ECRONICON OPEN ACCESS

EC MICROBIOLOGY
Review Article

Inflammatory Bowel Disease in Saudi Arabia: Challenges and Perspectives

Taghreed A Hafiz*

Department of Clinical Laboratory Sciences, College of Applied Medical Sciences, King Saud University, Riyadh, Saudi Arabia

***Corresponding Author:** Taghreed A Hafiz, Department of Clinical Laboratory Sciences, College of Applied Medical Sciences, King Saud University, Riyadh, Saudi Arabia.

Received: February 04, 2019; **Published:** February 27, 2019

Abstract

The recent upsurge in Inflammatory bowel disease (IBD) cases in the world has drawn attention to this important emerging public health problem. IBD is a term for two chronic diseases, ulcerative colitis and Crohn's disease. The growing prevalence of IBD in Saudi Arabia urged reviewing the latest research in this area toward having thoughtful picture of the situation. In general, various risk factors such as nutrition and medication have been linked to IBD prevalence and pathogenicity to a certain degree although the effect of other factors like smoking on IBD remain questionable. The occurrence of IBD is linked to hypothesis of a complex interaction between the host genotype, enteric commensal bacteria/pathogens and the immune system. This review serves to survey and compare the findings of studies through going on to various putative risk factors that have been implicated in the etiopathogenesis and ending with a note on the challenges currently faced in the management of this condition.

Keywords: *Crohn's Disease; Colitis; Microbiota; Etiopathogenesis*

Introduction

Inflammatory bowel disease (IBD), comprising of ulcerative colitis (UC) and Crohn's disease (CD), is an immune-mediated condition. The etiopathogenesis of this disease remains obscure despite extensive research. UC usually causes superficial inflammation that is limited to the colon, while CD can involve any part of the gastrointestinal tract in the form of transmural inflammation, strictures, fistulas, and abscess formation. While IBD is known to be prevalent predominantly in the Western world, recent studies show a pattern of rising incidence in previously low-prevalence regions such as Asia and the Middle East. Therefore, the upsurge of IBD in the Middle East not only highlights the importance of early recognition and accurate diagnosis but also warrants further detailed research to study this emerging health problem. Thus, founding the best medical management of IBD among children and adults urged reporting the changes of IBD prevalence in the context of new incidences and their demographic characteristics as well as addressing all the possible factors that contribute in IBD pathogenicity. This review describes the recent trends in the incidence of IBD in Saudi Arabia and amalgamates findings of various epidemiological studies to provide insights to the complex and dynamic interaction of genetics, gut microbiota, and environmental factors implicated in the etiopathogenesis of this disease.

Incidence and prevalence

Traditionally, Western Europe and North America are known to have the highest incidence of IBD, with the disease affecting an estimated 2.2 million Europeans and 1.5 million Americans [1-4]. While data on the prevalence of IBD is limited, Loftus (2004) estimated that there are 780,000 cases of UC and 630,000 cases of CD in North America [2].

A few decades ago, low rates of prevalence and incidence of IBD were reported in Eastern Europe, South America and the Asia-Pacific region [5-9]. However, while recent studies show an increasing prevalence of IBD in Japan, Hong Kong and Korea [10] between 1980 and 2003, other Asian countries, especially India and the Middle East, also report an increase in IBD cases with a dominance of UC, possibly as a consequence of lifestyle alteration and environmental changes [11-14]. Similarly, an increasing prevalence in central China and Saudi Arabia has also been reported [15-17]. Studies reveal that Australia has one of the highest incidence rates of IBD (29.6/100,000) with the predominance of CD [18], while very low incidence rates over a period of twelve years, have been reported in Sudan [19] and sub-Saharan Africa [20].

