IBD REVIEWS

Scientific and technological research article

ENVIRONMENTAL FACTORS (EXPOSOME) ASSOCIATED TO INFLAMMATORY BOWEL DISEASE DEVELOPMENT

Valeria C L Salgado[1], Paula A E Santo[2], Cyrla Zaltman[3*]

Department of Internal Medicine, Federal University of Rio de Janeiro., Brasil [1], Department of Internal Medicine, Federal University of Rio de Janeiro., Brasil [2], Department of Internal Medicine, Federal University of Rio de Janeiro., Brasil [3]

* Corresponding Author: c.zaltman@gmail.com.

Abstract

Inflammatory bowel disease (IBD) is multifactorial, with interactions between genetic susceptibility (genome), individual immunological factors (immunome), gut microbiota (microbiome), and environmental exposure (exposome). The exposome start their action at intrauterine life going through childhood to adulthood and act as likely triggers for the disease. Changes in the exposome favor the emergence of autoimmune diseases reinforced by non-modifiable genetic factors over the years, therefore the epidemiology of IBD might vary between countries, probably linked by the interaction between different gene pools and distinct environmental factor exposure. This article aims to review the main environmental factors related to the development of inflammatory bowel disease.

Keywords: Inflammatory bowel disease, exposome, environmental factors.

Inflammatory bowel disease (IBD) encompasses ulcerative colitis (UC) and Crohn's disease (CD), which are recurrent immune-mediated diseases characterized by a chronic inflammatory process that involves the gastrointestinal tract.[1,2] The etiology is multifactorial, with interactions between genetic susceptibility (genome), individual immunological factors (immunome), gut microbiota (microbiome), and environmental exposure (exposome). [3,4,5,6,7]

The epidemiology of IBD might vary among countries, probably linked by the interaction between different gene pools and distinct environmental factor exposure. [2] In the last two decades, the necessity of developing therapies that can alter the natural history of the disease favored the development of research on the pathogenesis of IBD, resulting in a better understanding of the favorable interaction of genome, exposome, microbiome and immunome. [8,9]

The genetic susceptibility was evidenced by studies in Askenazi Jews, monozygotic twins and first-degree relatives of patients, where the highest prevalence of IBD was demonstrated. [10, 11] Probably in these cases, the genetic factor has greater relevance than any environmental factor in the development of IBD. [12,13] Nowadays researchers are evaluating possible genetic risk factors related to IBD development, prognosis and therapeutic response to biological drugs, but as the disease is multifactorial, we can postulate that the genes involved are partially responsible for its development. [9, 14]

The immune response is the main determinant of chronic intestinal inflammatory process and understanding its function in the digestive tract and its dysregulation in CD and UC is fundamental for process control and disease remission induction. The main structural components of the intestinal mucosal immune system are present at birth, although their functional maturity is not complete until early adolescence. [15]

A single layer of epithelial cells separates all this large volume of bacteria from the largest immune apparatus in our body, formed by a large mass of lymphatic tissue, described as gut associated lymphoid tissue (GALT), thus allowing mucosa tolerance to commensal bacteria. [16,17,18] This tolerance depends on the active and reciprocal regulation between the intestinal microbiome and the different mucosal immune and non-immunological cells such as epithelial cells, Paneth cells, dendritic cells and B and T lymphocytes.[9] Thus, the intestinal mucosa must be able to develop an intense immune response to pathogens as well as maintain tolerance to the wide variety of non-pathogenic antigens from the diet and commensal microbiota.[15] This balance, maintained through innate or acquired immunities, prevents the occurrence of an inflammatory response mediated by the release of proteins classified as cytokines. The presence of IBD represents the loss of balance mentioned above, with elevation of proinflammatory cytokines and reduction of the antiinflammatory ones.[8] In addition, the innate immune response to the intestinal microbiota is currently considered a central event in the pathogenesis of IBD and other autoimmune diseases, and may exceed the recognized importance of the acquired immunity.[9,19]

The intestinal epithelial integrity selectively prevents antigen penetration and similarly allows the passage of fluids, nutrients and some microorganisms. Numerous proteins are required to maintain the mucosal barrier and changes in some of these proteins may be related to the loss of this integrity and the development of IBD.[20] Changes in the intestinal microbiota may modify the function of the epithelial barrier, with consequent activation of proinflammatory cytokine production and increased barrier permeability, favoring the development of the intestinal inflammatory process.[18,21] The involvement of intestinal barrier integrity in CD is well established and increased enteric permeability in first-degree relatives of individuals with CD has been reported. This observation was also performed in spouses of patients with CD, suggesting the action of environmental factors. [22]

The healthy human gut is inhabited by over 100 trillion microorganisms (bacteria, fungi and protozoa) from over 500 species. [8,14,16,23,24] The microbiota is responsible for the digestion, absorption and storage of nutrients, as well as protecting against pathogen colonization through the secretion of antimicrobial substances. In addition, they

promote angiogenesis, stimulate epithelial regeneration and modulate the intestinal immune system, inhibiting by competition the growth of pathogenic microorganisms. [25,26,27]

Dysbiosis is a phenomenon observed in IBD patients, not knowing if it would be an initiating factor or a consequence of the chronic inflammatory process.[9,28] It is postulated that the intestinal microbiota is fundamental not only in the pathogenesis of the disease, but also in the severity of the inflammatory process and in the different IBD phenotypes. [26]

ENVIRONMENTAL FACTORS (EXPOSOME)

The term exposome refers to all environmental factors that the individual is exposed throughout life.[29] Within this broad definition, the microbiome is considered an endogenous component of the exposome, while the other factors represent the exogenous exposome. Changes in the exposome favor the emergence of neoplasms and autoimmune diseases reinforced by non-modifiable genetic factors over the years.[9,31] The importance of this factor could be verified from migratory population studies, in which it was detected that adults' immigrants from countries with low incidence of IBD to countries with high incidence did not develop the disease. However, children or young people who migrated or belonging to the first generation of immigrants, had the same incidence of the disease as the local population.[32] Therefore, it is concluded that despite sharing the same genetics, the life phase of the individual and the place of immigration are important factors for the IBD development.[9,33] Other environmental risk factors have been also associated with IBD, such as local geography, social and educational situation, infections, smoking, diet, stress, appendectomy, increased permeability of the mucous barrier and Intestinal dysbiosis. [8,9,34]

