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## RESEARCH ARTICLE

# OVERVIEW OF ETIOLOGY AND RISK FACTORS OF INFLAMMATORY BOWEL DISEASE (IBD)

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**ABSTRACT**

The aim of this review study was to discuss and highlight the most important risk factors and causes of Inflammatory bowel disease (IBD), through reviewing the relevant evidence. We searched following electronic databases (PubMed and EMBASE) to May 2017. Search strategy targeted relevant studies to our main topic which is Inflammatory Bowel Disease (IBD), using Mesh terms through PubMed as following; "IBD" OR "Crohn's disease (CD)" OR "ulcerative colitis (UC)" combined with "Etiology" AND "Risk factors" AND "Epidemiology" AND "Pathogenesis". IBD is a growing disease that is pricey to the individual and culture. The underlying property of the hygiene hypothesis is that lowered microbial direct exposure in youth could cause the succeeding advancement of IBD appears to be possible. However, the evidence supporting that genetic, environmental factors and life style, as well as *H pylori* exposure, are the most factors contributing in causing of IBD.



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## INTRODUCTION

Inflammatory bowel disease (IBD), which compromised of Crohn's disease (CD) as well as ulcerative colitis (UC), is a complex genetic disorder that is influenced by environmental risk factors, as well as defined by progressive inflammatory disease that usually have a start throughout young their adult years as well as a training course defined by remission and regression, effecting the tiny digestive tract and/or the colon bring about frequent diarrhea as well as stomach pain. Anatomically, CD can impact the entire gastrointestinal system from mouth to rectum, although it commonly affects the incurable ileum as well as colon. UC is restricted to the rectum, caecum and colon. Microscopically, CD is commonly discontinuous as well as transmural while UC influences only the intestinal mucosa in a continual pattern (Aumgart and Sandborn, 2007; Strober *et al*., 2007). The frequency of IBD is comparable in males and females and optimal in young adults. The greatest incidences are reported in northern Europe as well as North America where they vary from 12 to 19/100,000/ year as well as from 5 to 29/100,000/ year, specifically (Loftus, 2004; Bernstein and Shanahan, 2008). Virtually 1.4 million Americans and also 2.2 million Europeans are affected (Loftus, 2004; Bernstein and Shanahan, 2008). In Asia for instance, the occurrence as well as prevalence of IBD are less than those reported from North America and also Europe. Recent researches have reported a rise in the prevalence of IBD with a predominance of ulcerative colitis (UC) in Asian communities (Sood and Midha, 2007; Niriella *et al*., 2010). Increasing rates have been reported especially from India, Japan, and also the Middle East (Goh and Xiao, 2009; Ahuja and Tandon, 2010). The prices are greater in Indians in Southeast Asia compared with the Chinese and also Malays and the rates of UC are more than those of Crohn's disease (CD). Several researches Saudi Arabia has showed a rapidly boosting rate of IBD and in particular CD in the Saudi Arabia (Al-Ghamdi *et al*., 2004; Al-Mofarreh *et al*., 2009). The pathogenesis of IBD is just partly comprehended; numerous environmental and also host (e.g., genetic, epithelial, nonimmune and immune) factors are involved. Complex communications between the immune system, enteric commensal bacteria/pathogens as well as host genotype are thought to underlie the development of IBD (Strober *et al*., 2007; Podolsky, 2002). The relevance of genetic susceptibility has been developed with genome-wide association scans, which have actually determined vulnerability genes connecting the pathogenesis of IBD to the dysregulation of the stomach immune system as well as the host microbiome (Jess *et al*., 2005; Gaya *et al*., 2006). Hereditary proneness, however, could not be solely responsible for disease etiology. The absence of total penetrance should be made up by extra consider disease etiology (Bernstein and Shanahan, 2008). The aim of this review study was to discuss

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and highlight the most important risk factors and causes of Inflammatory bowel disease (IBD), through reviewing the relevant evidence.

## MATERIALS AND METHODS

We searched following electronic databases (PubMed and EMBASE) to May 2017. Search strategy targeted relevant studies to our main topic which is Inflammatory Bowel Disease (IBD), using Mesh terms through PubMed as following; "IBD" OR "Crohn's disease (CD)" OR "ulcerative colitis (UC)" combined with "Etiology" AND "Risk factors" AND "Epidemiology" AND "Pathogenesis". Only English language articles with human subjects were restricted to our search. Furthermore, reference lists of retrieved studies manually screened for more relevant studies that could have useful evidence to our review.