With regards to the incidence of CD in Saudi Arabia, Mokhtar and Khan first reported the incidence of CD (0.32/100,000 population) in Saudi Arabia in 1982 [16], since then the incidence of CD has been increasing dramatically, reaching 6.72/100,000 population [21-27]. While Kelsen and Baldassano (2008) estimated that 25% of all CD patients had childhood onset of the disease [28], El-Mouzan., *et al.* (2014) found that the prevalence of CD in Saudi Arabia between 2003 and 2012 in children younger than 14 years was only 0.27/100,000 population [29]. Saudi children have been reported to have low incidence of early onset CD, high incidence of growth failure and long diagnostic delay comparable to Western patients [30]. However, studies on IBD incidence in Saudi populations are limited by a small sample size, short duration of study, or inadequate case-finding protocols.

Demographic characteristics

Although IBD can occur at any age, most studies describe a bimodal age of onset between 15 to 30 years, followed by 50 to 70 years, even as 10% of IBD has been reported in the pediatric age group. Several authors document that CD is relatively more prevalent in females, with an incidence ratio of 1.3, while UC is found to affect both sexes equally, with male predominance after 40 years of age [31-34]. While Caucasians have been traditionally thought to be at a greater risk of IBD, recent studies show no racial or ethnic differences in the incidence and prevalence of IBD in Caucasians, African-Americans, Asians and Hispanics [35], though Eastern European Ashkenazi Jews were found to be at a 5- to 8-fold greater risk of developing IBD than non-Jewish populations [36].

As for Saudi Arabia, Fadda., *et al.* (2012) reported that of the IBD patients diagnosed, 51.3% were females with a mean age of 25.5 years. CD was diagnosed in 63% of the patients and UC in the remaining 37% [37], re-enforcing the emerging pattern of CD predominance in the region [21]. Additionally, Al-Mofarreh and Al-Mofleh (2013), who studied 693 Saudi outpatients, found that the mean age of UC patients was 34 years, with a peak occurring between 21 years and 40 years, while the mean age of CD patients was 27 years with a peak between 11 years and 30 years. Male preponderance was observed for both UC (1.5:1) as well as CD (2:1) [21]. Another study involving 497 Saudi patients with CD showed male preponderance of 59%. At the time of diagnosis, 77% patients were in the age group of 17 - 40 years with mean age of 25 years [38]. Similar results were reported by Alharbi., *et al.* (2014), who examined data of 394 Saudi patients with UC and found that 68.4% belonged to the age group of 17 - 40 years, while 24.2% were older than 40 years, based on the Montréal classification of age of onset. Furthermore, they reported male preponderance of 51.0% [39]. Aljebreen., *et al.* (2014) observed that the trend of CD in Saudi Arabia was like that in western communities in terms of disease location, age of onset, and disease behavior [38].

Regarding the demographic features of IBD among Saudi children, a study by El Mouzan., *et al.* (2016) showed that males comprised 59% of CD and 57% of UC in the pediatric age group. The prevalence of UC was found to be significantly higher in the age group of 10 - 17 years [40]. Similar results were reported by an earlier study of 218 Saudi children with IBD, which found male preponderance of 56% among CD patients and female preponderance of 59% among UC patients, while no significant difference regarding the age of onset of symptoms was observed between patients with CD and UC [41].

Risk factors

The effect of environmental factors on the onset of IBD has been recognized although the relationship is yet unclear. Some of these environmental factors show a significant role in the development of IBD, in combination with genetic factors and gut microbiota.

Smoking

The effect of smoking on the progress of IBD is known to be multifactorial, affecting UC and CD differently. While cigarette smoking paradoxically has a beneficial effect on UC, it has been associated with an increased frequency of disease, necessity for surgery, and post-operative recurrence in CD [42-44]. However, this is fraught with contradicting evidence since the incidence of CD has been found to be higher in countries with low prevalence of smoking such as Canada [33,45], while its incidence is low in countries with relatively higher smoking prevalence, such as South Korea [46].

