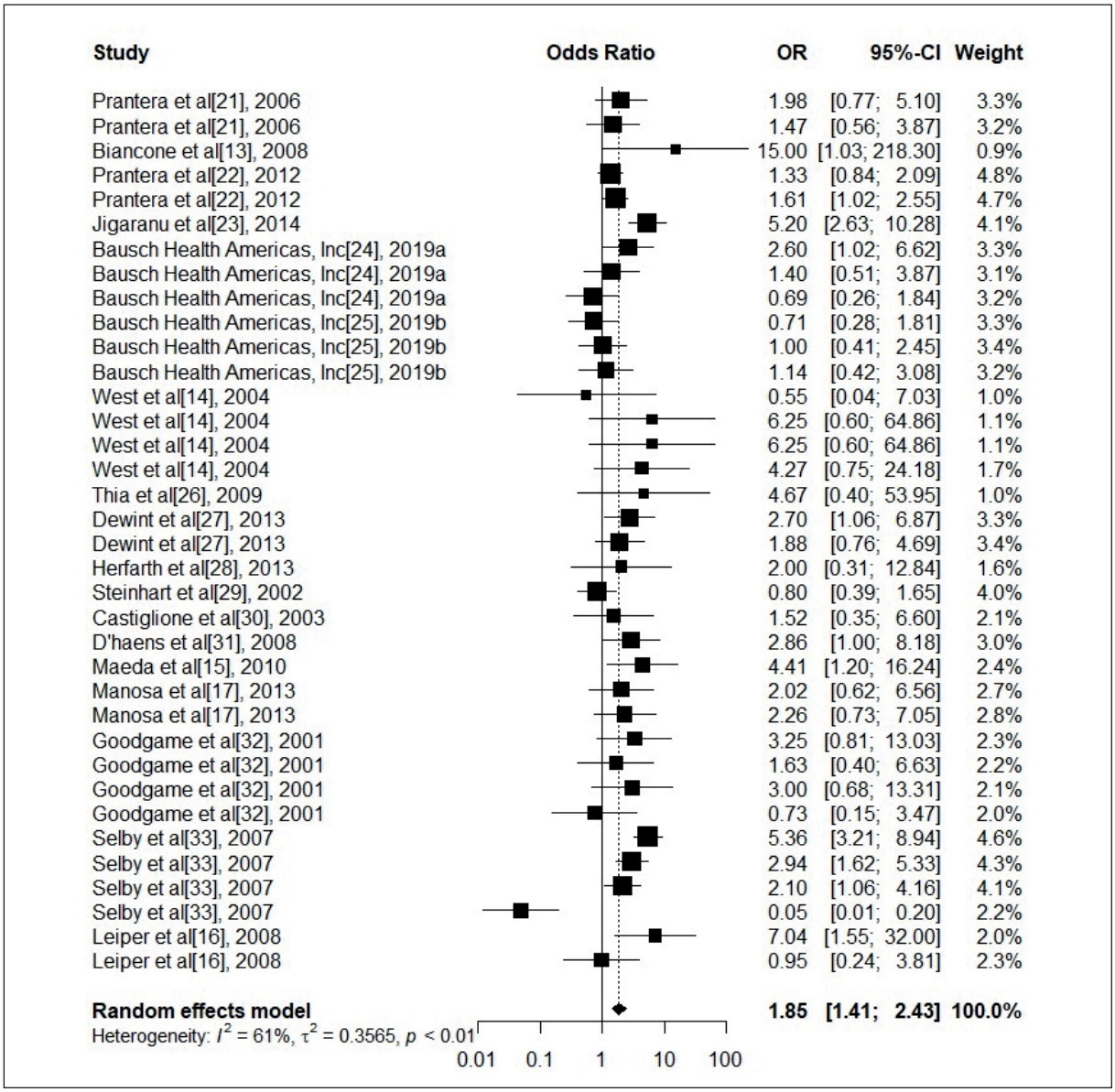


**Figure 4.** Odds of patients with active Crohn's Disease responding favorably to treatment with antibiotics relative to those treated with control. Odds ratio (OR) are indicated by the numbers on the x-axis. Weight: the percentage contribution of an individual study to the overall estimate. The vertical dashed line indicates the random effects odds ratio. The solid horizontal lines show the 95% confidence intervals (CI). The size of the black box and diamond is proportional to the corresponding weight.

was 12 weeks. Of the treatment group, a total of 916 (53.44%) reported a response (total response); 638 (39.09%) reported the same in the control group. Mathematically, this gives a log-odds ratio (LOR) of 0.313, and a probability difference (PD) of 0.143.

This calculation also gives an NNT of 6.97, which compares favorably against the NNT of anti-TNF therapy, whose NNT was calculated in one study to be 8.420 (lower number is a more effective treatment). What is remarkable about the results of this particular meta-analysis when it comes to the Number Needed to Treat is that all the antibiotics studied (in the exception of clarithromycin) had calculated NNTs that are lower than the current main-line treatment of CD.

Not only does this show that these antibiotics should be used as treatment, but also the nature of the antibiotics themselves gives insight into the causes of the disease. Biologics are

prescribed in order to block inflammatory signaling to lower a patient's inflammation. In other words, the treatment directly addresses the cause of a symptom. At a lower NNT than the anti-TNFs, antibiotics are shown to effectively treat active disease, revealing that bacteria must be a cause of CD. Notably, clarithromycin – an anti-mycobacterial drug – has an NNT that is lower than the anti-TNF [7.14 (CLR) *vs.* 8.4 (anti-TNF)]; this lends more evidence to the hypothesis that MAP causes CD.

Further research is needed to determine how antibiotic resistance may impact possible treatment of CD.

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## Authors' Contributions

JP the concept and design of the study; JP and KM the data acquisition; JP the data and statistical analysis; CW the data interpretation; JP drafted the manuscript; CW and KM revised the manuscript. All authors approved the final version to be published and agree to be accountable for all aspects of the work.

## Conflict of Interest

The authors declare no conflict of interest.

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