## RESULTS AND DISCUSSION

### Etiology and Risk factors

Idiopathic IBD involving Crohn disease and also ulcerative colitis happen in clinically immunocompetent people whose particular signs and symptoms and signs occur from a durable, cytokine-driven (yet noninfectious) inflammation of the intestine (Podolsky, 2002). Crohn disease is related to excess IL-12/ IL-23 as well as IFN-γ/ IL-17 production that impacts the small digestive tract and colon with discontinuous ulcer as well as full density bowel wall inflammation frequently consisting of granulomas. Current progression in the genetics of IBD holds a number of crucial messages in relation to the underlying mechanism of the disease. On one hand, the increasing variety of sensitivity genetics loci defined in IBD shows that genetic impacts are essential parts of the disease pathogenesis; while on the other hand, explainable vulnerability loci discovered up until now represent just 20%-25% of the heritability discovered in the above-mentioned researches (Bernstein and Shanahan, 2008; Goh and Xiao, 2009; Ahuja and Tandon, 2010). Raising a strong possibility for an environmental hypothesis in IBD. Are well established risk factors for IBD, although lots of others (including oral contraceptives and also diet regimen) (Logan and Kay, 1989; Mahmud and Weir, 2001) have been suggested to be important in the condition but with irregular results (Persson *et al*., 1987). One encouraging team of environmental factors that could be potentially connected with IBD are those related to the "hygiene hypothesis" (Strachan, 1989) which is closely linked to reduced microbial direct exposure in childhood.

### Roles of micro-organisms as etiology of IBD

The value of gut plants in IBD is directly supported by studies in a selection of murine versions in which 'spontaneous' chronic colitis seems to be totally dependent on the existence of a luminal flora (Hata *et al*., 2001; Rath *et al*., 2001). Hence, colitis could not create when these lines are maintained in a germ-free gnotobiotic state, yet quickly arises when they are reconstituted with germs that are thought about typical constituents of luminal vegetation (Elson *et al*., 2005; Onderdonk *et al*., 1977). At least 3 not always mutually exclusive theories can be suggested worrying the ramification of microorganisms in the etio-pathogenesis of IBD: (A) a participation of a consistent virus; (B) an abnormally absorptive mucosal obstacle leading to excessive microbial translocation; and also (C) a failure in the equilibrium between presumptive "protective" versus "dangerous" intestinal bacteria which could promote inflammation (Sartor, 2008). The possibility that IBD is an infection has been disputed given that the initial summary of CD. Many infectious agents (viral, microbial or parasitical representatives; (Table 1) (Tamboli *et al*., 2004) have actually been believed in IBD etiology however the toughest proof comes from researches indicating the duty of bacteria. In the intestinal mucosa of patients with IBD, germs that can possibly be pathogenic such as Escherichia coli, Listeria monocytogenes, Yersinia enterocolitica and also Mycobacterium avium paratuberculosis are discovered over (Tamboli *et al*., 2004).

**Table 1. Micro-organisms in tissues of patients with IBD (23)**

| Virus | Bacteria | Parasite |
|---|---|---|
| Adenovirus | Brucella spp. | Borrelia spp. |
| Epstein-Barr virus | Chlamidia spp. | *Toxoplasma gondii* |
| Cytomegalovirus | Campylobacter spp. | Treponema spp. |
| Flu virus | *Escherichia coli* | |
| Coronavirus | Helicobacter spp. | |
| Rotavirus | Legionella spp. | |
| Measles virus | Mycobacterium spp. | |
| Respiratory syncytial virus | Pseudomonas spp. | |
| Para-influenza type 2 and 3 virus | Salmonella spp. | |
| Bovine viral diarrhea virus | Staphylococcus spp. | |
| | Streptococcus spp. | |
| | Shigella spp. | |
| | Yersinia spp. | |
| | Enterococcus | |
| | *Listeria monocytogenes* | |
| | *Bacteroides vulgatus* | |
| | *Bacteroides burgdorferi* | |