I. PERINATAL FACTORS

1. Type of delivery

The type of delivery affects the composition of the child's intestinal microbiome. The newborn acquires its intestinal microbiota primarily through maternal contact and during the first year of life. The intestinal microbiota of infants born vaginally is similar to that of the vagina and maternal intestine. Those born by cesarean delivery have intestinal microbiota similar to that of maternal skin. These differences are reflected in the mechanism of tolerance and development of the infant's immune system in this period and is perpetuated until 7 years of age. [30,35] It is postulated that cesarean delivery increases 1.2 times the risk of developing IBD when compared to those born by vaginal delivery.[36,37,38,39,40] However , a recent control case study did not confirm this hypothesis.[30]

2. Breastfeeding

The composition of the infant's intestinal microbiota differs between those fed breast milk and those with adapted formula.[41,42] The breast milk contains lactoferrin which acts in preventing bacterial proliferation resulting from iron absorption and immunoglobulin A, in neutralizing toxins and preventing the binding of bacteria to intestinal epithelium.[1,43] This protection factor to the development of IBD may be related to breastfeeding time (required period of 3 to 12 months), or the amount of milk ingested, but there are still controversies. [1,44,45,46,47,48,49]

3. Vaccination

Previously, vaccination was believed to be responsible for reducing early childhood infections favoring the predisposition of immunological diseases. Viral and bacterial components existing in vaccines were also considered risk factors to a deregulated inflammatory response.[43,50] However, more recent studies do not confirm the association between childhood vaccination and the adult immunization against influenza H1N1 virus and IBD development.[50,51] Recent meta-analysis including 11 studies (2.400 IBD and 34.000 controls), did not show a significant increase of disease development risk after immunization with BCG, diphtheria, tetanus, chickenpox, pertussis, mumps, measles and rubella.[52] The reactivation or development of IBD related to vaccinations with inactivated viruses has not been established.[53]

II. HYGIENIC HYPOTHESIS

This hypothesis was originally proposed by Strachan in 1989, in which better hygienic conditions would lead to lack of exposure to enteric infections in childhood, favoring an inadequate response of the immune system in adulthood and the development of autoimmune diseases. [11,43,54,55]

The potential mechanisms have not yet been fully clarified, but it is known that failure in innate immunity and imbalances in the regulatory functions of T cells involved in acquired immunity are probably related. Moreover, changes in the microbiota from environmental stimuli can also mediate mechanisms of immunological tolerance. [43,48,49,56,57,58]

In developing countries, the emergence of IBD could be related to improvements of sanitary conditions, reduction in the prevalence of infectious and parasitic diseases, changes in dietary habits and quality of life, resembling what occurs in Westernized countries, where the prevalence of the disease is higher.[54,56,58,59] Thus, precarious hygiene conditions, low degree of industrial development and population clusters have been considered protective factors for the development of IBD. The prevalence of the disease has an inverse relationship in countries with a high infant mortality rate and high prevalence of infectious diseases. [33,47]

Several direct and indirect markers are used to evaluate this hypothesis, such as: the quality of ingested water, the number of household co-inhabitants, birth order among siblings, housing in urban and rural areas during the individual development, perinatal and early infections in childhood, the use of antibiotics, the intake of non-sterile foods, contact with domestic animals, vaccination, food, parasitosis, exposure to H. pylori and the use of refrigeration. [2,49,60,61,62]

Another item evaluated was the influence of the age ordering of siblings in families composed of more than one child. It is postulated that underage siblings would be more predisposed to the development of CD, due to the early acquisition of infections transmitted by older siblings. In contrast, the existence of younger siblings would reduce the risk of development of CD in older siblings, because it allows them to be submitted to repeated exposures to microorganisms, with consequent increase of individual immunological response.[63]

Individual living in urban area has a higher incidence of IBD in comparison to rural area, probably due to lower exposure to infectious agents and parasitosis. [60,62,64,65]

Items related to the individual's housing conditions such as hot and piped water use has been used in the evaluation of hygienic hypothesis, with a strong association between the best socioeconomic condition and CD development, but not established for UC. [31,62]

Although the results of these studies are controversial, we can say that the hygienic hypothesis contemplates in a global way the different aspects directly or indirectly related to the environment, being an interface in the interaction with immunological and genetic factors involved in the genesis of IBD.

III. AIR POLLUTION

The increased prevalence of IBD in Western countries, which occurred between the 1940s and 1980s, was proportional to the exponential increase in air pollution in developing countries prior to the implementation of environmental regulation measures.[66] At the experimental level it was verified that air pollution can lead to a pro-inflammatory response, with effects on the intestinal epithelium and intestinal microbiota, favoring the onset of IBD.[67,68] The increase of carbon dioxide in atmospheric air may also be associated with a higher risk of early-onset CD.[69]

IV. MICROBIAL AGENTS

1. Helicobacter pylori

Helicobacter pylori gastric infection is suggested to be a protective factor for IBD.[60] This is probably due to the regulation of the expression of anti-inflammatory mediators promoted by this infection, which would benefit the host. This effect seems to be significant even among children who have not previously been exposed to antibiotics. [70,71,72] Recent meta-analysis composed of 10 Asian studies including 1,299 patients with IBD and 1817 control individuals, demonstrated a detection of H. pylori in 24.9% of the cases and 48.3% of the controls (RR=0.48, 95%CI, 0.43-0.54; p< 0.001) corroborating the probable protective effect of this agent.[71] However, there are no data in the literature that prove the action of the bacterium in the degree of activity of the disease. [2]

2. Helminth infection

Similarly, helminth infection has been associated with a reduction in the prevalence of IBD, with an important role in immunoregulation of intestinal microbiota.[62,73] Helminths act on innate and acquired immunity, stimulating the immunological response of type Th2, with production of anti-inflammatory cytokines (IL-10 and IL-4), suppressing Th1 type response, predominant in CD and also lymphocyte response Th17.[1,74] Clinical protocols using helminth fractions (Trichuris suis) as treatment of IDI, has been performed demonstrating improvement in disease activity and quality of life scores of these patients. [2,75]

3. Mycobacterium Avium subspecies Paratuberculosis (MAP)

The MAP, agent of paratuberculosis, has been postulated as probable causal agent of CD due to the similarity between this and Johne's disease, manifested by granulomatous chronic ileitis in ruminants. Its transmission occurs through the consumption of contaminated raw meat and non-pasteurized cow's milk.[48] Although this agent was isolated in intestinal tissue and blood samples from patients with CD, the exact relationship between MAP and CD remains inconclusive to date.[48,76]

