

Environmental Influences on the Onset and Clinical Course of Crohn's Disease—Part 2: Infections and Medication Use

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Abstract: The pathogenesis of Crohn's disease (CD) involves host, genetic, and environmental factors. These factors result in disturbances in the innate and adaptive immune systems and composition of the intestinal microbiota. Epidemiologic and migration studies support an environmental component in the development of CD. Environmental risk factors include childhood hygiene, air pollution, breastfeeding, smoking, diet, stress, exercise, seasonal variation, appendectomy, medications, and infections. This 2-part series provides an overview of these external contributors to the development or exacerbation of CD. Part 1, which was published in a previous issue, focused on childhood factors, perinatal influences, and lifestyle choices. Part 2, presented here, details the effects of infections, antibiotics, nonsteroidal anti-inflammatory drugs, and oral contraceptives.

Genetic factors are well known to play a role in the pathogenesis of Crohn's disease (CD), although epidemiologic studies strongly suggest an environmental link as well.¹ This review focuses on environmental factors related to medication use (including oral contraceptives [OCPs], nonsteroidal anti-inflammatory drugs [NSAIDs], and antibiotics) and various infections in the development or exacerbation of CD.

Common Medications

Oral Contraceptives

Several case-control studies have suggested an increased risk of CD in women who take OCPs.²⁻⁴ Although cohort studies involving more than 80,000 women have suggested a 2- to 3-fold increase in inflammatory bowel disease (IBD) risk, the results were not statistically significant after adjusting for cigarette smoking.³⁻⁶ Additional case-control studies that have demonstrated an association noted that timing within 1 year of disease onset as well as a prolonged duration of OCP use influenced the risk of CD development.⁷⁻¹⁰ The proposed mechanism involves an estrogen-mediated pathway, given estrogen's proinflammatory properties¹¹ and thrombotic

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potential, which may lead to microvascular gastrointestinal infarction.⁶

In a meta-analysis of 2 cohort studies and 7 case-control studies, the pooled odds ratio (OR) for CD among users of OCPs, after adjusting for smoking, was 1.4 (95% CI, 1.1-1.9).¹² Another meta-analysis by Cornish and colleagues of 14 studies from 1983 to 2007 demonstrated that the pooled relative risk (RR) for CD among women currently taking an OCP, after adjusting for smoking, was 1.46 (95% CI, 1.26-1.70) and increased proportionately with prolonged exposure to OCPs.¹³ One limitation of this meta-analysis was that it did not take into account other factors, such as family history, that may influence the development of IBD.

In a recent prospective cohort of women, the multivariate-adjusted hazard ratios (HRs) for CD were 2.82 (95% CI, 1.65-4.82) among current users and 1.39 (95% CI, 1.05-1.85) among past users.¹⁴ For those women with CD who take OCPs, there appears to be no increased risk of disease exacerbation.¹⁵

In summary, the current evidence suggests that there is a moderate association between exposure to OCPs and the development of CD, particularly in women with increased length of exposure, although, upon cessation of the OCP, the risk of CD reverts to that of the nonexposed population. A key point made by Cornish and colleagues in their analysis is that many of these previous reports lacked information on the dosages of estrogen and progesterone in the OCPs studied.¹³ Given the evidence, no recommendations can be made regarding the use of OCPs and the risk of development of IBD. These data, however, may provide clinicians with information to consider in patients at higher risk who have a genetic predisposition to IBD. Similarly, the use of OCPs in the presence of CD does not appear to place a woman at risk for exacerbation of CD.