Nutrition

IBD patients often have nutrient deficiencies [47]. High dietary intake of fruits and vegetables has been found to be protective against IBD [48]. A case-control study demonstrated that intake of higher amounts of dietary fiber (fruits and vegetables) and long-chain omega-3/omega-6 fatty acids was associated with a lower risk of CD [49]. Moreover, a multicenter case-control study conducted in Asia showed that increased consumption of fats, oils, sugars, fish and shellfish were related to an elevated risk of CD, while higher consumption of sweets was associated with greater UC risk [50]. Similarly, another study revealed that a high intake of monounsaturated and polyunsaturated fat as well as vitamin B6 was associated with the occurrence of UC [51]. Correspondingly, oil, certain margarines, and red meat rich in linoleic acid were found to be associated with an increased risk of developing UC [52]. Literature suggests that the development of IBD may also be influenced by breastfeeding and hygiene levels, as expounded by the hygiene hypothesis [53,54]. In a study involving 374 Saudi children with IBD, history of anorexia was present in 25% of children with UC and 39% with CD. While 35% of CD patients and 24% of UC patients were thin, the prevalence of overweight individuals was 15% and 20%, respectively [40].

Medications

Nonsteroidal anti-inflammatory drugs

A prospective cohort study involving more than 76,000 American women reported that using nonsteroidal anti-inflammatory drugs (NSAIDs) for a minimum of 15 days in a month elevated the absolute risk of both UC and CD [55]. Likewise, Felder., *et al.* (2000) observed a correlation between disease activity and the use of NSAIDs in 31% of IBD patients in their study [56]. Notably, treatment of 4-week-old IL-10 deficient mice with NSAIDs was found to accelerate the development of IBD [57].

Oral contraceptive pills

A meta-analysis of 75,815 patients revealed evidence of a positive association between the use of contraceptive pills and IBD, especially CD [58]. Furthermore, a prospective cohort study in women with history of prolonged use of contraceptive pills reported a threefold increased risk of developing a relapse of CD [59].

Isotretinoin

While the United States Food and Drug Administration (FDA) via the MedWatch system recorded that many patients developed IBD after taking isotretinoin for acne [60] and another study demonstrated that isotretinoin was only related to UC [61], other researchers found no association between IBD and isotretinoin [62]. Therefore, further studies are needed to clarify the association between isotretinoin and IBD.

Antibiotics and gastrointestinal infections

It is known that antibiotics alter the composition of intestinal microflora by disrupting bowel colonization. Antibiotic consumption in childhood is thought to impair the body's natural tolerance to intestinal microflora, which may lead to IBD [63,64]. Furthermore, a positive correlation was found between the usage of antibiotics and the occurrence of IBD [65,66]. Notably, an elevated risk of pediatric-onset CD was related to introducing antibiotics in the first year of life [66]. However, the association between antibiotics and IBD is difficult to prove since patients with undiagnosed IBD may be prescribed antibiotics since the symptoms mimic gastrointestinal infection [65].

With regards to gastrointestinal infection, recent studies draw the attention toward the role of pathogenic organisms in initiation and exacerbation of IBD. *Mycobacterium avium* subspecies *paratuberculosis* (MAP) found to be significantly present in tissue samples of CD

patients [67] as well as been cultured from blood samples of up to 50% of CD patients and 22% of UC patients [68]. Meanwhile, the correlation of *Clostridium difficile* and *Escherichia coli* with IBD is still inconclusive [69].

Etiopathogenesis of IBD

The occurrence of IBD is linked to a complex and dynamic interaction of the host genotype, enteric commensal bacteria/pathogens and the immune system, resulting in autoimmune responses against ecological influences and some microbiomes that reside at the distal ileum [70-72]. There are various hypotheses explaining the etiopathogenesis of IBD. The leading hypothesis is that of genetic predisposition leading to immunological dysregulation of the gastrointestinal system. Essentially, the meticulous mechanism of immune hemostasis include protection against illness and infections as well as maintaining a tolerance response to harmless food materials and microbiota. This immune hemostasis found to be disturbed among patients with IBD [73].