4. Bacterial infections

Adherent invasive Escherichia Coli (AIEC) is able to survive and replicate in macrophages without inducing response from host cells, stimulating infected cells to release tumor necrosis factor (TNF-alpha), and can be found in patients with ileal CD.[1,8,53]

The previous acute gastroenteritis has been implicated as a trigger for the IBD development, as demonstrated in *Salmonella and Campylobacter* infections and may increase by up to three times the risk of disease's developing, mainly in the first year after infection.[2,43,77]

Another factor suggested in the increased risk of IBD appearance is the use of refrigerators because it allows an increase in contamination of food by psychotropic bacteria, which survive at low temperatures, such as *Listeria monocytogenes and Yersinia enterocolitica.*[16,62,78]

IBD patients have been shown to be more predisposed to enteric infections, particularly by *Clostridium difficile* (CDI). Infection by this agent has been gradually growing with significant morbidity and associated with relapses in disease activity. [11] Patients hospitalized with IBD and CDI have a risk of mortality four times higher than patients without infection and, as a treatment, fecal microbiota transplantation has been considered, favoring the control of diarrhea and disease activity. [16, 17]

5. Other infections

Infections by other opportunistic pathogens such as *Aspergillus* spp, Cytomegalovirus, Varicela Zoster virus, *Epstein Barr virus, Proteus spp and Staphylococcus aureus* may also be associated with the disease due to antibiotic therapy and/or immunosuppressive and/or surgical treatment. [55,79,80]

Paramyxovirus infection (measles virus) in the perinatal phase or childhood could cause infection of the mesenteric microvascular endothelium, and lead to a chronic granulomatous vasculitis, similar to CD.[48] It was postulated that this could be only a co-factor capable of increasing the risk of CD, however this theme is still controversial.[48,73]

V. DIETARY FACTORS

The diet has been addressed as a possible influencing factor in the etiopathogenesis of IBD, because it may predispose individuals to a pro-inflammatory process, with alteration of the mucus layer and increased permeability of the intestinal barrier.[55,66,81]

The Western diet with high levels of fat and carbohydrates and deficient in fiber, has been implicated in the increased incidence of IBD, as demonstrated in Asia. [55,60,82,83] The lipid intake (polyunsaturated long-chain fatty acids of the omega-6 type) has been associated with a higher risk of IBD, while the intake of polyunsaturated fatty acids of the omega-3 type, found in fish (Mediterranean diet) to lower risk of the disease. [17,82,84]

Diet rich of fibers has a protective role in IBD, particularly with soluble fibers, but not with insoluble fibers.[55,67] A prospective cohort study describes that high-fat diet intake in soluble fibers can reduce the CD risk by up to 40%. [85] Fibers are metabolized by the intestinal microbiota into short chair fatty acids and capable of inhibiting the transcription of pro-inflammatory mediators, reducing the inflammatory process.[55] In turn, vegetables and fruits that

are rich in antioxidants protecting the individual to develop the disease.[86]

Diet intake with high animal protein content may be associated with CD development due to higher lipid content, which is greater with a consumption of red meat in comparison to white or processed meats.[87] The diet rich in eggs and dairy products has already been described as risk factor to IBD, however the consumption of fish is considered as a protective factor for colonic and ileal CD.[88]

The excessive consumption of refined sugar and processed carbohydrates seems to have an implication of the higher risk for development of IBD.[64,67,88] The use of sweeteners such as saccharin and sucralose were also associated with a higher risk of IBD, and postulate so that they would act on the intestinal microbiota, inhibiting some strains and reducing the inactivation of digestive proteases, which would allow the reduction of the protective layer of mucus.[89] The final result would be the breakdown of the intestinal barrier and contrary hyperstimulation of the immune response of the mucosa.

Micronutrients, such as vitamins, are important allies in the nutritional support of patients with autoimmune diseases. Vitamin A acts in the migratory process of T and B lymphocytes to the intestine and vitamin D contributes to the increase of innate immunity in IBD by stimulating protein synthesis with antimicrobial management. They have immunoregulatory properties and are therefore described as a protective factor in IBD.[43,55,90]

Nowadays, vitamin D and the higher incidence of CD have been given great importance, especially in geographic regions with lower exposure to ultraviolet rays.[91,92] Deficiency of this vitamin was associated with higher morbidity and severity of IBD, justifying supplementation thereof. But there are still controversies whether this supplementation could act both in the prevention and treatment of IBD and the dose to be used.[90,93]

VI. HABITS OF LIFE

1. Obesity

The mesenteric adipose tissue of individuals with IBD presents morphological and functional changes where there is an increase in the infiltration of immune system cells, such as macrophages and T cells, which assist in maintaining the inflammatory bowel response and existing disease.[94] Obesity is also associated with intestinal dysbiosis, similar to that observed in IBD, with lower microbiome diversity and alterations in the predominant bacterial *phylums*.[95,96]

2. Physical activity

Recent studies propose that regular physical activity induces mechanisms of autophagy and immune system regulation, responsible for reducing the inflammatory process, through the production of anti-inflammatory cytokines.[97,98] Regular physical activity since childhood has been shown to reduce the risk of IBD development, with greater evidence for CD.[46] Some authors demonstrated a 44% of decrease in the risk of the disease, regardless of the effect of body mass index.[92]

3. Sleep quality

Recent studies have shown that sleep disorders and the interruption of the circadian cycle can trigger the activation of pro-inflammatory cytokines, and the emergence of several chronic inflammatory diseases.[99,100] Animal studies have shown that increased levels of interleukins 1(IL-1) and tumor necrosis factor (TNF-α) are associated with NREM sleep prolongation. Low levels of IL-1 induce NREM sleep, however at high levels there was a suppression of this phase of sleep, causing its fragmentation and interfering in their quality. Interleukins 6 (IL-6), in the acute phase of the disease, suppress the REM phase of sleep, promoting wakefulness in individuals with active IBD.[43]

4. Smoking

Smoking is considered an important environmental risk factor for IBD, capable of modifying the phenotype of diseases, with protective effect for UC and causal effect on CD.[55] It is active in the onset of IBD and its severity is an effect modulated by the sex and genetics of the individual, location and activity of the disease, daily consumption of cigarettes and concentration of absorbed nicotine.[60]

