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ASSOCIATION BETWEEN MICROBES AND IBD (CROHN'S DISEASE) AND THEIR SENSITIVITY/RESISTANCE TO DRUGS

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Abstract
Immune dysregulation and an imbalance in the gut microbiota are hallmarks of Crohn's disease (CD), a chronic, recurrent gastrointestinal disorder that is a subset of inflammatory bowel disease (IBD). The intricate interactions among host genetics, environmental variables, microbial dysbiosis, and immunological responses in CD pathogenesis are examined in this study. Recent research highlights a marked decline in microbial diversity and a move toward pro-inflammatory microbial communities in CD patients, including decreased *Faecalibacterium prausnitzii* and elevated *Escherichia coli.* The article describes the structural and functional functions of important gut microbes in health and how immune activation, chronic inflammation, and mucosal barrier dysfunction are all impacted by their alteration. Additionally, it looks at how biologics and antibiotics affect microbial resistance and composition, emphasizing both the therapeutic advantages and unforeseen side effects such dysbiosis and multidrug resistance. The report also highlights how precision medicine techniques, like bacteriophage therapy, targeted microbial therapies, and microbial sensitivity profiling, have potential for improving CD care. Developing tailored treatments and enhancing long-term results for Crohn's disease require a thorough grasp of gut microbial dynamics and resistance mechanisms.

Keywords: Crohn's Disease, Gut Microbiota, *Escherichia coli*, *Faecalibacterium prausnitzii*, Immune dysregulation, SCFAs, Immune dysregulation, Inflammation

Introduction

Inflammatory bowel disease (IBD) is a group of recurrent, chronic gastrointestinal disorders, of which Crohn's disease (CD) and ulcerative colitis (UC) are the two primary components (Ng et al., 2017). The hallmark of Crohn's disease is transmural inflammation, which can impact any area of the digestive system, from the mouth to the anus, though it typically affects the colon and terminal ileum (Baumgart & Sandborn, 2012). Crohn's disease is characterized by its patchy distribution (also known as "skip lesions") and the possibility of strictures, fistulas, and abscesses, in contrast to Ulcerative Colitis, which is limited to the colonic mucosa (Torres et al., 2017). Although the precise cause of Crohn's disease is unknown, it is generally believed that genetically predisposed people develop the condition as a result of an incorrect immune response to intestinal flora (Khor et al., 2011).
Numerous risk genes, including NOD2, ATG16L1, and IL23R, have been found by genome-wide association studies, indicating a crucial part of host-microbial interactions in the pathophysiology of

disease (Jostins et al., 2012). The start and progression of disease are also greatly influenced by environmental variables, including nutrition, urban living circumstances, smoking, and antibiotic use, which may have an effect on the gut microbiota (Singh & Bernstein, 2022). Recent research has revealed that people with Crohn's disease have "dysbiosis," or substantial changes in the composition of their gut microbiota, which are characterized by an increase in pathogenic species and a decrease in microbial diversity (Nishida et al., 2018). The gut microbiota, a rich and varied microbial population found in the human gastrointestinal system, is essential to preserving host health (Thursby & Juge, 2017).

The gut is thought to contain between 10^{13} and 10^{14} microorganisms, such as bacteria, viruses, fungus, and archaea, which outnumber human cells and account for 1-2 kg of body weight (Sender et al., 2016). The fermentation of dietary fibers to create short-chain fatty acids (SCFAs) like butyrate, acetate, and propionate, which provide energy to colonocytes and have anti-inflammatory qualities, is one way that the gut microbiota supports nutrition metabolism in a healthy state (Koh et al., 2016). Additionally, important vitamins including vitamin K and B group vitamins (e.g., B12, folate) are synthesized in large part by the microbiota (Leblanc et al., 2013). Gut microbes have a crucial role in immune system development and function in addition to metabolism. They support the development of regulatory T cells, the maturation of gut-associated lymphoid tissue (GALT), and the regulation of both innate and adaptive immune responses (Belkaid & Hand, 2014). In order to maintain a balanced immunological tone, the gut microbiota teaches the immune system to tolerate commensal species while remaining alert against pathogens (Littman, n.d.).