Genetic predisposition

With regards to host genetics, CD has been found to run in families more commonly than UC [74]. Moreover, studies in monozygotic and dizygotic twins show concordance of CD in identical twins [75,76], although other study stated that 40% - 50% of people with identical genetic makeup are not in a concordance with CD [2]. These studies point to the inevitable conclusion that dysbiosis of the gut microbiota and environmental influences play a significant role in the development of IBD [2,77]. Moreover, studies show an association between host genetics and dysbiosis. Mutant genes of the host give rise to an abnormal immune response leading to altered gut microbiota. In 2001, polymorphisms in the *NOD_2/CARD15* gene were observed to contribute to CD in Caucasians [78]. At least 70 susceptibility loci for CD and 40 loci for UC were identified. Furthermore, Frank., *et al.* (2011) found a significant association of IBD with *NOD_2* and *ATG16L1* risk alleles, which are related to alteration of microbiotas [79]. This, in turn, confirms that IBD is linked to significant changes in the composition of these microbial assemblages. The role of microbiota in the phenotypic characteristics of IBD has increasingly drawn the attention of researchers in the recent years.

Alterations in the intestinal microbiome

Intestinal dysbiosis is one of the hypothesis that may explain the pathogenesis of IBD. Recent studies have observed that dysbiosis causes a generalized reduction or alteration in the biodiversity and taxonomic levels of gut microbial phyla including *Firmicutes* and *Bacteroidetes* in individuals with IBD [80,81]. A study conducted on newly diagnosed, treatment-naïve children with CD showed abundance of *Enterobacteriaceae, Fusobacteriaceae, Veillonellaceae,* and *Pasteurellaceae* but low percentage of *Bacteroidales* and *Clostridia* in the gut [81]. Similarly, other studies report colonization of the gut in IBD patients by either the resident or introduced aerobic bacteria, especially the *Enterobacteriaceae* family [82,83].

Regarding the association of fungal microbiota to CD, Li., *et al.* (2014) found an increase in the fungal diversity in colonic and ileal biopsy samples in patients with CD compared to healthy controls [84]. In children with CD, five mycological species were observed to be linked with CD: *Cyberlindnera jadinii*, *Saccharomyces cerevisiae, Kluyveromyces marxianus, Candida albicans,* and *Clavispora lusitaniae.* Abundance of these different fungi highly correlated with each other [85]. Additionally, anti-*Saccharomyces cerevisiae* mannan antibodies (ASCA) are used in the diagnosis of CD and are considered a serological marker for ileal CD [86]. Interestingly, an abundance of *Candida tropicalis* was found to be present in CD patients compared to healthy relatives, which was associated with ASCA titers and abundance of *Serratia marcescens* and *E. coli* [87]. Regarding the enteric virome in IBD, Norman., *et al.* (2015) found that the number of bacteriophages in colonic mucosal biopsy samples from CD individuals was significantly greater than that found in healthy persons [88].

Medical management

The medical management of IBD is aimed at its multifactorial etiology. The classical therapeutic strategy aims to regulate the exacerbated host immune response using antibiotics, corticosteroids, methotrexate, thiopurines, aminosalicylates and anti-tumor necrosis

factor biological agents. However, not only do these drugs have limited efficacy, but different patient responses may lead to unpredictable results. The challenge faced by health care personnel in developing an ideal therapy for IBD lies in the fact that such therapy must only reduce inflammation rather than cause immunosuppression. Newer modes of therapy, such as new target molecules for biological agents and cellular therapy, show promising results [89] and improve the chances of IBD patients to achieve disease mitigation.

As regards transitioning period, emerging illnesses such as IBD, often occur in multiple age groups, leading to a gradual increase in incidence and (subsequently) prevalence rates, especially in the older age groups. This trend continues unless there is an increase in mortality or discovery of a cure. While the prevalence of IBD may increase in adults, it remains constant among children despite upsurges in incidence rates. This phenomenon is due to the transfer of patients from the pediatric to the adolescent age group, with time. Thus, part of the disease burden observed in adults originates from childhood diagnosis of IBD. While it is important to acknowledge that IBD among children is a source of significant disease burden from a public health point of view, it is equally imperative to understand the impact that proper transitioning has on the course of IBD in these patients. Recently, recommendations and guidelines regarding smooth transitioning of care have been drafted [90-92].