While in CD smoking interferes in the clinical course of the disease, in the UC its non-use (non-smokers and former smokers) favors the development and clinical worsening of the disease.[101,102] However, the mechanism of this action remains unknown. Nicotine seems to be one of the main factors responsible for this effect of tobacco in the course of diseases, by increasing mucus synthesis, reducing the expression of IL-1beta, IL-2, IL-8, IL-10 and the production of TNFα through its binding in the acetylcholine receptor, favoring development of UC.[101] The higher production of intestinal mucus in more distal regions, such as the rectum and left colon, stimulated by nicotine action, plays an important role in the protection of UC.[43,48]

Another possibility refers to the performance of oxygenase heme1 (HO1) and carbon monoxide (CO), cigarette constituents in the regulation of intestinal homeostasis and mucosal immune response to enteric microbiota. These agents modulate innate immunity, such as cytokine expression and bactericidal activity of macrophages, forming an interaction with the genetic and immunopathological aspects of IBD.[103,104]

The risk of CD development increases twice when comparing smokers and non-smokers, as well as tobacco increases the risk of relapses, complications (stenosis and fistulas), hospitalizations and surgeries in these patients.[67,102] The literature has demonstrated an interaction between sex and the effects of smoking on IBD. According to most authors, CD is more prevalent in females, and particularly if associated with smoking tends to occur more severe forms of the disease. It is postulated that women with CD would be more vulnerable to the immunomodulatory effects of tobacco due to the negative effect of estrogen on the gene regulation of pro-inflammatory cytokines and the interaction of cellular immunity.[67,105,106]

Smoking cessation should be considered within the CD therapeutic strategy favoring the reduction of the risk of poor evolution after the four-year withdraw period.[11,49,67,107] The anti-tobacco strategy based mainly on the education and counseling of CD patients has already been demonstrated how feasible and effective in helping to sleep in smoking allowing complete abstinence to achieve complete abstinence, and consequent evolutionary improvement of your disease.[108]

Regarding the evolutionary course of UC, this tends to be more benign in smokers when compared to non-smokers, as can be verified by the lower risk of recurrences, lower use of corticosteroids and immunosuppressants, less severe clinical evolution and better prognosis, with lower colectomy and hospitalization rate.[43,49,66] Smoking suspension is associated with increased risk of development of UC,

especially about 2 to 5 years after this, and may remain at high risk for more than 20 years.[106]

Nevertheless, there are controversies regarding exposure to tobacco in the prenatal period or in childhood and the development of IBD. [36,47]

VII. STRESS AND NEUROBEHAVIORAL FACTORS

Stress is defined as a state of disharmony or acute threat to homeostasis being an important role in the pathogenesis of IBD. In the presence of stress, the hypothalamus-pituitary-adrenal axis (HHA) and the associated immune system initiate a neuroendocrine cascade, and the HHA axis that stimulates the release of glucocorticoids (cortisol) and the axis of the autonomic nervous system (ANS), stimulates the release of adrenaline. Disorders in both pathways result in the production of pro-inflammatory cytokines, interfering in the inflammatory and behavioral course of IBD.[11,43,48,55]

Some studies have shown the association of stress with increased relapse of IBD activity.[48,109] Depression and anxiety are common psychological alterations in these individuals, mainly after the first year of diagnosis of CD. [17,110] These may be associated with an increased disease activity and risk of surgeries.[17,88]

VIII. SURGERIES

1.Appendicectomy

Although is not clear whether appendicitis increases this risk or if individuals at risk of CD tend to develop more appendicitis, it was described that 47% of individuals submitted to this surgery were more likely to develop CD than those who were not.[111] Some reports demonstrated this association mainly in the first postoperative year, when incipient CD could lead to undue appendectomies. [1,48,55,112] However, this risk appears to be reduced if appendectomy occurs before 10 years of age and CD patients submitted to appendectomy have a more frequently a proximal involvement, a worse prognosis, with higher risk of stenosis and surgeries.[11,113]

Pathophysiological mechanisms are unclear, but it is known that the appendix is an immune organ related directly to the immunomediated response by extra-thymic B and T lymphocytes. It is also a reservoir predisposing bacterial proliferation, and consequent local inflammatory process.[48,114] The presence of primary cecal inflammation in CD patients or a transmural form of terminal ileum can mimic primary appendicitis, being considered confounding factors.

Regarding UC, appendectomy has been described as a protective factor mainly among children operated before the age of 10, when the risk of appendicitis is considerable. [1,48,55,115] It is postulated that the greater activation of the Th1 immunological pathway existing in the generation of appendicitis could modify the activation of the predominant Th2 pathway in the UC genesis.[48,116]

2.Tonsillectomy

Evidence of association of tonsillectomy with CD is weak, although a recent meta-analysis with 23 studies has shown a risk association for CD, and not an association with UC. [112,117]

IX. DRUGS

1. Antibiotics

The microbiome imbalance associated with antibiotic exposure is the main cause of the increase of the risk of developing IBD. [17] A dose-response effect seems to be present, as well as an inverse relationship between the age at which exposure to antibiotics occurs and the increased risk of IBD.[118] In adulthood, the individual exposure to antibiotics in the last 2 to 5 years prior to the onset of the disease increases the risk of developing IBD.[119,120]

Opportunistic infections secondary to antibiotic therapy, such as C. difficile, are not related to the onset of IBD, but may exacerbate the underlying disease, being a confounding factor. [11, 121]

Evidence that antibiotics would interfere with IBD activity and recurrence is limited due to the diversity of substances with different spectrums of action. Which is why these are still widely used during infectious complications of IBD, especially in the presence of abscesses and perianal CD.[43]

2.Nonsteroidal anti-inflammatory drugs (NSAIDs)

These drugs promote direct damage to the intestinal mucosa, increasing intestinal permeability by inhibition of cycloxigenase (COX), and reducing the production of prostaglandins. They may act as a trigger of the disease, favoring relapses in 20% of cases of quiescent IBD. [1,2,11,55,88] A prospective population study revealed that regular use of acetylsalicylic acid increases by 6 times the possibility of DC development, without association with UC. [112] The frequent use for prolonged periods of high doses of NSAIDs can increase the risk of both IBD.[113]

3. Contraceptive

The association between the use of contraceptives and IBD development is not yet established. The thrombogenic property of the drug, related to gastrointestinal microinfarctions, may explain this hypothesis.[124] Estrogen stimulates an immunological response and proliferation of macrophages, while progesterone acts as immunosuppressive.[2,48] This action would not be reduced with dose reduction, but would be reversible with its discontinuity.[124]