### Roles of H pylori in IBD

Multiple research studies given that 1994 have actually located a substantially reduced sero-prevalence of H pylori in patients with IBD compared with both matched controls, and also "disease" controls (Halme *et al*., 1996; Wagtmans *et al*., 1997). The occurrence of this microbial infection is lower in CD compared with UC, most of these researches. Possible confounders consist of the impact of salazopyrine, various other 5-ASA substances, and anti-biotics on the carriage and also obliteration of H pylori (Parlak *et al*., 2001; Piodi *et al*., 2003). Furthermore, research studies of IBD patients and disease control groups consisting of patients with COPD, show that the H pylori prices in those people revealed to several prescription antibiotics are in fact higher compared to those subjected to either no prescription antibiotics or less courses (Pronai *et al*., 2004). This mutual relation, much like that seen in between UC and appendectomy, has actually additionally been connected to refined modifications in disease nature. Vare *et al*, investigating the connection between H pylori and CD, found that seropositive patients presented at a significantly later age (40 years) as compared to seronegative CD patients (30 years, $P < 0.001$) (Vare *et al*., 2001). Alteration of phenotype was additionally determined in a separate study where seropositive non-smoking CD patients had significantly fewer relapses and a lower risk of digestive tract resection as compared to seronegative non-smoking patients ($P < 0.01$ and $P < 0.05$, respectively) (Puspok *et al*., 1999).

**Environment factors and Life style**

There is no question that environmental factors play an essential role in the pathogenesis of IBD. A great deal of environmental factors are taken into consideration risk factors for IBD, including cigarette smoking, diet plan, medications, geography, social stress and anxiety, as well as emotional element (Loftus, 2004). Amongst them, cigarette smoking remains the most commonly researched as well as replicated environmental prompter for IBD. Since the initial described inverse organization in between UC and cigarette smoking in 1982, subsequent researches have actually confirmed the protective impact of hefty smoking cigarettes on the development of UC with a lower rate of regression (Cosnes, 2004; Cosnes, 2008; Lakatos *et al*., 2007). Conventional conception for vitamin D is concentrated in calcium metabolic process and bone health and wellness. Nowadays, there has actually been increasing acknowledgment of the immunologic role of vitamin D (Garg *et al*., 2012). Recent literary works suggests that the duty of vitamin D is various and also related to varied diseases including IBD. Leslie *et al*ia (Leslie *et al*., 2008) found that vitamin D deficiency had actually prevailed in detected IBD patients as well as mentioned that reduced vitamin D had actually added to the enhanced risk of IBD. In computer mouse versions, vitamin D shortage is associated with a raised susceptibility to dextran sodium sulfate-induced colitis and 1,25(OH)2D3 supplements ameliorates the seriousness of intestinal inflammation (Cantorna *et al*., 2000).
The impact of pain killers and also nonsteroidal anti-inflammatory medicines (NSAIDs) in the intestinal system is well acknowledged. Limited high quality proof is available to support the idea that aspirin as well as NSAIDs have a result in triggering start or relapse of IBD. Ananthakrishnan *et al*. (2012) found no association in between the dose, period, or regularity of aspirin usage as well as the risk for CD or UC; however, the high dose, extended using period, as well as regular use NSAIDs had been connected with a raised risk of CD and UC. A current research has found that making use of prescription antibiotics is a vital environmental factor, influencing the risk of IBD through their effect on the microbiome. Antibiotic use within the very first year of life is more typical amongst pediatric IBD situations as compared to controls (Shaw *et al*., 2010).

Stress has long been proposed to play a role in the pathogenesis of CD and also UC (Maunder, 2005; Mawdsley and Rampton, 2005), Bitton *et al*. (2008) suggested that individuals with reduced levels of anxiety had a reduced risk of the disease start. Mood components of perceived anxiety, including depression and also stress and anxiety, may play a solid duty in moderating the degeneration of IBD (Cámara *et al*., 2011). The hygiene theory as a possible explanation for IBD comes from monitoring that the rise in the occurrence of IBD, both in developed and also establishing nations (Askling *et al*., 1999; Yao *et al*., 2000), has actually accompanied enhancements in hygiene over the 20th century. These improvements in hygiene include accessibility to clean water, a hot water tap, a smaller family size as well as hence much less crowding, non-contaminated food and hygiene products such as tooth paste (Feeney *et al*., 2002; Sullivan, 1990).