A study found that only 26% of medical centers in Saudi Arabia follow an institutionally-developed protocol for transitioning IBD patients to adult care, although 79% of participants considered the transitioning protocol to be "very important". This contradiction demonstrates the need for developing a transition protocol, preferably at the national level rather than physician-level or institution-level. Furthermore, following a standardized protocol for the transition of IBD patients in Saudi Arabia may have a definite effect on patients' behavior toward their disease. However, the impact of such an intervention on long-term outcomes of IBD are yet to be determined [93].

Conclusion

To conclude, the role of microbiota in the phenotypic characteristics of IBD is defined through the host genotype and some factors such as age, diet and antibiotics. These factors could be applied and evaluated clinically to ameliorate the therapeutic strategies of IBD. However, the limited number of studies on Saudi population hinder drawing the actual picture of IBD in Saudi Arabia. Therefore, the need to feed the health scientific literature with updated epidemiological data of the current IBD status in Saudi Arabia is urgently needed. Moreover, exploring the new risk factors that associate with the diseases and investigating the actual mechanism that associate the disease with other factors that related to Saudi population is critical in managing Inflammatory bowel diseases in Saudi Arabia. According to this, the first recommendation would be avoiding the limitations of previous studies such as the small sample size and short time frame of the study. Accordingly, the second recommendation would be developing a transition protocol for the transition of IBD patients in Saudi Arabia is highly recommended at the national level rather than health practitioner-level or institutional-level.

Bibliography

1. Abraham C and Cho JH. "Inflammatory bowel disease". *New England Journal of Medicine* 361.21 (2009): 2066-2078.

2. Loftus EV. "Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence, and environmental influences". *Gastroenterology* 126.6 (2004): 1504-1517.

3. Cosnes J., *et al*. "Epidemiology and Natural History of Inflammatory Bowel Diseases". *Gastroenterology* 140.6 (2011): 1785-1794.

4. Molodecky NA., *et al*. "Increasing Incidence and Prevalence of the Inflammatory Bowel Diseases With Time, Based on Systematic Review". *Gastroenterology* 142.1 (2012): 46-54.

5. Powell JJ., *et al*. "Immune potentiation of ultrafine dietary particles in normal subjects and patients with inflammatory bowel disease". *Journal of Autoimmunity* 14.1 (2000): 99-105.

6. Shivananda S., *et al*. "Incidence of inflammatory bowel disease across Europe: Is there a difference between north and south? Results of the European Collaborative Study on Inflammatory Bowel Disease (EC-IBD)". *Gut* 39.5 (1996): 690-697.

7. Tan CC., *et al*. "Inflammatory bowel disease: An uncommon problem in Singapore". *Journal of Gastroenterology and Hepatology* 7.4 (1992): 360-362.

8. Sung JJ., *et al*. "Crohn's disease in the Chinese population. An experience from Hong Kong". *Diseases of the Colon and Rectum* 37.12 (1994): 1307-1309.

9. Jakobsen C., *et al*. "Incidence of ulcerative colitis and Crohn's disease in Danish children: Still rising or levelling out?" *Journal of Crohn's and Colitis* 2.2 (2008): 152-157.

10. Thia KT., *et al*. "An Update on the Epidemiology of Inflammatory Bowel Disease in Asia". *American Journal of Gastroenterology* 103.12 (2008): 3167-3182.

11. Sood A and Midha V. "Epidemiology of inflammatory bowel disease in Asia". *Indian Journal of Gastroenterology* 26.6 (2007): 285-289.

12. Niriella MA., *et al*. "Prevalence of inflammatory bowel disease in two districts of Sri Lanka: A hospital based survey". *BMC Gastroenterology* 10 (2010): 32.

13. Goh K and Xiao SD. "Inflammatory bowel disease: A survey of the epidemiology in Asia". *Journal of Digestive Diseases* 10.1 (2009): 1-6.

14. Ahuja V and Tandon RK. "Inflammatory bowel disease in the Asia-Pacific area: A comparison with developed countries and regional differences". *Journal of Digestive Diseases* 11.3 (2010): 134-147.