Prolonged exposure to contraceptive use has already been shown to increase the risk of recurrence of CD by up to three times, and this effect is greater in smokers and reverted with the suspension of medication.[1,55] In relation to UC, this increase in risk appears to be lower than that of CD.[2,49] A cohort study conducted by JESS et al, in 2012, revealed that endometriosis is associated with a highest frequency of IBD, confirming the influence of hormonal factors on the development of this disease.[125]

4.Isotretinoin

It is a retinoid derived from vitamin A used in the treatment of severe acne and folliculitis and was implicated as a promoter of IBD. [1,126] Retinoids are verified to be involved in regulating the immune response of the intestinal mucosa, but its mechanism is uncertain.[1] In 2010, CROCKETT et al. demonstrated a strong association between UC and previous exposure to high doses of isotretinoin, but not with CD.[127] However, this finding is not confirmed by further study.[60]

In conclusion, the detection of environmental risk factors and their interaction can provide an opportunity for

preventive strategies against IBD development, mainly early in life. Other factors that can influence disease development later in life, such as tobacco use and diet, can be easily changeable. Future studies are necessary to detect and confirm the predictive risk factors to IBD expansion, mainly in developing countries where its incidence is increasing.

REFERENCES

1. Frolkis A, Dieleman LA, Barkema HW, et al. Alberta IBD Consortium. Environment and the inflammatory bowel diseases. Can J Gastroenterol. 2013; 27(3): e18-24.
2. Ponder A, Long MD. A clinical review of recent findings in the epidemiology of inflammatory bowel disease. Clin Epidemiol. 2013; 5: 237-47.
3. Kotze PG, Damião AO, Ferraz J, et al. The Progression of Inflammatory Bowel Disease Throughout Latin America: A Systematic Review. Clin Gastro Hep. 2019; In press.
4. Victoria CR, Sassak LY, Nunes HRC. Incidence and prevalence rates of inflammatory bowel diseases, in midwestern of São Paulo State, Brazil. Arq. Gastroenterol. 2009; 46(1): 20-25.
5. Parente JM, Coy CS, Campelo V, et al. Inflammatory bowel disease in an underdeveloped region of Northeastern Brazil. World J Gastroenterol. 2015; 21(4): 1197-206.
6. Martins AL, Volpato RA, Gomes MP. The prevalence and phenotype in Brazilian patients with inflammatory bowel disease. Gastroenterology. 2018;18(1):1-7.
7. Kaplan GG, Ng SC. Understanding and Preventing the Global Increase of Inflammatory Bowel Disease. Gastroenterology 2017; 152(2):313-21.
8. Zhang Y-Z, LI Y-Y. Inflammatory bowel disease: pathogenesis. World J Gastroenterol, 20(1):91–99, 2014.
9. Fiocchi C. Inflammatory Bowel Disease pathogenesis: where are we? J Gastroenterol Hepatol, 30(Suppl 1):12–18, 2015.
10. Liu JZ, Anderson CA. Genetic studies of Crohn´s disease: Past, present and future. Best Practise & Research Clinical Gastroenterology, 28: 373-386, 2014.
11. Ananthakrishnan AN. Environmental Risk Factors for Inflammatory Bowel Disease: A Review. Dig Dis Sci, 60 (2): 290-298, 2015.
12. Gordon H, Moller FT, Andersen V et al. Heritability in Inflammatory Bowel Disease: from the first twin study to genome-wide association studies. Inflamm Bowel Dis, 21(6):1428–34, 2015.
13. Gupta A, Bopanna S, Kedia S et al. Familial aggregation of inflammatory bowel disease in patients with ulcerative colitis. Intest. Res,15 (3): 388-394, 2017.
14. Actis GC, Pellicano R, Rosina F. Inflammatory Bowel Disease: traditional knowledge holds the seeds for the future. World J Gastrointest Pharmacol Ther,6(2):10–16, 2015.
15. Denson LA. The role of the innate and adaptive immune system in pediatric Inflammatory Bowel Disease. Inflamm Bowel Dis,19(9):2011–2010, 2013.
16. Carrière J, Darfeuille-Michaud A, Nguyen HTT. Infectious etiopathogenesis of Crohn´s disease. World J Gastrenterol, September 14; 20(34):12102-12117, 2014.
17. Ananthakrishnan AN et al. Environmental risk factors for Inflammatory Bowel Disease Gastroenterol Hepatol, 9(6):367–74, 2013.
18. Zhou M et al. New Frontiers in Genetics, Gut Microbiota, and Immunity: A Rosetta Stone for the Pathogenesis of Inflammatory Bowel Disease. Bio Med Research International, vol 2017: 1-17, 2017.
19. Abraham C, Medzhitov R. Interactions between the host innate imune system and microbes in inflammatory bowel disease. Gastroenterology, 140:1729-37, 2011.
20. Huang Y, Chen Z. Inflammatory bowel disease related innate immunity and adaptive immunity. Am J Transl Res, 8 (6):2490-2497, 2016.
21. Goto Y, Kurashima Y, Kiyono H. The gut microbiota and Inflammatory Bowel Disease. Curr Opin Rheumatol, 27(4):388–96, 2015.
22. Baumgart DC, Sandborn WJ. Crohn´s disease. Lancet,380:1590-1065, 2012.
23. Scaldaferri F, Gerardi V, Lopetuso LR et al. Gut Microbial Flora, Prebiotics and probioticos in IBD: Their Current Usage and Utility. BioMed Research International, vol 2013: 1-9, 2013.
24. Cammarota G, Laniro G, Cianci R et al. The Involvement of Gut Microbiota in Inflammatory Bowel Disease Pathogenesis: Potential for Therapy. Pharmacol Ther, 149:191–212, 2015.
25. Abraham C, Cho JH. Inflammatory Bowel Disease. N Engl J Med,361(21):2066–78, 2009.
26. Ordás I et al. Ulcerative colitis. Lancet, 380:1606-19, 2012.
27. Goulet O. Potential role of the intestinal microbiota in programming health and disease. Nutr Ver, 73(Supp 1):32–40, 2015.
28. Chassaing B, Darfeuille-Michaud A. The commensal microbiota and enteropathogens in the pathogenesis of inflammatory bowel diseases. Gastroenterology,140 (6):1720-28, 2011.
29. Rogler G, Zeitz J, Biedermann L. The Search for Causative Environmental Factors in Inflammatory Bowel Disease. Dig Dis, 34: 48-55, 2016.
30. Bernstein CN, Banerjee A, Targownik LE et al. Cesarean section delivery is not a risk factor for development of Inflammatory Bowel Disease: a population-based analysis. Clin Gastroenterol Hepatol, 14(1):50–7, 2016.
31. Bernstein CN, Shanahan F. Disorders of a modern lifestyle: reconciling the epidemiology of inflammatory bowel diseases. Gut, 57(9):1185–1191, 2008.
32. Shanahan F. The gut microbiota a clinical perspectiveon lessons learned. Nat Rev Gastroenterol Hepatol,9:609-14, 2012.
33. Ko Y, Butcher R, Leong RW. Epidemiological studies of migration and environmental risk factors in the inflammatory boqel diseases. World Journal of Gastroenterology, 20 (5): 1238-1247, 2014.
34. Danese S, Sans M, Fiocchi C. Inflammtory bowel disease: the role of environmental factors. Autoimmun. Rev, 3:390-400, 2004.
35. Rautava S. Early microbial contact, the breast milk microbiome and child health. J Dev Orig Health Dis, 7(01):5–14, 2016.
36. Roberts SE et al. Perinatal and early life risk factors for Inflammatory Bowel Disease. World J Gastroenterol,17(6):743–9, 2011.
37. Bager P et al. Cesarean section and offspring's risk of Inflammatory Bowel Disease: a national cohort study. Inflamm Bowel Dis, 18(5):857–62, 2012.

