

Probiotic Possibilities In Crohn's Disease: A Research Review Article

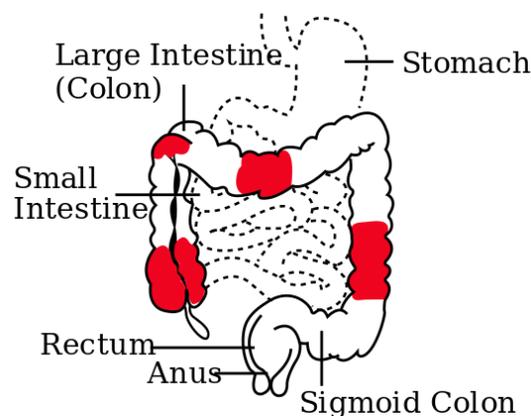
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ABSTRACT:

Crohn's Disease (CD) is a chronic autoimmune disease in the Inflammatory Bowel Disease (IBD) family. The presence of certain pathogenic bacteria can cause the disease, but so can the absence of helpful ones. The microorganisms in the gut microbiome carry out many vital tasks, and with missing bacteria these tasks are not carried out. Main treatments for CD are: immunosuppressants, anti-inflammatory drugs, steroids, antibacterial drugs, and biologics, each one offers particular benefits and harmful side effects. Treatments have increased the chances of developing cancers, and illnesses, since the immune system is oftentimes compromised. In a healthy individual these microbes play a large part in our bodies, protecting us from pathogens, "teaching" the immune system, aiding in digestion and improving nutrient absorption. In CD patients the microbial composition in the gut microbiome is unbalanced, introduction of probiotics would bring balance back to the gut. All clinical trials performed so far gave patients the same formula of probiotics. However, each individual has a unique microbiome composition, which these trials failed to take into consideration. Considering this, a possible treatment plan may require a multi-strain probiotic treatment that is tailor fitted for each individual. Therefore, moving forward clinical trials should test tailor fitted probiotic formulas, which could show more promising results.

What is Crohn's Disease? And what do we know?:

Crohn's Disease (CD) is a chronic disease in the Inflammatory Bowel Disease (IBD) family. CD is an autoimmune disease, meaning that the immune system attacks the body itself. The disease causes inflammation of the gastrointestinal (GI) tract, from the mouth to the anus, leading to abdominal pain, diarrhea, fatigue, weight loss, and other health complications. The disease causes inflammation and lesions in different parts of the digestive tract, and the location varies person to person. Though CD is not life-threatening by itself, it can lead to life threatening complications such as severe infections or colorectal cancers if not dealt with.



Crohn's Disease

Figure 1. Shows the different parts of the gastrointestinal tract (GI Tract) that can be affected by Crohn's Disease.

The causes of CD are unknown, but many different theories and ideas have been proposed. One believed cause of the disease is the possibility of bacteria or viruses (Bertani & Ruiz, 2018). Bacteria and viruses can activate

our immune system, which then causes the inflammation seen during cases of CD. The presence of certain pathogenic bacteria can cause the disease, but so can the absence of helpful ones. A theory about the cause of CD that has been proposed and has evidence to back it up is the Hygiene Hypothesis. The Hygiene Hypothesis is the theory that people who grow up in more developed countries, which are “cleaner”, lack certain helpful bacteria during childhood (Clinic, 2006). With the absence of these bacteria from the microbiome, the body did not properly develop “immunity” to IBDs such as CD. The gut microbiome consists of trillions of microorganisms, and is housed in the intestinal tract. The microorganisms in the gut microbiome carry out many tasks, for example *Lactobacillus* is a microorganism that helps the body break down and absorb nutrients, and if some are absent, these tasks would not be completed (Harvard, 2020). Evidence that supports this theory is the fact that these so-called developed countries have larger amounts of CD diagnoses (Koloski et al., 2008). Bacteria may play a large role in the development of CD, but factors excluding bacteria may also play a role.

Risk Factors:

Certain habits and risk factors that increase the chance of developing CD are family history, age, and smoking. CD and other IBDs move down the family: having a first-degree family member with Crohn’s increases your chance of developing the disease as well. From studies and observations, 1 in 5 people with CD has a family member with the condition as well. (Cirino, 2020) . Age also plays a big role in the chance of developing CD. Even though CD can occur at any given age, it has a tendency to develop at younger ages. Most patients are diagnosed before the age of 30 (Figure 2, shows the ages of Crohn’s Disease diagnoses, Mayo Clinic, 2020) Cirino, 2020). Cigarette smoking is the most impactful controllable risk factor. Smoking causes changes in the gut microbiome which as discussed before can lead to CD. The relative risk of developing CD while actively smoking was 3.5 times higher than that of a nonsmoker (*Smoking and IBD: Crohn’s & colitis UK 2017*). Similar to smoking, drinking also plays a large role in changing the chance of developing CD. Alcohol consumption has also been associated with worsening symptoms, as 75% of IBD patients reported a worsening of symptoms with alcohol consumption (Feldman, 2021). We know of all these risk factors but the root cause of CD is still unknown.