Nonsteroidal Anti-Inflammatory Drugs

Pain can be difficult to manage in CD, and affected patients are often prescribed NSAIDs, acetaminophen, or opiates. Although the topic of pain management in the patient with IBD is beyond the scope of this paper, NSAIDs have been associated with the development and exacerbation of IBD. Case reports and small case-control studies have demonstrated an effect from NSAID exposure when used between 1 to 6 months prior to the onset of disease activity.^{16,17} A prospective cohort study of female nurses found that NSAIDs used with high frequency (at least 15 days/month), greater weekly doses (>5 tablets/week), and for longer duration (>6 years) were associated with an increased risk of CD.¹⁸ Previous studies that addressed the onset of CD reported similar findings.^{16,19}

In addition, NSAIDs are associated with exacerbations of IBD in case reports and small series.^{16,17,20,21}

Prospective data on patients with ulcerative colitis (UC) or CD in remission showed that the 83 patients receiving nonselective NSAIDs had a higher risk of clinical relapse compared with the 26 patients receiving acetaminophen (17%-29% vs 0%, respectively).²² Selective cyclooxygenase (COX)-2 inhibitors have been endorsed as having lower gastrointestinal toxicity, but data on the safety of selective COX-2 inhibitors in IBD are controversial.²³⁻²⁵ The short-term use of selective COX-2 inhibitors was not associated with exacerbation of disease in prospective studies.^{26,27} Although the evidence is not definitive, the American College of Gastroenterology practice guidelines currently recognize NSAID use, including use of COX-2 inhibitors, as a potential exacerbating factor for development of CD.²⁸ The decision to recommend NSAIDs in patients with IBD should be individualized, with close monitoring for worsening of disease activity.

Antibiotics on the Onset of Crohn's Disease

Antibiotics can alter the balance of the intestinal microbiota and, as a result, modulate the gut immune response, thereby potentially creating a predisposition for the development of IBD. Observational and population studies have shown an association between early antibiotic exposure and CD in children. These studies suggest that antibiotic use in early infancy and childhood confers a 3- to 5-fold increased risk of development of pediatric CD.^{29,30} In addition, a consistent dose-dependent effect was observed, with the strongest risk occurring in children who have been prescribed several courses of antibiotics.^{29,30} In one study, the risk was greatest in the first 3 months after exposure.²⁹ Because IBD symptoms can exist prior to diagnosis, these studies may pose a risk for bias due to reverse causality. To reduce this bias, Virta and colleagues excluded antibiotic use for 6 months preceding the index diagnosis in their analysis and still demonstrated a link between antibiotic use and CD up to 2 years after exposure, although the magnitude of the association was decreased compared with previous studies (adjusted OR, 1.46; 95% CI, 1.08-1.98).³¹ In contrast to other studies, Virta and colleagues did not observe a clear link between antibiotic use in early infancy and onset of CD. Recently, Kronman and colleagues found that earlier (including early infancy) and cumulative antibiotic exposure were linked to the development of IBD in children in the United Kingdom.³² In adults, the association between antibiotic use and CD has been described as well. Two studies showed that antibiotic exposure 2 to 5 years prior to the diagnosis was associated with a 1.3-fold increased risk of adult-onset CD.^{33,34}

Data on specific antibiotics associated with the development of IBD are limited to the pediatric literature. Hviid and colleagues showed that the majority of CD cases in childhood occurred after exposure to penicillin V

and extended-spectrum penicillins.²⁹ Virta and colleagues showed associations with infant use of penicillin V and childhood use of cephalosporins.³¹ In contrast, Card and colleagues showed that only tetracyclines were correlated with IBD.³³ In another study of patients being treated for acne, tetracyclines, particularly doxycycline (HR, 2.25; 95% CI, 1.27-4.0), were associated with development of CD.³⁵ Although penicillins, cephalosporins, and tetracyclines have been associated with the development of CD, the exact mechanism is not well understood.

In conclusion, there is a growing body of literature that supports a link between antibiotic exposure and the onset of CD, although causality has not been firmly established. The durability of this association from infancy to adulthood and the dose-response with more courses of antibiotics strengthen this association. The prolonged effect of a single antibiotic exposure, extending over 5 years, needs to be clarified. Although the interaction is likely complex, the evidence suggests an association between antibiotic use and the development of CD. The judicious use of antibiotics in childhood and adulthood is good clinical practice. Further prospective and genetic-based studies will help elucidate the complex interaction among the intestinal microbiota, antibiotics, and the immune response.