38. Disanto G, Chaplin G, Morahan JM et al. Month of birth, vitamin D and risk of immunemediated disease: a case control study. BMC Med,10:69, 2012.

39. Shaw SY, Nugent Z, Targownik LE et al. Association between spring season of birth and Crohn's Disease. Clin Gastroenterol Hepatol,12(2):277–82, 2014.

40. Sevelsted A et al. Cesarean section and chronic immune disorders. Pediatrics, 135(1):e92–8, 2015.

41. Mikhailov TA, Furner SE. Breastfeeding and genetic factors in the etiology of inflammatory bowel disease in children. World J. Gastroenterol, 15 (3): 270-279, 2009.

42. Barclay AR, Russell RK, Wilson ML et al. Systematic review: the role of breastfeeding in the development of pediatric Inflammatory Bowel Disease. J Pediatr, 155:421–426, 2009.

43. Abegunde AT et al. Environment risk factors for inflammatory bowel disease:Evidence based literature review. World J Gastroenterology, 22: 6296-6317, 2016.

44. Gearry RB, Richardson AK, Frampton CM et al. Population-based cases control study of inflammatory bowel disease risk factors. Journal of Gastroenterology and Hepatology, 25: 325-333, 2010.

45. Hansen TS, Jess T, Vind I et al. Environmental factors in Inflammatory Bowel Disease: a case-control study based on a danish inception cohort. J Crohns Colitis, 5(6):577–84, 2011.

46. Hlavaty T, Toth J, Koller T et al. Smoking, breastfeeding, physical inactivity, contact with animals, and size of the family influence the risk of Inflammatory Bowel Disease: a slovak case-control study. United Eur Gastroenterol J, 1(2):109–19, 2013.

47. Guo AY, Stevens BW, Wilson RG et al. Early life environment and natural history of Inflammatory Bowel Diseases. BMC Gastroenterol,14(1):216, 2014.

48. Molodecky NA, Kaplan GG. Environmental risk factors for Inflammatory Bowel Disease. Gastroenterol Hepatol, 6(5):339–46, 2010.

49. Dutta AK, Chacko A. Influence of environmental factors on the onset and course of inflammatory bowel disease. World J Gastroenterol, 22: 1088-1100, 2016

50. Pineton de Chambrun G et al. Vaccination and risk for developing Inflammatory Bowel Disease: a meta-analysis of case-control and cohort studies. Clin Gastroenterol Hepatol, 13(8):1405–15, 2015.

51. Shaw SY, Blanchard JF, Bernstein CN. Early childhood measles vaccinations are not associated with paediatric Inflammatory Bowel Disease: a population-based analysis. J Crohns Colitis, 9(4):334–8, 2015.

52. Hansen TS, Jess T, Vind I et al. UEG Week Poster Presentations. Unit Eur Gastroenterol J, 3: 146-687, 2015.

53. Berg AM, Dam AN, Farraye FA. A. Environmental Influences on the Onset and Clinical Course of Crohn's Disease - Part 2: Infections and Medication Use. Gastroenterology & Hepatology, 9 (12):803- 810, 2013.

54. Foster A, Jacobson K. Changing incidence of inflammatory bowel disease:environmental influences and lessons lerant from the South Asian population. Frontiers in Pediatrics, 1 (34):1-7, 2013.

55. Ye Y et al. Review Article: The epidemiology and risk factors of inflammatory bowel disease. Int J Clin Exp Med, 8(12): 22529- 42, 2015.

56. Castiglione F, Diaferia M, Morace F et al. Risk factors for Inflammatory Bowel Diseases according to the "hygiene hypothesis": a case-control, multi-centre, prospective study in Southern Italy. J Crohns Colitis, 6(3):324–9, 2012.

57. Saidel-Odes L, Odes S. Hygiene hypothesis in inflammatory bowel disease. Annals of Gastroenterology, 27:189-190, 2014.

58. Salgado VCL et al. Crohn´s disease environmental factors in the developing world: A case-control study in a statewide catchment area in Brazil. World J Gastroenterol, 23: 5549-5556, 2017.

59. Vargas RD. Epidemiology of inflammatory bowel disease (IBD): Why are there diferences between North America and Latin America? Rev Col Gastroenterol, 25:103-105, 2010

60. Bernstein CN, Rawsthorne P, Cheang M et al. A population-based case control study of potential risk factors for Inflammatory Bowel Disease. Am J Gastroenterol, 101(5):993–1002, 2006

61. Lashner BA, Loftus EV. True or False? The Hygiene Hypothesis for Crohn's Disease. Am J. Gastroenterol, 101:1003-1004,2006.

62. Koloski, NA, Bret L, Radford-Smith G. Hygiene hypothesis in Inflammatory Bowel Disease: a critical review of the literature. World J Gastroenterol, 14(2):165–73, 2008.