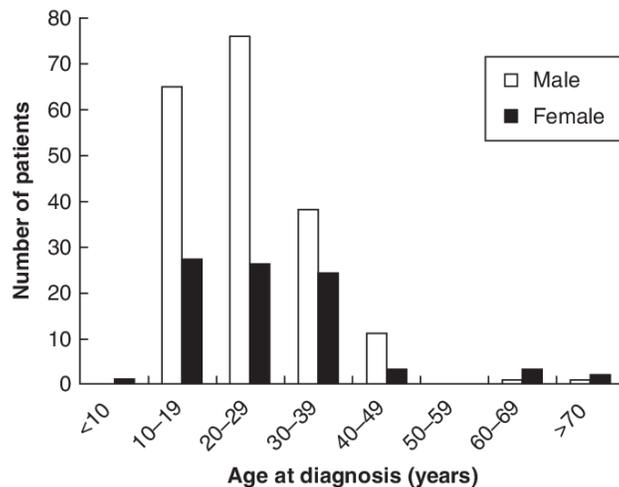


Figure 2. The chart shows the ages of diagnosis for male and female.

Medication:

There are many different classes of drugs that are used for CD: immunosuppressants, anti-inflammatory drugs, steroids, antibacterial drugs, and biologics. Each of these treatments have their own benefits and drawbacks. Immunosuppressants work in treating CD, because CD is an autoimmune disease, but it also means that your body will not be able to protect itself as well. Anti-inflammatory drugs reduce the amount of inflammation in the digestive tract, but oftentimes it only hides CD for short periods of time. Steroids are man-made versions of hormones that are usually created in the body. Steroids can create immediate reactions and work very quickly, but can cause steroid dependence, meaning the body starts to rely completely on the steroids. The steroids also cause other undesirable

side effects: increased appetite, changes in mood, and weight gain. Steroids reduce inflammation by reducing the activity of the body's immune system. Steroids also inhibit the synthesis of many inflammatory proteins. Antibacterial drugs like anti-inflammatory drugs only hide the symptoms, and can sometimes cause "good" bacteria to die. There are a few anti-inflammatory medications available to treat CD, such as infliximab (Remicade) and adalimumab (Humira). Infliximab is an antibody that works by binding to and suppressing TNF- α , which is an inflammatory cytokine that worsens CD. Like infliximab, adalimumab also works by neutralizing TNF- α (Poggioli et al., 2007). Medication in treating Crohn's disease works by suppressing the body's immune system. By doing this the inflammation caused by the immune system decreases, thus reducing your symptoms. Decreasing the inflammation allows symptoms such as fever and diarrhea to die down, but the biggest benefit is the fact that the body is able to heal the intestines. Inflammation causes tissues to become aggravated, hence reducing the inflammation will allow the body to heal. Some antibiotic treatments have also been shown to increase the severity or allow the disease to become apparent (Ledder, 2019). Antibiotics work by killing microbes within the gut microbiome, good and bad, disrupting the composition within the gut microbiome. Unlike the medication mentioned previously biologics are formulas made from unknown parts. Biologics are the most intensive drug used for treating CD, these drugs work for longer periods of time, and require an infusion. These biologics increase the chance of developing cancers and tumors by 1% (MD Anderson Cancer Center & Underferth, 2021).

These medications have many benefits but they also produce many side effects. These medications hide the condition instead of solving it, and the reduced immunity makes the medicine unhelpful. Chances of developing side effects are also a reason to look for other solutions: 65% of CD patients experience side effects while taking the medication. One major side effect of medication can be seen with the use of remicade: chances of developing cancers increase (4.3% to 7%) (MD Anderson Cancer Center & Underferth, 2021). Fistula cancer and cancer of the small bowel are some cancers that have been noticed more in CD patients than in healthy people.

Surgery:

Even with all the medications available many CD patients still require surgery. Like medication, surgery also does not completely cure CD but does save parts of your GI tract. Symptoms like fissures, fistulas, and intestinal blockages all require surgeries to fix. One of the most common surgeries for CD is a colectomy, which is a bowel resection of the large bowel. Oftentimes patients chose to get surgeries done, to better their life, while for others it is a necessity due to other medical complications. These surgeries cause symptoms to disappear for many years, but CD tends to recur in these patients (Mayo Clinic, 2020). Like all surgeries there are many complications that can occur, muscle & tissue damage, scarring, and infections to name some.

