Antibiotics for Crohn's Disease: What Are We Treating?

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What causes Crohn's disease (CD)? This is a question that almost all patients ask for which no answer exists, despite great strides in the understanding genetic and environmental risk factors for CD. One of the most commonly accepted theories of CD pathogenesis is a triggering environmental exposure in a genetically susceptible host. An additional factor complicating understanding of the causative factors for CD is that an exposure may trigger the onset of intestinal inflammation, but may not be necessary for perpetuation of inflammation if the innate immune system is dysregulated. The implication of this concept is that even if a causative agent is identified and eliminated, eradication of that agent may not stop the inflammatory cascade that has already been set in motion.

One of the most confusing associations in the pathogenesis of CD is the contribution of antibiotics toward disease pathogenesis. Antibiotic exposure is linked to an increased risk of CD development, though antibiotics are also used to treat active CD. In a US population-based study, antibiotic use was associated with an increased risk of CD development with an adjusted odds ratio of 3.01, 95% confidence interval 2.27–4.0 and was significant for each antibiotic class individually, including quinolones, tetracyclines, and metronidazole [1]. Similar findings were also observed in a Canadian population-based study, with significant associations with all antibiotic classes except for clindamycin [2]. A challenge with associations in retrospective studies that are particularly relevant to the current question is confounding by indication and protopathic bias. For example, patients may have gastrointestinal symptoms prior to a formal CD diagnosis that was erroneously treated empirically with antibiotics, or CD patients had an infection as a triggering event

for their CD, which was treated with antibiotics. In the later situation, the triggering event may be an infection rather than the antibiotic exposure itself. Conversely, antibiotics are useful in the treatment of CD and related complications such as perianal fistula and pouchitis. Although systematic reviews have suggested a benefit of antibiotics for induction of remission for CD, study heterogeneity and the different types of antibiotics used cloud their interpretation [3].

Two microbial infections that are potentially pathogenic for CD are *E. coli* species and *Mycobacterium avium* subsp. *paratuberculosis* (MAP) [4]. Data supporting the contribution of MAP to Crohn's pathogenesis includes the parallels in clinical presentation of Johne's disease in cattle and CD in humans and suggestive epidemiologic trends, although systematic reviews and metaanalyses have not supported a strong causal relationship of MAP and CD [4]. For *E. coli*, the observation of bacterial serologic markers and CD also point toward a potential causal relationship. There is a higher rate of microbial and microbial component antibodies (Anti-*Saccharomyces cerevisiae* antibodies [ASCA], Outer membrane protein Complex [OmpC], and the flagellin antibodies CBir, FlaX, and Fla2) among CD patients compared with non-CD patients leading some to postulate a contribution of these microbes and microbial structures to CD pathogenesis. There is a large gap between studies that rigorously evaluate the efficacy of antibiotics to treat CD and studies of the mechanism of antibiotics used for CD.

In this issue of *Digestive Diseases and Sciences*, Rhodes et al. conducted an open-label randomized trial of a prolonged antibiotic course of ciprofloxacin, doxycycline, and hydroxychloroquine for 4 weeks, followed by 20 weeks of doxycycline plus hydroxychloroquine, compared with budesonide to treat active CD [5]. Hydroxychloroquine was added as it is able to enter macrophage vesicles in order to enhance efficacy against mucosal *E. coli*. The subjects in the arm randomized to budesonide received 9 mg/day for 8 weeks, subsequently tapered to 6 mg/day for 2 weeks, and then to 3 mg/d for 2 weeks. Subjects who failed to respond by 10 weeks were offered crossover to the other treatment arm. The primary endpoints were clinical remission

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(Crohn's disease activity Index [CDAI] ≤ 150) at week 10, maintained through week 24, and maintained through week 52. Though the target enrollment of the study as 50 per arm, only 61 patients total were randomized to the study; enrollment was terminated prematurely due to slow recruitment and the recommendation by the data monitoring committee that data were sufficient to address the primary aim.

For the primary outcomes of clinical remission, no significant difference was detected between antibiotics compared with budesonide at any time point. Including patients who crossed over to antibiotics, maintenance of remission at week 24 was higher in the antibiotic arm compared with budesonide (6 of 39 vs. 1 of 39, $p=0.001$), although only one patient in each treatment arm remained in remission through week 52. Between weeks 10–24, although patients in the antibiotic arm were continued on hydroxychloroquine and doxycycline, the budesonide arm was converted to no therapy. Since an extended benefit of steroids after discontinuation of budesonide would be unlikely, the decrease in patients in remission from 10 to 1 by week 24 is expected. Patients continued on antibiotic treatment mostly maintained remission with 6/39 patients in remission at week 24. Yet, this includes 3 patients who were not in remission at week 10 but went into remission by week 24. Antibiotics were discontinued at week 24, with a loss of response by all but one patient by week 52, suggesting that the response (if any) is limited to the time and duration of antibiotic therapy. Trends in calprotectin mirrored the clinical remission rates with a statistically significant decrease in the antibiotic arm through week 24 ($p=0.03$), followed by an increase to baseline by week 52.