Antibiotics on the Course of Crohn's Disease

As microbes are likely involved in the chronic inflammatory response in patients with established CD, antibiotics may have a beneficial effect on the clinical course of CD. A meta-analysis that combined data from 6 randomized controlled trials (RCTs) found that patients with CD with active luminal disease were 2.26 times more likely to have had clinical improvement if they received broad-spectrum antibiotics (metronidazole, ciprofloxacin, cotrimoxazole, or combination therapy) than if they had received placebo.³⁶ Subsequently, a systematic review of 10 RCTs involving 1160 patients also showed a statistically significant effect of antibiotics to induce remission in active CD compared with placebo (RR, 0.85; 95% CI, 0.73-0.99; $P=.03$).³⁷ In this analysis, there was moderate heterogeneity between studies, and multiple antibiotics were tested (antituberculosis therapy, macrolides, fluoroquinolones, 5-nitroimidazoles, and rifaximin [Xifaxan, Salix]) either alone or in combination.³⁷ In a subgroup analysis of patients with CD and perianal fistula, a statistically significant benefit of antibiotics (metronidazole or ciprofloxacin) was observed in reducing fistula drainage. Given the numerous antibiotics tested in these systematic reviews, the data are difficult to interpret, and additional studies are needed to address whether specific antibiotics are more effective in active CD. In addition, due to the higher prevalence of *Clostridium difficile* infection

(CDI) in patients with IBD and the increased morbidity associated with CDI,³⁸ the benefits of antibiotic use must clearly outweigh the risks.

Infections

The role of systemic infections on the intestinal microbiota and on the etiology of CD remains to be clarified. In CD, exposure to microorganisms at an early age is thought to influence the gut's microbiota, thereby modulating the mucosal immune system and changing its response to antigens later in life.³⁹ Studies have found that recurrent respiratory infections, early gastroenteritis, and pharyngeal infections in childhood have been associated with an increased risk of CD.⁴⁰⁻⁴² In one study, respiratory pathogens in children accounted for exacerbations of IBD, although limited conclusions can be drawn from this study because of the absence of matched control groups.⁴³ Other viral agents, such as herpes simplex virus⁴⁴ and Epstein-Barr virus,⁴⁵ have also been implicated in relapses of IBD in small studies. Key points are summarized in Table 1.

Two specific infections that have generated significant interest among researchers and are linked to the hygiene hypothesis are *Helicobacter pylori* and helminths. In addition, numerous other infections also have been studied and include *Mycobacterium avium* subspecies *paratuberculosis* (MAP), the measles virus, and various enteric infections.

Helicobacter pylori

H pylori, a spiral-shaped gram-negative bacillus, is a well-known cause of peptic ulcer disease and has been associated with gastric adenocarcinoma and, as a proxy marker, with childhood hygiene and socioeconomic status.^{46,47} Evidence is emerging on its role in IBD. A meta-analysis of 23 studies suggested a potential protective benefit of *H pylori* infection against the development of IBD.⁴⁸ Sonnenberg and colleagues evaluated 1064 cases of IBD in which *H pylori* status was confirmed with pathology. Similar to previous analyses, this study found an inverse association between *H pylori* and CD (adjusted OR, 0.48; 95% CI, 0.27-0.79) compared with controls.⁴⁶ The mechanism for this protective effect has been postulated to be through an immune-mediated process. Specifically, *H pylori* infection is associated with an increased expression of Foxp 3, a T-cell regulatory marker.⁴⁸ Further clinical studies will clarify this relationship and its influence on IBD.

Helminths

Reduced immunologic exposure to helminths, which is also a proxy for sanitation, may account for an increased incidence