The Gut Microbiome and Microbes:

The human gut microbiome consists of all the viruses, bacteria, archaea, and eukaryotic microbes. The microbiome includes microorganisms on our body as well, and not only within us. In a healthy individual these microbes play a large part in our bodies, protecting us from pathogens, "teaching" the immune system, aiding in digestion and improving nutrient absorption, when these microbes do not function as required it leads to diseases like CD and overall poor health. Increased levels of nitrogen in the gut promotes the growth of many bacterial colonies, some of which could increase the amount of inflammation, leading to worsening CD symptoms. Influx and changes in bacterial composition of the gut microbiome have been linked to causing ailments like CD (Citation?). Bacteria can also induce inflammation by harming tissues. When tissues are damaged they release chemicals like histamine and bradykinin, which also cause swelling and inflammation, which is how inflammation in CD arises.

Microbes in the gut microbiome can prevent illnesses such as CD from developing by adhering to the walls of the GI tract. When these microbes adhere to walls of the GI tract they prevent the harmful bacteria from also adhering, thus preventing illnesses (Thursby & Juge, 2017).

Probiotics are live bacteria and yeasts which can be given to an individual to benefit their health. When eaten, probiotics mainly take root in the digestive system, and help your gut stay healthy. These probiotics play a large role in the early life of a person, as they help train the body and build immunity to some diseases. This can directly be related to the Hygiene Hypothesis, the theory that the absence of certain microbes can cause diseases to arise in an individual later. Absent microbes from childhood cause CD to arise during growth. Probiotics would be able to fill in for the absent microbes and carry out functions, potentially preventing CD (Bull & Plummer, 2014).

As highlighted above, current treatments for CD have many drawbacks. Probiotics are an attractive alternative to these drugs for many reasons; probiotics evolved alongside us and naturally exist within our gut.

Probiotics over Drugs:

The use of probiotics would greatly reduce the amount of side effects, since they are meant to be within the human body and evolved with us. The gut microbiome goes awry when compositions of microbes are at abnormal levels, above or under. Probiotics can be used to “fix” this by repopulating the gut with the required probiotics. Repopulation of the beneficial bacteria reduces inflammation levels and decreases bloating. Harmful microbes would also have a hard time growing in population because helpful bacteria would take up space. All in all probiotics can “fix” an unhealthy gut microbiome by restoring populations of healthy bacteria and preventing the growth of harmful bacteria.

Clinical Trials:

Clinical trials with probiotics to this point have shown promising results but none have given a clear treatment plan to cure CD. One clinical trial run on the potential of *Lactobacillus johnsonii* yielded little to no difference. The authors believed that *Lactobacillus johnsonii*, a probiotic, could be used to prevent the formation of lipopolysaccharides (Bertani & Ruiz, 2018), which are highly inflammatory molecules. The test group was split into two groups, one received a placebo, while the other received the *Lactobacillus* treatment. After a 12 week period each patient’s endoscopic score- a four point scoring system based on size of ulcers and endoscopic extension of condition- was recorded, and it was noticed that the placebo group and the treatment group had a difference of ~ 0.3 (mean endoscopic score). Some patients recorded a very high endoscopic score while others reported the same, if not worse scores. The authors believe this was caused by the fact that each individual has a unique gut microbiome composition. The authors of the article later go on to say that the use of a mixture of probiotics may offer a better therapeutic result. Another clinical trial that attempted to treat CD with probiotics used a multi-strain probiotic, a cocktail of probiotics. One group was given a placebo, while another was given the multi-strain probiotic. After the 4 weeks of treatments, a placebo group vs treatment group different statistics were measured, including FCAL (faecal calprotectin), which is a sensitive marker for inflammation. Patients with CD had no difference from the initial measures. This clinical trial likely failed to show results because the same multi-strain probiotic was given to all the patients, again not taking into consideration that each individual has unique gut microbiome compositions (Bjarnason et al., 2019).

All clinical trials performed so far gave patients the same formula of probiotics. However, each individual has a unique microbiome composition, which these trials failed to take into consideration. Because each individual has a unique gut microbiome, certain probiotic formulas “fill” in for missing microbes of certain individuals, while having little to no effect on others. Therefore each individual may need to have a tailor fitted probiotic formula.

Conclusion:

CD is an illness that remains a mystery to us, with unknown causes and no known cure. CD is unique to an individual but they all have similar characteristics, such as an unbalanced microbial composition in the gut microbiome. Current treatments for CD have many negative side effects, which is why more research is being done with probiotics treatments. However, research done on probiotic treatments for CD has not yielded universally positive results. Each individual has a unique microbial composition, and therefore requires specific probiotic treatments. Considering this, a possible treatment plan may require a multi-strain probiotic treatment that is tailor fitted for each individual. Therefore, moving forward clinical trials should test tailor fitted probiotic formulas, which could show more promising results.