15. Jiang L., *et al*. "Retrospective survey of 452 patients with inflammatory bowel disease in Wuhan city, central China". *Inflammatory Bowel Diseases* 12.3 (2006): 212-217.

16. Mokhtar A and Khan MA. "Crohn's disease in Saudi Arabia". *Saudi Medical Journal* 3 (1982): 270-274.

17. Al-Mofarreh MA., *et al*. "Crohn's disease in Saudi outpatient population: Is it still rare?" *Saudi Journal of Gastroenterology* 15.2 (2009): 111-116.

18. Wilson J., *et al*. "High incidence of inflammatory bowel disease in Australia: A prospective population-based Australian incidence study". *Inflammatory Bowel Diseases* 16.9 (2010): 1550-1556.

19. Khalifa SE., *et al*. "Presentation and management outcome of inflammatory bowel disease in Sudan". *Tropical Gastroenterology* 26.4 (2005): 194-196.

20. Ukwenya AY., *et al*. "Inflammatory bowel disease in Nigerians: Still a rare diagnosis?" *Annals of African Medicine* 10.2 (2011): 175-179.

21. Al-Mofarreh MA and Al-Mofleh IA. "Emerging Inflammatory Bowel Disease in Saudi Outpatients: A Report of 693 Cases". *Saudi Journal of Gastroenterology* 19.1 (2013): 16-22.

22. Mohamed AE., *et al*. "Lower Gastrointestinal Tract Pathology in Saudis: Results of Endoscopic Biopsy Findings in 1,600 Patients". *Annals of Saudi Medicine* 7.4 (1987): 306-311.

23. Hossain J., *et al*. "Crohn's disease in Arabs". *Annals of Saudi Medicine* 11.1 (1991): 40-46.

24. Al-Gindan YM., *et al*. "Crohn's disease in Saudi Arabia: A clinicopathological study of 12 cases". *Saudi Journal of Gastroenterology* 2.3 (1996): 150-155.

25. Al-Ghamdi AS., *et al*. "Epidemiology and outcome of Crohn's disease in a teaching hospital in Riyadh". *World Journal of Gastroenterology* 10.9 (2004): 1341-1344.

26. Al Salamah SM. "Surgery for small bowel Crohn's disease: Experience of a tertiary referral center". *Saudi Journal of Gastroenterology* 11.2 (2005): 85-92.

27. Al-Mofleh IA and Azzam NA. "Crohn's disease Increasing trend in Saudi Arabia". *Saudi Medical Journal* 34.11 (2013): 1105-1113.

28. Kelsen J and Baldassano RN. "Inflammatory Bowel Disease: The Difference Between Children and Adults". *Inflammatory Bowel Diseases* 14.2 (2008): S9-S11.

29. El Mouzan MI., *et al*. "Incidence of pediatric inflammatory bowel disease in Saudi Arabia: A multicenter national study". *Inflammatory Bowel Diseases* 20.6 (2014): 1085-1090.

30. Saadah OI., *et al*. "Characteristics of Pediatric Crohn's Disease in Saudi Children: A Multicenter National Study". *Gastroenterology Research and Practice* (2016): 7403129.

31. Loftus EV., *et al*. "Crohn's disease in Olmsted county, Minnesota, 1940–1993: Incidence, prevalence, and survival". *Gastroenterology* 114.6 (1998): 1161-1168.

32. Loftus E., *et al*. "Ulcerative colitis in Olmsted county, Minnesota, 1940–1993: Incidence, prevalence, and survival". *Gut* 46.3 (2000): 336-343.

33. Bernstein CN., *et al*. "The epidemiology of inflammatory bowel disease in Canada: A population-based study". *American Journal of Gastroenterology* 101.7 (2006): 1559-1568.

34. Hanauer SB. "Inflammatory bowel disease: Epidemiology, pathogenesis, and therapeutic opportunities". *Inflammatory Bowel Diseases* 12.1 (2006): S3-S9.

35. Ogunbi SO., *et al*. "Inflammatory bowel disease in African-American children living in Georgia". *Journal of Pediatrics* 133.1 (1998): 103-107.