Additionally, the gut microbiota helps to maintain the intestinal epithelial barrier by encouraging the formation of mucus and tight junction integrity, which stops dangerous pathogens and antigens from moving into the systemic circulation (Chelakkot et al., 2018). Beyond gastrointestinal disorders, dysbiosis—an imbalance in the composition of gut microbes—has been linked to a variety of illnesses, such as metabolic syndrome, obesity, type 2 diabetes, cardiovascular diseases, and neuropsychiatric conditions like depression and autism spectrum disorders (Lynch & Pedersen, 2016)(Sharon et al., 2016). The microbiome may be a key target for enhancing treatment outcomes, as recent research has shown demonstrated the significance of gut microorganisms in regulating responses to different medicines, including immunotherapies in cancer. Therefore, preserving a healthy gut microbiota is essential for general health, and any disturbance of this intricate ecosystem may play a role in the etiology of a variety of illnesses. By customizing antibiotic treatments according to distinct microbial sensitivity profiles, harmful bacteria can be specifically eradicated with the least amount of adverse effects on the beneficial microbiota (Feagan et al., 1995).

Furthermore, antibiotic resistance can exacerbate dysbiosis by promoting the growth of multi-drug resistant (MDR) organisms, which exacerbates mucosal inflammation. For instance, resistant strains of *E. coli* have been associated with increased inflammatory responses and intestinal epithelial barrier collapse in CD patients (Palmela et al., 2018). Beyond traditional antibiotics, new microbiota-targeted treatments may also be impacted by the susceptibility and resistance patterns of gut microorganisms. For instance, the baseline antibiotic resistance genes ("resistome") found in the gut microbiome may have an impact on the efficacy of probiotics and fecal microbiota transplantation (FMT) (Zuo & Ng, 2018). Additionally, researching patterns of microbial resistance can aid in the creation of next-generation treatments that can specifically target harmful bacteria without upsetting the balance of the microbiota, such as bacteriophage therapy, narrow-spectrum antibiotics, and antimicrobial peptides (Alimuddin, 2006). Using microbial sensitivity and resistance profiling in the treatment of Crohn's disease should greatly improve treatment results, lower complications, and support the preservation of long-term gut health in the age of customized medicine.

Overview of Gut Microbiota in Health

The human gastrointestinal (GI) tract harbors a vast and diverse population of microorganisms collectively known as the gut microbiota. These microorganisms include bacteria, archaea, viruses (mainly bacteriophages), and eukaryotic microbes (e.g., fungi), with bacteria being the most extensively studied and abundant. The Dominant Bacterial Phyla in which four primary phyla

comprise the majority of gut bacteria: With over 90% of the total bacterial population in the healthy human gut belonging to the phyla *Firmicutes* and *Bacteroidetes,* these two groups are the most prevalent (Qin et al., 2010). *Actinobacteria* (e.g., *Bifidobacterium*) and *Proteobacteria* (e.g., *Escherichia coli*) are present in smaller proportions (Huttenhower et al., 2012). *Verrucomicrobia*, especially *Akkermansia muciniphila*, has garnered interest for its function in mucin breakdown and host metabolism (Derrien et al., 2004).
Composition at the Genus level Some of the common bacterial genera include: *Bacteroides***:** These are the Gram Negative, Anaerobic bacteria are crucial for the fermentation of carbohydrates (Wexler, 2007). *Firmicutes:* This group of bacteria includes types like *Ruminococcus*, *Lactobacillus, Clostridium,* and *Faecalibacterium* (e.g., *F. prausnitzii*). They are very important for making short-chain fatty acids (SCFAs) (Louis & Flint, 2009). *Bifidobacterium***:** is common in babies and is good for them because it helps the immune system and breaks down carbohydrates (Turroni et al., 2018). *Escherichia Coli:* A facultative anaerobe, *Escherichia coli* is a minor but vital element of the gut flora (Tenaillon et al., 2010).
Some other microbiota are Fungi: Although they are less common, fungi like *Candida, Saccharomyces*, and *Malassezia* have a role in regulating immunological responses (Nash et al., 2017). Archaea: The predominant archaea in the human gut that aid in energy metabolism and hydrogen disposal are methanogenic archaea, such as *Methanobrevibacter smithii* (Samuel & Gordon, 2006). Viruses and Bacteriophages: The gut virome is dominated by bacteriophages (viruses that infect bacteria), particularly from the order Caudovirales and family Microviridaes (Reyes et al., 2010).