**Genetic factors**

The IBD hereditary study began in 2001 with the discovery of NOD2 (nucleotide-binding oligomerization domaincontaining 2), the very first susceptibility gene for CD (Ogura *et al*., 2001). The NOD2 genetics codes for a protein that was originally described as an intracellular receptor recognizing the muramyl dipeptide (MDP), a conserved concept present in peptidoglycan from both Gram-positive and also-unfavorable bacteria (Inohara *et al*., 2003). MDP stimulation generates autophagy which manages microbial duplication and also antigen presentation (Cooney *et al*., 2010; Travassos *et al*., 2010), and also regulates both adaptive and innate immune reactions (Shaw *et al*., 2011). NOD2 takes part in distinctive MDP-independent paths such as the regulation of the T-cell feedback (Ogura *et al*., 2001; Shaw *et al*., 2011). The organization in between CD and NOD2 has actually already been duplicated at the genome-wide value degree. Genetic analyses have actually shown a vital role for autophagy in immune feedbacks in IBD, and also reported 2 autophagy-related genetics named ATG16L1 and also IRGM. Autophagy is involved in intracellular homeostasis, contributing to the degradation and recycling of cytosolic materials as well as organelles, along with to the resistance versus infection and elimination of intracellular microorganisms (Travassos *et al*., 2010; Shaw *et al*., 2011).

**Conclusion**

IBD is a growing disease that is pricey to the individual and culture. The underlying property of the hygiene hypothesis is that lowered microbial direct exposure in youth could cause the succeeding advancement of IBD appears to be possible. However, the evidence supporting that genetic, environmental factors and life style, as well as *H pylori* exposure, are the most factors contributing in causing of IBD.

## REFERENCES

Ahuja V. and Tandon RK. 2010. Inflammatory bowel disease in the Asia-Pacific area: A comparison with developed countries and regional differences. *J Dig Dis*., 11:134–47.

Al-Ghamdi AS, Al-Mofleh IA, Al-Rashed RS, Al-Amri SM, Al-Jebreen AM and Isnani AC. 2004. Epidimiology and outcome of Crohn's disease in a teaching hospital in Riyadh. *World J Gastroenterol*., 10:1341–4.

Al-Mofarreh MA, Al-Mofleh IA, Al-Teimi IN. and Al-Jebreen AM. 2009. Crohn's disease in Saudi outpatient population: Is it still rare? *Saudi J Gastroenterol*., 15:111–6.

Ananthakrishnan AN, Higuchi LM, Huang ES, Khalili H, Richter JM, Fuchs CS. and Chan AT. 2012. Aspirin, nonsteroidal anti-inflammatory drug use, and risk for Crohn disease and ulcerative colitis: a cohort study. *Ann Intern Med*., 156:350–359.

Askling J, Grahnquist L, Ekbom A. and Finkel Y. 1999. Incidence of paediatric Crohn's disease in Stockholm, Sweden. *Lancet*, 354:1179.

Baumgart DC. and Sandborn WJ. 2007. Inflammatory bowel disease: clinical aspects and established and evolving therapies. *Lancet*, 369:1641–1657.

Bernstein CN. and Shanahan F. 2008. Disorders of a modern lifestyle: reconciling the epidemiology of inflammatory bowel diseases. *Gut*., 57:1185–1191.

Bitton A, Dobkin PL, Edwardes MD, Sewitch MJ, Meddings JB, Rawal S, Cohen A, Vermeire S, Dufresne L, Franchimont D, *et al*. 2008. Predicting relapse in Crohn's disease: a biopsychosocial model. *Gut*., 57:1386–1392.

Cámara RJ, Schoepfer AM, Pittet V, Begré S. and von Känel R. 2011. Mood and nonmood components of perceived

stress and exacerbation of Crohn's disease. *Inflamm Bowel Dis*., 17:2358–2365.

Cantorna MT, Munsick C, Bemiss C. and Mahon BD. 2000. 1,25-Dihydroxycholecalciferol prevents and ameliorates symptoms of experimental murine inflammatory bowel disease. *J Nutr*., 130:2648–2652.

Cooney R, Baker J, Brain O, Danis B, Pichulik T, Allan P, Ferguson DJ, Campbell BJ, Jewell D. and Simmons A. 2010. NOD2 stimulation induces autophagy in dendritic cells influencing bacterial handling and antigen presentation. *Nat Med*., 16:90–97.

Cosnes J. 2004. Tobacco and IBD: relevance in the understanding of disease mechanisms and clinical practice. *Best Pract Res Clin Gastroenterol*., 18:481–496.