63. Montgomery SM, Lambe M, Wakefield et al. Siblings and the risk of inflammatory bowel disease. Scand J Gastroenterol, 37: 1301-1308, 2002.

64. Jakobsen C, Paerregaard A, Munkholm P et al. Environmental factors and risk of developing paediatric Inflammatory Bowel Disease - a population based study 2007-2009. J Crohns Colitis, 7(1):79–88, 2013.

65. Soon IS et al. The relationship between urban environment and the inflammatory bowel diseases: a systematic review and meta-analysis. BMC Gastroenterology,12:51, 2012.

66. Vedamurthy A, Ananthakrishnan NA. Influence of Environmental Factors in the Development and Outcomes of Inflammatory Bowel Disease. Gastroenterology &Hepatology,15 (2): 72-79, 2019.

67. Dam AN, Berg AM, Farraye FA. Environmental Influences on the Onset and Clinical Course of Crohn's Disease - Part1: An Overview of External Risk Factors. Gastroenterol and Hepatol 2013; 9: 711-717, 2013.

68. Salim SY, Kaplan GG, Madsen KL. Air pollution effects on the gut microbiota: a link between exposure and inflammatory disease. Gut Microbes,5(2):215–9, 2014.

69. Kaplan GG, Hubbard J, Korzenik J et al. The Inflammatory Bowel Diseases and ambient air pollution: a novel association. Am J Gastroenterol, 105(11):2412–9, 2010.

70. Papamichael K, Konstantopoulos P, Mantzaris GJ. Helicobacter pylori infection and Inflammatory Bowel Disease: is there a link? World J Gastroenterol,20(21): 6374–85, 2014.

71. Wu X-W et al. Helicobacter pylori infection and Inflammatory Bowel Disease in asians: a meta-analysis. World J Gastroenterol, 21(15):4750–6, 2015.

72. Rokkas, T et al. The association between Helicobacter pylori infection and Inflammatory Bowel Disease based on meta-analysis. United Eur Gastroenterol J, 3(6):539–50, 2015.

73. Korzenik JR. Past and Current Theories of Etiology of IBD. Toothpaste, Worms, and Refrigerators. J. Clin. Gastroenterol, 39 (2): S59 - S65, 2005.

74. Helmby H. Human helminth therapy to treat inflammatory disorders- where do we stand? BMC Immunolog,16 (12):1-5, 2015.

75. Kozuch PL, Hanauer SB. Treatment of inflammatory bowel disease: A review of medical therapy. World J. Gastroenterol, 14 (3): 354-377, 2008.

76. Mendoza JL, Lana R, Díaz-Rubio M. Mycobacterium avium subspecies paratuberculosis and its relationship with Crohn's Disease. World J Gastroenterol, 15(4):417–22, 2009.

77. Jess T, Simonsen J, Nielsen NM et al. Enteric Salmonella or Campylobacter infections and the risk of Inflammatory Bowel Disease. Gut, 60(3):318–24, 2011.

78. Andersen V, Olsen A, Carbonnel F et al. Diet and risk of Inflammatory Bowel Disease. Dig Liver Dis, 44:185–94, 2012.

79. De Hertogh G, Aerssens J, Geboes KP, Geboes K. Evidence for involvement of infectious agents in the pathogenesis of Crohn`s disease. World J Gastroenterol, 14 (6):845-852, 2008.

80. Freeman HJ. Recent development on the role of Clostridium difficile in inflammatory bowel disease. World Journal Gastroenterol, 14 (18): 2794-2796, 2008.

81. Rapozo D, Bernadazzi C, Souza HSP. Diet and microbiota in inflammatory bowel disease: The gut in disharmony. World J Gastroenterol, 23: 2124-2140, 2017.

82. Kanai T, Matsuoka K, Naganuma M et al. Diet, microbiota, and inflammatory bowel disease: lessons from japanese foods. Korean J Inter Med, 29: 409-415, 2014.

83. Lee D, Albenberg L, Compher C et al. Diet in the pathogenesis and treatment of inflammatory bowel diseases. Gastroenterology,148(6):1087–106, 2015.

84. Ananthakrishnan NA et al. Long-term intake of dietary fat and risk of Ulcerative Colitis and Crohn's Disease. Gut, 63(5):776–84, 2014.

85. Ananthakrishnan NA et al. A prospective study of long-term intake of dietary fiber and risk of Crohn's Disease and Ulcerative Colitis. Gastroenterology, 145(5):970–7, 2013.

86. Sobczak M et al. Current overview of extrinsic and intrinsic factors in etiology and progression of Inflammatory Bowel Diseases. Pharmacol Rep, 66(5):766–75, 2014

87. Hou JK, Abraham B, El-serag H. Dietary intake and risk of developing Inflammatory Bowel Disease: a systematic review of the literature. Am J Gastroenterol,106(4):563–73, 2011.

88. Legaki E, Gazouli M. Influence of environmental factors in the development of inflammatory bowel disease. World J Gastrointestinal Pharmacol Ther, 7: 112-125, 2016.

89. Qin X. Etiology of inflammatory bowel disease: A unified hypothesis. World J Gastroenterol, 18 (15): 1708-1722, 2012.

90. Del Pinto R, Pietropaoli D, Chandar AK et al. Association Between Inflammatory Bowel Disease and Vitamin D Deficiency: A Systematic Review and Meta-analysis. Inflamm Bowel Dis, 21 (11): 2708-2717, 2015.

91. Nerich V, Jantchou P, Boutron-Ruault M-C et al. Low exposure to sunlight is a risk factor for Crohn's Disease. Aliment Pharmacol Ther, 33(8):940–5, 2011.

92. Khalili H, Ananthakrishnan NA, Konijeti GG et al. Physical activity and risk of Inflammatory Bowel Disease: prospective study from the Nurses' Health Study cohorts. BMJ,347:f6633, 2013.

93. Torki M et al. Vitamin D Deficiency Associated with Disease Activity in Patients with Inflammatory Bowel Diseases. Dig Dis Sci, 60 (10):3085-91, 2015.

94. Gonçalves P, Magro F, Martel F. Metabolic inflammation in Inflammatory Bowel Disease: crosstalk between adipose tissue and bowel. Inflamm Bowel Dis, 21(2):453–67, 2015.

95. Wong SH, Ng SC. What can we learn from Inflammatory Bowel Disease in developing countries? Curr Gastroenterol Rep,15:313–21, 2013.