Role in Digestion, Immune modulation and Protection of Gut bacteria like *Bacteroides* and *Ruminococcus* ferment indigestible carbohydrates to create short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate. These SCFAs are then absorbed and utilized by host tissues as an energy source (Macfarlane & Macfarlane, 2003). Microbial bile salt hydrolases (BSHs**)** modify bile acids, influencing fat emulsification and host lipid metabolism (Ridlon et al., 2006). Polysaccharide A, which is produced by *Bacteroides fragilis*, stimulates Tregs and balances Th1/Th2 responses, so promoting immunological tolerance (Round & Mazmanian, 2010a). Commensals generate antimicrobial substances that stop the growth of pathogens, including hydrogen peroxide, bacteriocins, and SCFAs (Sousa, 2014).

Dysbiosis in Crohn's Disease

An imbalance or maladaptation in the gut microbiota's composition and function is referred to as dysbiosis, and it is usually linked to adverse health outcomes. The balance between commensal, helpful, and potentially harmful microbes in the gut ecology is upset (Petersen & Round, 2014). In microbial communities, dysbiosis can manifest as either qualitative (loss of variety or functional capacity) or quantitative (loss or overgrowth) (Lozupone et al., 2012). Numerous internal and external causes can cause dysbiosis like One of the main causes is the use of antibiotics, which alter the diversity and abundance of gut flora (Dethlefsen & Relman, 2010). Diet, particularly Western diets that are high in fat or poor in fiber, decreases microbial diversity and encourages the proliferation of pro-inflammatory bacteria (Filippo et al., 2010). Dysbiotic changes are also influenced by aging, stress, illness, and chronic inflammation (Mahony et al., 2009).
The gut microbiota of Crohn's disease patients shows noticeably less alpha diversity, or fewer bacterial species. According to studies, CD patients have much lower microbial richness and evenness than healthy controls, which suggests an ecological imbalance (Manichanh et al., 2012). Patients with CD had far lower levels of *Faecalibacterium prausnitzii*, a large butyrate-producing bacterium with well-known anti-inflammatory properties (Droz et al., 1990). Active inflammation is correlated with increased Proteobacteria abundance, especially Enterobacteriaceae (Frank et al., 2007). Pro-inflammatory bacteria have been shown to survive in CD patients due to increased expression of microbial genes linked to oxidative stress (Morgan et al., 2012).

Gevers et al., 2014 – Treatment-Naïve Pediatric CD Patients- This groundbreaking study compared the microbiome of pediatric Crohn's disease patients who had just received a diagnosis and were not yet receiving treatment to that of non-IBD controls. The findings revealed a notable rise in *Proteobacteria*, particularly *Escherichia coli*, and a decrease in anti-inflammatory bacteria such as *Faecalibacterium prausnitzii*. Treatment or diet had little effect on these microbial changes, suggesting a possible causative involvement in the onset of the disease (Gevers et al., 2014).

Knights et al., 2014 – Genetic-Microbiome Interaction- This study showed that some alterations in the gut microbiota, specifically an increase in Proteobacteria, were connected to host genetic variations linked to CD, such as NOD2 and ATG16L1. It supports a hypothesis of gene–microbiota interaction where genetic predisposition affects microbial imbalance and plays a role in the emergence of disease (Knights et al., 2014).

Table 1: - Important Microbes Linked to Crohn's Disease.