References:

About crohn's disease. Genome.gov. (n.d.). Retrieved January 13, 2022, from <https://www.genome.gov/Genetic-Disorders/Crohns-Disease#:~:text=They%20also%20have%20a%2010,Crohn's%20disease%20is%2035%20percent>.

Bertani, B., & Ruiz, N. (2018, August). *Function and biogenesis of lipopolysaccharides.* EcoSal Plus. Retrieved January 13, 2022, from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6091223/>

Clinic, 1C. (n.d.). *True or false? the hygiene hypothesis for crohn's disease : Official Journal of the American College of Gastroenterology: ACG.* LWW. Retrieved January 13, 2022, from https://journals.lww.com/ajg/Abstract/2006/05000/True_or_False__The_Hygiene_Hypothesis_for_Crohn_s.15.aspx#:~:text=The%20%2E%80%9Chygiene%20hypothesis%20for%20Crohn's,likely%20to%20develop%20Crohn's%20disease.

Harvard. (2020, May 1). *The microbiome.* The Nutrition Source. Retrieved January 13, 2022, from <https://www.hsph.harvard.edu/nutritionsource/microbiome/>

Cirino, E. (2020, October 2). *Is Crohn's Disease genetic? statistics and more.* Healthline. Retrieved February 15, 2022, from <https://www.healthline.com/health/crohns-disease/genetic#:~:text=Yes%2C%20genetics%20do%20appear%20to,immediate%20relative%20with%20the%20disease>.

Smoking and IBD: Crohn's & colitis UK. Smoking and Crohn's or Colitis | Crohn's & Colitis UK. (n.d.). Retrieved February 15, 2022, from <https://www.crohnsandcolitis.org.uk/about-crohns-and-colitis/publications/smoking-and-ibd#:~:text=How%20does%20smoking%20affect%20Crohn's,smoking%20can%20make%20Crohn's%20worse.&text=Research%20suggests%20that%20women%20who,surgery%2C%20than%20men%20who%20smoke>.

Feldman, L. (2021, March 15). *Does smoking, alcohol, or coffee put you at risk for crohn's disease or ulcerative colitis?* Crohn's & Colitis Foundation. Retrieved February 15, 2022, from <https://www.crohnscolitisfoundation.org/blog/does-smoking-alcohol-or-coffee-put-you-risk-crohns-disease-or-ulcerative-colitis>

MD Anderson Cancer Center, & Underferth, D. (2021, April 8). *Does crohn's disease affect your cancer risk?* MD Anderson Cancer Center. Retrieved February 15, 2022, from <https://www.mdanderson.org/cancerwise/does-crohns-disease-affect-your-cancer-risk.h00-159460056.html>

Poggioli, G., Laureti, S., Campieri, M., Pierangeli, F., Gionchetti, P., Ugolini, F., Gentilini, L., Bazzi, P., Rizzello, F., & Coscia, M. (2007, June). *Infliximab in the treatment of crohn's disease.* Therapeutics and clinical risk management. Retrieved February 15, 2022, from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1936311/>

Mayo Foundation for Medical Education and Research. (2020, October 13). *Crohn's disease.* Mayo Clinic. Retrieved February 15, 2022, from <https://www.mayoclinic.org/diseases-conditions/crohns-disease/diagnosis-treatment/drc-20353309>

Thursby, E., & Juge, N. (2017, May 16). *Introduction to the human gut microbiota.* The Biochemical journal. Retrieved February 15, 2022, from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5433529/>

Bull, M. J., & Plummer, N. T. (2014, December). *Part 1: The human gut microbiome in health and disease.* Integrative medicine (Encinitas, Calif.). Retrieved February 15, 2022, from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4566439/#:~:text=Imbalance%20of%20the%20normal%20gut,type%20%20diabetes%2C%20and%20atopy>.

Bertani, B., & Ruiz, N. (2018, August). *Function and biogenesis of lipopolysaccharides*. EcoSal Plus. Retrieved February 15, 2022, from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6091223/>

Koloski, N.-A., Bret, L., & Radford-Smith, G. (2008, January 14). *Hygiene hypothesis in inflammatory bowel disease: A critical review of the literature*. World journal of gastroenterology. Retrieved February 16, 2022, from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2675108/>

Ledder, O. (2019, January). *Antibiotics in inflammatory bowel diseases: Do we know what we're doing?* Translational pediatrics. Retrieved February 16, 2022, from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6382505/>

Bjarnason, I., Sission, G., & Hayee, B. H. (2019, June). *A randomised, double-blind, placebo-controlled trial of a multi-strain probiotic in patients with asymptomatic ulcerative colitis and crohn's disease*. Inflammopharmacology. Retrieved February 17, 2022, from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6554453/>