96. Kim A. Dysbiosis: a review highlighting obesity and Inflammatory Bowel Disease. J Clin Gastroenterol, 49(Suppl 1):S20–4, 2015.

97. He C, Bassik MC, Moresi V et al. Exercise-induced BCL2-regulated autophagy is required for muscle glucose homeostasis. Nature, 481(7382):511–5, 2012.

98. Bilski J, Brozozowski B, Mazur-Bialy A et al. The role of physical exercise in inflammatory bowel disease. Biomed Res Int, Art. No.: 429031:1–14, 2014.

99. Kinnucan JA, Rubin DT, Ali T. Sleep and Inflammatory Bowel Disease: exploring the relationship between sleep disturbances and inflammation. Gastroenterol Hepatol, 9(11):718–27, 2013.

100. Ali T, Orr WC. Sleep disturbances and Inflammatory Bowel Disease. Inflamm Bowel Dis,20(11):1986–95, 2014.

101. Birrenbach T, Bocker U. Inflammatory bowel disease and smoking: a review of epidemiology, pathophysiology and therapeutic implications. Inflamm Bowel Dis, 10: 848-859, 2004.

102. Mahid SS, Minor KS, Soto RE et al. Smoking and Inflammatory Bowel Disease: a meta-analysis. Mayo Clin Proc., 81(11):1462–71, 2006.

103. Parkes GC et al. Smoking in inflammatory bowel disease: impact on disease course andinsights into the aetiology of its effect. J Crohns Colitis, 8: 717-725, 2014.

104. Zhai H et al. Current smoking improves ulcerative colitis patients disease behaviour in the northwest of China. Gastroenterology Ver, 12 (4): 286-290, 2017

105. Zeman MV, Hiraki L, Sellers EM. Genders differences in tobacco smoking: higher relative exposure to smoke than nicotine in women. J Womens Health Gend Based Med,11:147-53, 2002.

106. Higuchi LM, Khalili H, Chan AT et al. A prospective study of cigarette smoking and the risk of Inflammatory Bowel Disease in women. Am J Gastroenterol,107(9):1399–406, 2012.

107. Frolkis AD et al. The Association of Smoking and Surgery in the Inflammatory Bowel Diseases isModified by Age at Diagnosis. Clinical and Translational Gastroenterology, 7: e165, 2016.

108. Nunes T, Etchevers MJ, Merino O et al. High smoking cessation rate in Crohn´s disease patients after physician advice - The TABACROHN STUDY. Journal of Crohn´s and Colitis, 7:202-7, 2013.

109. Bitton A, Dobkin PL, Edwardes MD et al. Predicting relapse in Crohn´s disease: a biopsychosocial model. Gut, 57: 1386-1392, 2008.

110. Lerebours E, Gower-Rousseau C, Merle V et al. Stressful life events as a risk factor for Inflammatory Bowel Disease onset: a population-based case-control study. Am J Gastroenterol,102(1):122–31, 2007.

111. Andersson RE et al. Appendectomy is followed by increased risk of Crohn's disease. Gastroenterology, 124 (1): 40-46, 2003.

112. Firouzi F, Bahari A, Aghazadeh R et al. Appendectomy, tonsillectomy, and risk of Inflammatory Bowel Disease: a case control study in Iran. Int J Colorectal Dis, 21(2):155–9, 2006.

113. Cosnes J, Seksik P, Nion-Larmurier I et al. Prior appendectomy and the phenotype and course of Crohn ´s disease.World J Gastroenterol,12 (8): 1235-42, 2006.

114. Cheluvappa R, Luo AS, Palmer C et al. Protective pathways against colitis mediated by appendicitis and appendectomy. Clin Exp Immunol,165(3):393–400, 2011.

115. Vcev A et al. A retrospective, case-control study on traditional environmental risk factors in inflammatory bowel disease in Vukovar-Srijem County, northeastern Croatia, 2010. Wien Klin Wochenschr,127:345–54, 2015.

116. Radford-Smith GL et al. Protective role o appendicectomy on onset and severity of ulcerative colitis and Crohn's disease. Gut, 51(6): 808-813, 2002.

117. Sun W et al. Tonsillectomy and the risk of Inflammatory Bowel Disease: a systematic review and meta-analysis. J Gastroenterol Hepatol. 2016 Jun;31(6):1085-94

118. Kronman MP, Zaoutis TE, Haynes K et al. Antibiotic exposure and Inflammatory Bowel Disease development among children: a population-based cohort study. Pediatrics,130(4):e794–803, 2012.

119. Shaw SY, Blanchard JF, Bernstein CN. Association between the use of antibiotics in the first year of life and pediatric Inflammatory Bowel Disease. Am J Gastroenterol,105(12):2687–92, 2010.

120. Ungaro R et al. Antibiotics associated with increased risk of new-onset Crohn's Disease but not Ulcerative Colitis: a meta-analysis. Am J Gastroenterol, 109(11):1728–38, 2014.

121. Singh S, Graff LA, Bernstein CN. Do NSAIDs, Antibiotics, Infections, or Stress Trigger Flares in IBD? Am J Gastroenterol,104: 1298-1313, 2009.

122. Chan SSM, Luben R, Bergmann MM et al. Aspirin in the aetiology of Crohn's Disease and Ulcerative Colitis: a european prospective cohort study. Aliment Pharmacol Ther, 34(6):649–55, 2011.

123. Ananthakrishnan AN et al. Aspirin, nonsteroidal anti-inflammatory drug use and risk for Crohn Disease and Ulcerative Colitis: a cohort study. Ann Intern Med, 156(5):350–9, 2012.

124. Cornish JA, Tan E, Similis C et al. The risk of oral contraceptives in the etiology of Inflammatory Bowel Disease: a meta-analysis. Am J Gastroenterol 2008;103 (9):2394–2400

125. Jess T, Frisch M, Jorgensen KT et al. Increased risk of Inflammatory Bowel Disease in women with endometriosis: a nationwide danish cohort study. Gut, 61(9):1279–83, 2012.

126. Papageorgious NP, Altman A, Schoenfeld Y. Inflammatory Bowel Disease: Adverse Effect of Isotretinoin. IMAJ,11: 505-506, 2009.

127. Crockett SD, Porter CQ, Martin CF et al. Isotretinoin Use and the Risk of Inflammatory Bowel Disease: A Case-control Study. Am J Gastroenterol, 124(10):1038, 2010.