Cosnes J. 2008. What is the link between the use of tobacco and IBD? *Inflamm Bowel Dis*., 14 Suppl 2:S14–S15.

Elson CO, Cong Y, McCracken VJ, Dimmitt RA, Lorenz RG. and Weaver CT. 2005. Experimental models of inflammatory bowel disease reveal innate, adaptive and regulatory mechanisms of host dialogue with the microbiota. *Immunol Rev*., 206:260–276.

Feeney MA, Murphy F, Clegg AJ, Trebble TM, Sharer NM. and Snook JA. 2002. A case-control study of childhood environmental risk factors for the development of inflammatory bowel disease. *Eur J Gastroenterol Hepatol*., 14:529–534.

Garg M, Lubel JS, Sparrow MP, Holt SG. and Gibson PR. 2012. Review article: vitamin D and inflammatory bowel disease-established concepts and future directions. *Aliment Pharmacol Ther*., 36:324–344.

Gaya DR, Russell RK, Nimmo ER. and Satsangi J. 2006. New genes in inflammatory bowel disease: lessons for complex diseases? *Lancet*, 367:1271–1284.

Goh K. and Xiao SD. 2009. Inflammatory bowel disease: A survey of the epidemiology in Asia. *J Dig Dis*., 10:1–6.

Halme L, Rautelin H, Leidenius M. and Kosunen TU. 1996. Inverse correlation between Helicobacter pylori infection and inflammatory bowel disease. *J Clin Pathol*., 49:65–67.

Hata K, Andoh A, Sato H, Araki Y, Tanaka M, Tsujikawa T, *et al*. 2001. Sequential changes in luminal microflora and mucosal cytokine expression during developing of colitis in HLA-B27/beta2-microglobulin transgenic rats. *Scand J Gastroenterol*., 36:1185–1192.

Inohara N, Ogura Y, Fontalba A, Gutierrez O, Pons F, Crespo J, Fukase K, Inamura S, Kusumoto S, Hashimoto M. *et al*. 2003. Host recognition of bacterial muramyl dipeptide mediated through NOD2. Implications for Crohn's disease. *J Biol Chem*., 278:5509–5512.

Jess T, Riis L, Jespersgaard C, *et al*. 2005. Disease concordance, zygosity, and NOD2/ CARD15 status: follow-up of a population-based cohort of Danish twins with inflammatory bowel disease. *Am J Gastroenterol*., 100:2486–2492.

Lakatos PL, Szamosi T. and Lakatos L. 2007. Smoking in inflammatory bowel diseases: good, bad or ugly? *World J Gastroenterol*., 13:6134–6139.

Leslie WD, Miller N, Rogala L. and Bernstein CN. 2008. Vitamin D status and bone density in recently diagnosed inflammatory bowel disease: the Manitoba IBD Cohort Study. *Am J Gastroenterol*., 103:1451–1459.

Loftus E., Jr 2004. Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence and environmental influences. *Gastroenterology*, 126:1504–1517.

Logan RF. and Kay CR. 1989. Oral contraception, smoking and inflammatory bowel disease-findings in the Royal College of General Practitioners Oral Contraception Study. *Int J Epidemiol*., 18:105–107.

Mahmud N. and Weir DG. 2001. The urban diet and Crohn's disease: is there a relationship? *Eur J Gastroenterol Hepatol*., 13:93–95.

Maunder RG. 2005. Evidence that stress contributes to inflammatory bowel disease: evaluation, synthesis, and future directions. *Inflamm Bowel Dis*., 11:600–608.

Mawdsley JE. and Rampton DS. 2005. Psychological stress in IBD: new insights into pathogenic and therapeutic implications. *Gut*., 54:1481–1491.

Niriella MA, De Silva AP, Dayaratne AH, Ariyasinghe MH, Navarathne MM, Peiris RS. *et al*. 2010. Prevalence of inflammatory bowel disease in two districts of Sri Lanka: A hospital based survey. *BMC Gastroenterol*., 10:32–32. PP not available in Pubmed and not mentioned in PDF.

Ogura Y, Bonen DK, Inohara N, Nicolae DL, Chen FF, Ramos R, Britton H, Moran T, Karaliuskas R, Duerr RH. *et al*. 2001. A frameshift mutation in NOD2 associated with susceptibility to Crohn's disease. *Nature*, 411:603–606.