Microorganism	Role in CD	Effect on Host	Reference
Enterococcus faecalis	Opportunistic pathobiont	Can exacerbate inflammation and epithelial barrier dysfunction	(Satsangi et al., 2011)
Lactobacillus spp.	Sometimes depleted; some strains may offer therapeutic benefits	Produces lactic acid; supports gut barrier and immune homeostasis	(Orel & Trop, 2014)
Bacteroides fragilis (with Polysaccharide A)	Protective; modulates immune system	Induces Treg cells; promotes immune tolerance	(Round & Mazmanian, 2010b)
Akkermansia muciniphila	Variable presence in CD; often reduced	Mucin degrader; contributes to mucus layer integrity	(Sokol et al., 2009)
Candida albicans	Significantly increased in CD patients	Promotes inflammation; induces Th17 immune response; may disrupt epithelial barrier	(Iliev et al., 2012)
Caudovirales bacteriophages	Significantly expanded in CD patients	Alter bacterial population dynamics: contribute to dysbiosis and inflammation	(Lipton et al., n.d.)
Malassezia restricta	Enriched in colonic mucosa of CD patients (esp. CARD9 mutations)	Activates CARD9-mediated inflammation pathways; associated with disease severity	(Zhao et al., 2019)

Mechanisms of Microbial Contribution to Crohn's Disease

One of the main characteristics of Crohn's disease (CD) pathophysiology is disruption of the mucosal barrier, which leads to increased intestinal permeability, immunological activation, and chronic inflammation.

Structural Alterations in Tight Junctions (TJs)- To control paracellular permeability, the intestinal epithelial barrier depends on tight junctions (TJs), which are made up of proteins like occludins, claudins, and junctional adhesion molecules (JAMs). Increased intestinal permeability results from a

significant decrease in the expression of sealing TJ proteins such as occludins, claudin-5, and claudin-8 in CD. The integrity of the barrier is further compromised by the upregulation of the pore-forming protein claudin-2 (Wang et al., 2016).

Influence of Pro-inflammatory Cytokines- The disruption of the mucosal barrier is largely caused by pro-inflammatory cytokines, specifically interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α) and another interleukin-6 (IL-6). TJ disintegration and enhanced permeability can result from these cytokines' propensity to down regulate TJ proteins and encourage their internalization. Furthermore, TNF-α causes epithelial cells to undergo apoptosis, which exacerbates barrier failure (Rashed et al., 2022) (Antoni et al., 2014).

Tumor necrosis factor-alpha (TNF-α):
The level of mucosal inflammation is correlated with the amount of TNF-α produced by lamina propria mononuclear cells (LPMNCs) from CD patients (Reinecker et al., 1993). TNF-α increases adhesion molecules, triggers apoptotic pathways, and induces other cytokines such as IL-1β and IL-6 to enhance inflammation (Sanchez-Muñoz et al., 2008). Infliximab and adalimumab, two anti-TNF-α medications, have demonstrated effectiveness in lowering inflammation and causing remission in patients with CD (Muzes et al., 2012).

Interleukin-6 (IL-6):
The activity and severity of the disease are correlated with elevated levels of IL-6 in the intestinal mucosa and serum of CD patients (Guan, 2019). IL-6 causes intestinal epithelial cells to activate the JAK/STAT3 and NF-κB pathways, which results in the production of proinflammatory genes and T cell resistance to apoptosis (Sitaraman, 2008). Tocilizumab, an anti-IL-6 receptor antibody, has demonstrated clinical benefits in CD, highlighting IL-6 as a potential therapeutic target (Guan, 2019).