Table 1. Infectious Agents Linked to the Onset of Inflammatory Bowel Disease

Bacteria	Evidence
<i>Helicobacter pylori</i>	Inverse association with CD ⁴⁶
Adherent-invasive <i>Escherichia coli</i>	More prevalent in ileal mucosa of patients with CD than in controls ⁸¹
<i>Mycobacterium paratuberculosis</i>	More common in patients with CD than in controls; causality not established ^{66,67}
<i>Campylobacter concisus</i>	Detected and isolated in children with CD ⁸⁶
<i>Campylobacter jejuni</i> and <i>Salmonella</i> species	Infection with these species is associated with an increased risk of IBD. The link may be more related to a surveillance bias. ^{106,107}
<i>Listeria</i> species	Early reports suggested a link with CD ⁸⁷ ; subsequent studies using PCR have not yielded confirmatory results. ^{88,89}
<i>Yersinia</i> species, ⁸⁴ <i>Pseudomonas</i> species ⁸⁵	Possible triggers for the onset of CD; small sample size
<i>Clostridium difficile</i>	Unique risk factors in IBD population. Worse outcomes. Not clear if trigger for exacerbation. ^{38,93,94}
Viruses	Evidence
Childhood respiratory and GI infections ⁴⁰⁻⁴³	Further prospective studies are needed to determine if a true link exists.
Measles	The most recent evidence argues against a relationship between measles and CD. ⁷⁹
Parasites	Evidence
Helminths	Protective effect in CD. ^{56,108}

CD, Crohn's disease; GI, gastrointestinal; IBD, inflammatory bowel disease; PCR, polymerase chain reaction.

of CD in industrialized societies.⁴⁹ Animal models demonstrate a helminth-mediated attenuation of the Th1 pathway with upregulation of Th2 cytokines and other regulatory cells (macrophages and dendritic cells) in the gut intestinal mucosa that suppresses inflammation and enhances the mucosal barrier.⁵⁰⁻⁵³ In addition, helminth infection can shift the bacterial composition of the intestinal flora.^{54,55}

In a small, open-label, clinical trial of patients with active CD, ingestion of live porcine whipworm ova (*Trichuris suis*) resulted in a decrease in disease activity index scores, and 72.4% of patients achieved remission at 24 weeks.⁵⁶ Concerns have been voiced regarding aberrant migration of *T suis* in the gut mucosa,⁵⁷ but such events have been rare.^{53,58,59} Ongoing clinical trials of *T suis* as a therapeutic modality in IBD are currently underway.

Mycobacterium avium subspecies paratuberculosis

MAP, a subspecies of *Mycobacterium avium*, is an obligate intracellular pathogenic organism that has been studied extensively regarding its role in the etiology of CD. The organism is known to cause Johne disease in cattle and sheep, which resembles CD and presents as a chronic granulomatous infection of the small intestine, specifically in the terminal ileum.^{60,61} In the 1980s, Chiodini and colleagues first reported the isolation of MAP from diseased intestinal tissue from 2 patients with CD and demonstrated the development of chronic ileitis in a goat following oral inoculation.⁶¹ The role of MAP in the pathogenesis of CD is uncertain, as subsequent studies have not shown a consistent relationship. Early investigators faced significant difficulty in culturing the organism because of its slow growth and fastidious characteristics; however, newer techniques using polymerase chain reaction (PCR) and identification of the species-specific insertion element (IS900) have improved detection rates.⁶⁰⁻⁶²

In clinical studies, MAP has been detected in ileocolonic biopsies and in peripheral blood more often in patients with CD than in controls.⁶³⁻⁶⁵ In addition, meta-analyses have shown MAP to be significantly more common in patients with CD, independent of the type of testing used.^{66,67} However, the presence of MAP in patients with CD is not sufficient to establish MAP as a causative agent, as it may represent opportunistic colonization of the gut mucosa rather than a pathogenic agent.^{60,66,67}

A number of open-label studies have also examined the effect of antimycobacterial therapy on patients with CD.⁶⁸⁻⁷⁰ In a subgroup analysis, antimycobacterial therapy was found to be effective in maintaining a remission in patients with CD who achieved a corticosteroid-induced remission.⁷¹ The largest RCT enrolled 213 patients with active CD and found no sustained benefit in maintaining clinical remission for up to 2 years using combination therapy with clarithromycin, rifabutin, and clofazamine after a 16-week corticosteroid withdrawal period.⁷² Although the hypothesis involving mycobacteria in the pathogenesis of CD is intriguing, antimycobacterial therapy cannot be recommended in the management of CD.