Onderdonk AB, Hermos JA. and Bartlett JG. 1977. The role of the intestinal microflora in experimental colitis. *Am J Clin Nutr*., 30:1819–1825.

Parlak E, Ulker A, Disibeyaz S, Alkim C. and Dali U. 2001. There is no significant increase in the incidence of Helicobacter pylori infection in patients with inflammatory bowel disease in Turkey. *J Clin Gastroenterol*., 33:87–88.

Persson PG, Ahlbom A. and Hellers G. 1987. Crohn's disease and ulcerative colitis. A review of dietary studies with emphasis on methodologic aspects. *Scand J Gastroenterol*., 22:385–389.

Piodi LP, Bardella M, Rocchia C, Cesana BM, Baldassarri A. and Quatrini M. 2003. Possible protective effect of 5-aminosalicylic acid on Helicobacter pylori infection in patients with inflammatory bowel disease. *J Clin Gastroenterol*., 36:22–25.

Podolsky, DK. 2002. Inflammatory bowel disease. *N Engl J Med*., 347:417–429.

Pronai L, Schandl L, Orosz Z, Magyar P. and Tulassay Z. 2004. Lower prevalence of Helicobacter pylori infection in patients with inflammatory bowel disease but not with chronic obstructive pulmonary disease - antibiotic use in the history does not play a significant role. *Helicobacter*, 9:278–283.

Puspok A, Dejaco C, Oberhuber G, Waldhor T, Hirschl AM, Vogelsang H. and Gasche C. 1999. Influence of H pylori infection on the phenotype of Crohn's disease. *Am J Gastroenterol*., 94:3239–3244.

Rath HC, Schultz M, Freitag R, Dieleman LA, Li F, Linde HJ, *et al*. 2001. Different subsets of enteric bacteria induce and perpetuate experimental colitis in rats and mice. *Infect Immun*., 69:2277–2285.

Sartor, RB. 2008. Microbial influences in inflammatory bowel diseases. *Gastroenterology*, 134:577–594.

Shaw MH, Kamada N, Warner N, Kim YG, Nuñez G. 2011. The ever-expanding function of NOD2: autophagy, viral recognition, and T cell activation. *Trends Immunol*., 32:73–79.

Shaw SY, Blanchard JF. and Bernstein CN. 2010. Association between the use of antibiotics in the first year of life and pediatric inflammatory bowel disease. *Am J Gastroenterol*., 105:2687–2692.

Sood A. and Midha V. 2007. Epidemiology of inflammatory bowel disease in Asia. *Indian J Gastroenterol*., 26:285–9.

Strachan DP. 1989. Hay fever, hygiene, and household size. *BMJ*, 299:1259–1260.

Strober W, Fuss I. and Mannon P. 2007. The fundamental basis of inflammatory bowel disease. *J Clin Invest*., 117:514–521.

Sullivan SN. 1990. Hypothesis revisited: toothpaste and the cause of Crohn's disease. *Lancet*, 336:1096–1097.

Tamboli CP, Neut C, Desreumaux P. and Colombel JF. 2004. Dysbiosis as a prerequisite for IBD. *Gut*., 53:1057.

Travassos LH, Carneiro LA, Ramjeet M, Hussey S, Kim YG, Magalhães JG, Yuan L, Soares F, Chea E, Le Bourhis L. *et al*. 2010. Nod1 and Nod2 direct autophagy by recruiting ATG16L1 to the plasma membrane at the site of bacterial entry. *Nat Immunol*., 11:55–62.

Vare PO, Heikius B, Silvennoinen JA, Karttunen R, Niemela SE, Lehtola JK. and Karttunen TJ. 2001. Seroprevalence of Helicobacter pylori infection in inflammatory bowel disease: is Helicobacter pylori infection a protective factor? *Scand J Gastroenterol*., 36:1295–1300.

Wagtmans MJ, Witte AM, Taylor DR, Biemond I, Veenendaal RA, Verspaget HW, Lamers CB. and van Hogezand RA. 1997. Low seroprevalence of Helicobacter pylori antibodies in historical sera of patients with Crohn's disease. *Scand J Gastroenterol*., 32:712–718.

Yao T, Matsui T. and Hiwatashi N. 2000. Crohn's disease in Japan: diagnostic criteria and epidemiology. *Dis Colon Rectum*., 43:S85–S93.

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