Microbial invasion of Gut epithelial cells- The adherent-invasive *Escherichia coli* (AIEC), especially strains like LF82 that are commonly isolated from the ileal mucosa of CD patients, play a key role in this process (Nguyen et al., 2014). The capacity of AIEC strains to adhere to intestinal epithelial cells is impressive. Type 1 pili, which identify and attach to enterocyte surface-expressed carcinoembryonic antigen-related cell adhesion molecule 6 (CEACAM6), are the main mediators of this adherence. Interestingly, CD patient's ileal mucosa has elevated CEACAM6 expression, which promotes more bacterial adherence (Migliore et al., 2018). After adhering, AIEC strains use a process akin to macropinocytosis to infiltrate intestinal epithelial cells. These bacteria can persist and avoid immune clearance once they have been internalized because they can live and multiply inside epithelial cells without causing host cell death (Croxen et al., 2013)(Migliore et al., 2018). AIEC activates the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathways in epithelial cells when it is present intracellularly. Proinflammatory cytokines like interleukin-8 (IL-8), which are produced as a result of this activation, attract neutrophils to the infection site and exacerbate inflammation (Nguyen et al., 2014). The intestinal epithelial barrier is compromised by AIEC infection. Changes in tight junction proteins are indicative of this disruption, which raises intestinal permeability. The weakened barrier makes it easier for bacteria and luminal antigens to move around, which feeds the inflammatory cycle.
The pathophysiology of Crohn's disease (CD) is significantly influenced by immune evasion tactics, which allow harmful bacteria to survive inside the host and sustain chronic inflammation.
One essential cellular mechanism that breaks down intracellular infections is autophagy. To prevent disintegration and increase their chances of surviving inside host cells, some bacteria, including *Listeria monocytogenes*, have evolved defenses against autophagic identification. In CD patients, this avoidance leads to chronic inflammation and recurring infections (Levine et al., 2011).

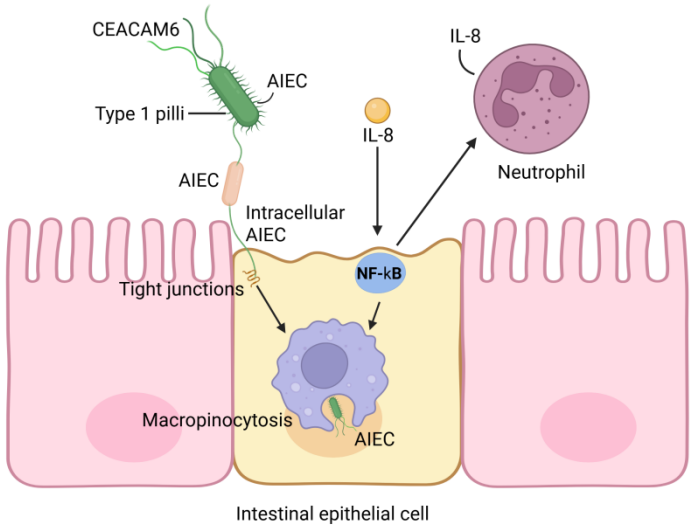

Fig 1: Mechanisms of Microbial Contribution to Crohn's Disease

Defects in the innate immune system, namely in the acute inflammatory response, are what define CD. This deficiency makes it easier for infections to stay in the gut mucosa by avoiding early immune identification and clearance. Studies have revealed that this impairment in innate immunity contributes to the persistent pattern of inflammation observed in CD (Marks et al., 2015).

Table 2: - Antibiotic Used in Crohn's Disease.

Antibiotic	**Effectiveness**	**Limitations**	**Impact on Gut Microbiota**	**References**
Metronidazole	Effective in reducing disease activity and preventing recurrence.	Long-term use associated with peripheral neuropathy; symptoms may recur after discontinuation	Can cause dysbiosis, reducing microbial diversity and beneficial bacteria.	(Fetter et al., 2023)
Ciprofloxacin	May induce remission and reduce inflammation.	High resistance rates in Gram-negative aerobes; symptoms may reappear post-treatment.	Reduces beneficial bacteria like *Bifidobacterium* and *Faecalibacterium*; increases *Bacteroides*	(Fetter et al., 2023)(Shah et al., 2021)
Vancomycin	May be effective in primary sclerosing cholangitis (PSC); limited data in CD.	Potential for resistance; not commonly used in CD.	Can significantly alter gut microbiota; reduces diversity	(Fetter et al., 2023)
Nitroimidazoles (e.g., metronidazole	Effective in inducing remission	Side effects include neuropathy; long-term use not recommended	Can cause significant alterations in gut microbiota composition	(Feller et al., 2010)
Azithromycin	Limited evidence; not commonly used as monotherapy.	Potential to disrupt gut microbiota; limited data on long-term efficacy	Decreases microbial diversity; alters composition of gut bacteria.	(Shah et al., 2021)

Table 3: - Microbial Sensitivity and Resistance Patterns.