Measles Virus

The measles virus, a paramyxoviral infection, also has been explored in the pathogenesis of IBD. The hypothesis regarding association gained interest in the 1950s when an increased incidence of CD was observed among persons born during measles epidemics in Sweden.⁷³ It has been postulated that a persistent infection of the mesenteric microvascular endothelium by the measles virus leads to a chronic granulomatous vasculitis and the onset of CD.⁷⁴ Epidemiologic studies have suggested an association with early exposure to measles virus and later

onset of CD.^{75,76} These findings have not been supported in subsequent studies.^{77,78} In a population study in Manitoba, Canada, seropositivity for measles virus was similar between patients with CD and controls, suggesting that there was no relationship between infection and CD.⁷⁹

Enteric Infections

The gut flora is composed of numerous microorganisms that interact with the human host, immune system, and pathogenic bacteria. This section will highlight some of the enteric agents that have been evaluated in the literature and their relationship to the onset and relapse of IBD, although no causative single agent has been identified in CD development or exacerbation.

One microorganism that has undergone extensive study is adherent-invasive *Escherichia coli* (AIEC). AIEC colonizes the intestinal mucosa by adhering to intestinal epithelial cells and replicating intracellularly. AIEC also can replicate in macrophages, resulting in a secretion of high amounts of tumor necrosis factor α .⁸⁰ AIEC has been found to be more prevalent in the ileal mucosa of patients with CD compared with controls.⁸¹ Host genetic factors may increase the susceptibility for colonization by pathogenic bacteria, such as AIEC, resulting in a chronic dysregulated immune response.⁸²

Several other mucosa-associated bacteria, including *Yersinia* species,^{83,84} *Pseudomonas* species,⁸⁵ and *Campylobacter concisus*,⁸⁶ have been proposed as triggers for CD. In addition, an increased risk of IBD was observed in persons with exposure to *Salmonella* or *Campylobacter* gastroenteritis. An additional foodborne infection linked to IBD in some reports is *Listeria monocytogenes*,⁸⁷ although subsequent evaluation using PCR methods of testing has not yielded significant results.^{88,89}

Epidemiologic studies also have examined the link between enteric agents and CD relapse. Mylonaki and colleagues evaluated stool samples in 213 patients who presented with relapses over a period of 4 years.⁹⁰ Among the patients enrolled, there were 237 total relapses, and enteric infections were found in 10.5% of relapses in 24 patients. The most common bacteria were *C difficile* in 13 cases (5.5%) and *Campylobacter* species in 12 cases (5%).⁹⁰ Antonelli and colleagues evaluated 113 patients with IBD who were hospitalized with moderate-to-severe active disease and observed that 13.3% had intestinal superinfection (mostly *Campylobacter jejuni*, *C difficile*, and *Cytomegalovirus*).⁹¹ These data stress the importance of microbiologic testing during relapses of IBD, although they do not necessarily indicate that these enteric infections are triggers of IBD flares.⁹⁰⁻⁹²

CDI is more common in the IBD population than the general population, and rates of infection are increasing.^{38,93} CDI in hospitalized patients with IBD negatively

impacts clinical outcomes⁹³ and results in higher mortality rates than in patients without IBD.⁹⁴ Patients with IBD do not have traditional risk factors for CDI, such as antibiotic use, increased age, or recent hospitalization.^{38,95} Specific risk factors for CDI include corticosteroid use, ulcerative colitis, colonic CD, and community acquisition.³⁸

Vaccinations

Vaccinations are recommended in patients with IBD and are not associated with the onset or exacerbation of disease; however, concern in the community still exists. Inactive vaccines, including injectable influenza; combination vaccine against tetanus, diphtheria, and acellular pertussis; pneumococcus; meningococcus; human papillomavirus; hepatitis A virus; and hepatitis B virus, are routinely administered to patients with IBD regardless of immune status.⁹⁶ Conversely, live vaccines, including intranasal influenza vaccine, Bacille Calmette-Guérin vaccine, and vaccines for varicella, measles-mumps-rubella (MMR), yellow fever virus, oral typhoid, and oral polio, are contraindicated while on immunosuppressive therapy.⁹⁶ The Advisory Committee on Immunization Practices does not recommend avoiding the live herpes zoster vaccine for patients on low-dose immunomodulators (methotrexate ≤ 0.4 mg/kg/week, azathioprine ≤ 3.0 mg/kg/day, or 6-mercaptopurine ≤ 1.5 mg/kg/day).⁹⁷ Case-control data also suggest that the live herpes zoster vaccine may be safe while taking biologic agents, although no guidelines have formally included this recommendation.⁹⁸