Rates of adverse events in the antibiotic arm are notable: eleven out of 39 subjects in the antibiotic treatment arm had an adverse event that led to discontinuation compared to 2 out of 39 in the budesonide arm. If the benefit of antibiotics persists only while receiving therapy, antibiotic therapy will have limited adherence due to adverse effects unless a more tolerable regimen can be identified.

One the most interesting aspects of the study was the evaluation of CD serologies in predicting response to antibiotic therapy. The rationale for antibiotic selection with hydroxychloroquine was for mucosal *E. coli* with penetration into macrophage vesicles. Nevertheless, CD serologies had essentially no effect in predicting response to antibiotics. Although analyses of the association of CD serologies in this study are limited due to sample size and early termination of enrollment, there was no numerical trend to suggest benefit based on baseline serological status, with no Flax positive patients in remission at week 24 or 52 with antibiotic treatment, compared with 23% and 12% of Flax negative patients, respectively. Similarly, 20% and 7% of OmpC/ASCA positive patients achieved remission on antibiotics at week 24 and 52,

compared with 18% and 12% of OmpC or ASCA negative patients, respectively. This finding does not necessarily negate the hypothesis of a bacterial infection initiating CD although it argues against the pathogenicity of continued active mucosal *E. coli* infection as the cause of intestinal inflammation and serological positivity. Though a bacterial infection may have helped initiate CD immune dysregulation, it may not be necessary to perpetuate the inflammation. As above, the negative finding needs to be understood in the context of a likely underpowered and complex experimental design that requires further study of the association of CD serologies and antibiotic response in order to draw firmer conclusions.

In addition to sample size limitations, another aspect of this study which may cloud interpretation is the heterogeneous population of CD patients by disease location, with the inclusion of isolated colonic disease. In subgroup analyses of patients with isolated colonic CD, only 1 patient achieved remission by week 10, and no patients were in remission weeks 24 or 52. CD location may also influence response to antibiotics as small intestinal bacterial overgrowth may be a contributing factor to symptoms of CD and influence response rates related to antibiotics, especially on outcomes based on subjective measures such as the CDAI [6].

How do these observations increase the understanding of how antibiotics affect CD risk and management? This was a negative study designed to demonstrate that a tailored antibiotic approach to treat active CD was superior than budesonide. Since it did not reach its enrollment target and was not powered for non-inferiority, it cannot be concluded that this antibiotic regimen is “as good as” budesonide. This study, although negative, does provide useful insight into the relationship of bacteria, antibiotics and Crohn's disease. One key mechanistic aspect of antibiotic therapy that was not addressed in this study is how antibiotics affect gut microbiome composition and whether changes in composition correlate with the clinical response. Microbiome composition in CD patients also varies according to other environmental exposures such as diet, and antibiotics have been associated with gut dysbiosis [7]. Antibiotics remain an attractive potential therapeutic approach as a means to quickly modulate the microbiome, which may be maintained in the long term with other approaches, such as diet, in order to reduce the adverse effects of long-term antibiotic therapy.

Compliance with Ethical Standards

Conflict of interest Research funding: Redhill Biosciences, Janssen, Abbvie, Celgene, Genentech, Eli-Lily, Lycera, Bristol-Myers Squibb, Allergan, Boehringer Ingelheim, and American Regent Pfizer Inc. Consultant: Abbvie, Janssen, and Pfizer.

References

1. Aniwan S, Tremaine WJ, Raffals LE, Kane SV, Loftus EV Jr. Antibiotic use and new-onset inflammatory bowel disease in Olmsted County, Minnesota: a population-based case-control study. *J Crohns Colitis*. 2018;12:137–144.
2. Shaw SY, Blanchard JF, Bernstein CN. Association between the use of antibiotics and new diagnoses of Crohn's disease and ulcerative colitis. *Am J Gastroenterol*. 2011;106:2133–2142.
3. Khan KJ, Ullman TA, Ford AC, et al. Antibiotic therapy in inflammatory bowel disease: a systematic review and meta-analysis. *Am J Gastroenterol*. 2011;106:661–673.
4. Feller M, Huwiler K, Stephan R, et al. Mycobacterium avium subspecies paratuberculosis and Crohn's disease: a systematic review and meta-analysis. *Lancet Infect Dis*. 2007;7:607–613.
5. Rhodes JM, Subramanian S, Flanagan PK, et al. Randomized Trial of Ciprofloxacin Doxycycline and Hydroxychloroquine Versus Budesonide in Active Crohn's Disease. *Dig Dis Sci*. (Epub ahead of print). <https://doi.org/10.1007/s10620-020-06477-y>.
6. Shah A, Morrison M, Burger D, et al. Systematic review with meta-analysis: the prevalence of small intestinal bacterial overgrowth in inflammatory bowel disease. *Aliment Pharmacol Ther*. 2019;49:624–635.
7. Lewis JD, Chen EZ, Baldassano RN, et al. Inflammation, antibiotics, and diet as environmental stressors of the gut microbiome in pediatric Crohn's disease. *Cell Host Microbe*. 2015;18:489–500.

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