Microbial Taxon	Role in CD	Antibiotic Sensitivity/Resistance	References
Adherent-Invasive Escherichia coli (AIEC)	Pro-inflammatory; invades ileal mucosa.	Sensitive to rifaximin in vitro; in vivo efficacy not fully established.	(Longman & Swaminath, 2013)
Bifidobacterium spp.	Beneficial; supports gut health.	Reduced by antibiotics like ciprofloxacin and metronidazole.	(Wright et al., 2015)
Klebsiella spp.	Potentially pathogenic; increased in CD.	Often resistant to multiple antibiotics; specific resistance patterns vary	(Lewis et al., 2017)
Enterococcus spp.	Opportunistic pathogen; increased in CD.	Some strains exhibit resistance to antibiotics; patterns vary.	(Lewis et al., 2017)
Ruminococcus spp.	Reduced in CD; contributes to SCFA production.	Susceptible to broad-spectrum antibiotics; depletion linked to dysbiosis.	(Wright et al., 2015)

Impact of Biological Therapies on Gut Microbiota

Increased alpha diversity in the gut microbiota of patients responding to anti-TNFα medication suggests a more robust microbial environment (Pu et al., 2022). Short-chain fatty acids (SCFAs), such butyrate, are produced more often as a result of therapy and are essential for immunological and intestinal function (Wu et al., 2021). Vedolizumab, targeting α4β7 integrin, has shown (Qusty et al., 2024) Modified Metabolic Pathways- Patients who experience remission have a decrease in oxidative stress indicators and an enrichment in pathways linked to amino acid synthesis (Pu et al., 2022). A promising treatment option for Crohn's disease (CD), an inflammatory bowel condition marked by persistent gastrointestinal inflammation, is fecal microbiota transplantation (FMT). Although FMT has shown great effectiveness in treating recurring *Clostridium difficile* infections, there are both encouraging results and major obstacles when using it in CD. According to a different meta-analysis, 79% of CD patients had a clinical response to FMT, and 62% of them achieved clinical remission. These results imply that FMT may be useful in causing remission in a subgroup of people with CD. But there are obstacles that need to be overcome, like inconsistent protocols, safety issues, and legal restrictions. To find the best way to employ FMT in CD care, more randomized controlled trials are necessary (Cheng et al., 2021).

Conclusion

An intricate interaction between genetic predisposition, environmental variables, immunological responses, and the gut flora characterizes Crohn's disease (CD), a chronic inflammatory disorder of the gastrointestinal system. Recent studies have demonstrated how important gut microbial dysbiosis is to the etiology and development of CD. Future tailored microbial therapeutics and efficient management techniques depend on an understanding of the sensitivity and resistance characteristics of microbial communities. A disturbed gut microbiota, characterized by decreased diversity and an imbalance between harmful and helpful microorganisms, is frequently seen in CD patients. Notably, anti-inflammatory bacteria like *Faecalibacterium prausnitzii* and *Roseburia spp.* are decreasing, while pro-inflammatory bacteria like *Escherichia coli* and *Fusobacterium spp*. are increasing. This dysbiosis prolongs the illness cycle by causing intestinal inflammation and mucosal damage. The current microbial makeup and its resistance patterns can affect the effectiveness of treatments such as fecal microbiota transplantation (FMT), probiotics, and antibiotics. By using bacteriophages to target particular harmful bacteria, it is possible to precisely alter the gut microbiota without upsetting beneficial species. Preclinical research has demonstrated promise in lowering dangerous bacterial

populations linked to CD. These kinds of discoveries are essential for creating targeted microbial medicines and customizing efficient treatment plans. In order to manage Crohn's disease more effectively and sustainably, future research should concentrate on individualized strategies that take into account each person's unique microbiome composition.

Conflict of Interest

Authors declare no conflict of interest.

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