Despite well-documented safety, there have been 2 case reports and 2 population studies that suggest an association between vaccinations and either the development or exacerbation of IBD. Specifically, single patient case reports noted flare of UC after influenza vaccination.^{99,100} A population study in Denmark that was subject to recall bias suggested that vaccination against pertussis (OR, 2.08; 95% CI, 1.07-4.03) and polio (OR, 2.38; 95% CI, 1.04-5.43) was associated with an increased risk of IBD.¹⁰¹ In 1995, Thompson and colleagues were the first to suggest that measles vaccination produced a 3-fold increased risk of development of CD and UC compared with unvaccinated controls¹⁰²; however, this study was limited by methodologic flaws, and subsequent studies have not confirmed these findings.¹⁰³ In addition, no increased risk of CD was demonstrated in children vaccinated with MMR.^{104,105} Based on all of the available evidence, no link can be drawn between CD and vaccinations. Clinicians should, thus, offer routine vaccines per guidelines.

Summary

Overall, the evidence highlights the importance of the environment in the pathogenesis of CD in a susceptible host.

Table 2. Medications/Vaccinations and the Risk of Crohn's Disease: Key Points

Oral Contraceptives
<ul style="list-style-type: none"> • Evidence supports a significant association between OCPs and development of CD.¹²⁻¹⁴ • The risk of CD increases proportionally with prolonged length of exposure to OCPs.¹³ • Risk reverts to that of the nonexposed population upon cessation of OCPs.¹³ • The majority of studies lack information on the dosages of estrogen and progesterone in the OCPs reported in relation to CD development.¹³
NSAIDs
<ul style="list-style-type: none"> • High frequency and long duration of exposure to NSAIDs are associated with an increased risk of CD.¹⁸ • The American College of Gastroenterology recognizes NSAIDs as an exacerbating factor in CD.²⁸
Antibiotics
<ul style="list-style-type: none"> • Early antibiotic use in children confers an increased risk of development of CD.^{29,30,32} • A dose-dependent effect is observed, with the strongest risk of CD occurring in children who have been prescribed several courses of antibiotics.^{29,31} • Antibiotic exposure 2 to 5 years prior to diagnosis is associated with a 1.3-fold increased risk of adult-onset CD.^{33,34} • A systematic review showed a significant effect of antibiotics in inducing remission in patients with active CD.³⁷ Additional studies are needed to make specific recommendations for which type of antibiotics are most effective. • In patients with CD and perianal fistula, a statistically significant benefit of antibiotics (metronidazole or ciprofloxacin) was observed in reducing fistula drainage.³⁷
Vaccinations
<ul style="list-style-type: none"> • No firm evidence exists to suggest that routine vaccinations have an effect on the development or exacerbation of CD.

CD, Crohn's disease; NSAIDs, nonsteroidal anti-inflammatory drugs; OCPs, oral contraceptives.

Medications, antibiotics, diet, breastfeeding, hygiene, and infections can influence the intestinal microbiota and alter its complex interplay with the immune system and the mucosal barrier (Table 2). Currently, other than smoking, no specific environmental factors or infections have been clearly linked to the onset of CD, although the data on OCPs and antibiotics are highly suggestive. Clinicians should have a heightened awareness when prescribing NSAIDs, OCPs, and antibiotics because these agents may play a role in CD pathogenesis in patients who may be predisposed to CD. Additionally, there is some evidence to suggest that NSAIDs may exacerbate CD and that certain antibiotics may play a role in induction or maintenance of remission and in decreasing fistula drainage. Routine vaccinations do not appear to cause or exacerbate CD and should be offered per guidelines.

Future prospective studies are needed to better understand the effects of childhood hygiene, breastfeeding, air pollution, diet, stress, antibiotics, OCPs, NSAIDs, infections, and vaccinations on the onset and disease course of CD.

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