36. Mayberry JF., *et al*. "Crohn's disease in Jewish people-an epidemiological study in south-east Wales". *Digestion* 35.4 (1986): 237-240.

37. Fadda MA., *et al*. "Inflammatory bowel disease in Saudi Arabia: A hospital-based clinical study of 312 patient". *Annals of Saudi Medicine* 32.3 (2012): 276-282.

38. Aljebreen AM., *et al*. "Clinical epidemiology and phenotypic characteristics of Crohn's disease in the central region of Saudi Arabia". *Saudi Journal of Gastroenterology* 20.3 (2014): 162-169.

39. Alharbi OR., *et al*. "Clinical epidemiology of ulcerative colitis in Arabs based on the Montréal classification". *World Journal of Gastroenterology* 20.46 (2014): 17525-17531.

40. El Mouzan MI., *et al*. "Nutritional status of children with inflammatory bowel disease in Saudi Arabia". *World Journal of Gastroenterology* 22.5 (2016): 1854-1858.

41. El Mouzan MI., *et al*. "Presenting features of childhood-onset inflammatory bowel disease in the central region of Saudi Arabia". *Saudi Medical Journal* 33.4 (2012): 423-428.

42. Calkins BM. "A meta-analysis of the role of smoking in inflammatory bowel disease". *Digestive Diseases and Sciences* 34.12 (1989): 1841-1854.

43. Rubin DT and Hanauer SB. "Smoking and inflammatory bowel disease". *European Journal of Gastroenterology and Hepatology* 12.8 (2000): 855-862.

44. Cosnes J., *et al*. "Effects of cigarette smoking on the long-term course of Crohn's disease". *Gastroenterology* 110.2 (1996): 424-431.

45. Shields M. "Smoking bans: Influence on smoking prevalence". *Health Reports* 18.3 (2007): 9-24.

46. Ouyang Q., *et al*. "The emergence of inflammatory bowel disease in the Asian Pacific region". *Current Opinion in Gastroenterology* 21.4 (2005): 408-413.

47. Wild GE., *et al*. "Nutritional modulation of the inflammatory response in inflammatory bowel disease - From the molecular to the integrative to the clinical". *World Journal of Gastroenterology* 13.1 (2007): 1-7.

48. Russel MG., *et al*. "Modern life in the epidemiology of inflammatory bowel disease: A case-control study with special emphasis on nutritional factors". *European Journal of Gastroenterology and Hepatology* 10.3 (1998): 243-249.

49. Amre DK., *et al*. "Imbalances in dietary consumption of fatty acids, vegetables, and fruits are associated with risk for Crohn's disease in children". *American Journal of Gastroenterology* 102.9 (2007): 2016-2025.

50. Sakamoto N., *et al*. "Dietary risk factors for inflammatory bowel disease: A multicenter case-control study in Japan". *Inflammatory Bowel Diseases* 11.2 (2005): 154-163.

51. Geerling BJ., *et al*. "Diet as a risk factor for the development of ulcerative colitis". *American Journal of Gastroenterology* 95.4 (2000): 1008-1013.

52. Tjonneland A., *et al*. "Linoleic acid, a dietary n-6 polyunsaturated fatty acid, and the aetiology of ulcerative colitis: A nested case-control study within a European prospective cohort study". *Gut* 58.12 (2009): 1606-1611.

53. Klement E., *et al*. "Breastfeeding and risk of inflammatory bowel disease: A systematic review with meta-analysis". *American Journal of Clinical Nutrition* 80.5 (2004): 1342-1352.

54. Koloski N-A., *et al*. "Hygiene hypothesis in inflammatory bowel disease: A critical review of the literature". *World Journal of Gastroenterology* 14.2 (2008): 165-173.

55. Ananthakrishnan AN., *et al*. "Aspirin, nonsteroidal anti-inflammatory drug use, and risk for Crohn disease and ulcerative colitis: A cohort study". *Annals of Internal Medicine* 156.5 (2012): 350-359.

56. Felder JB., *et al*. "Effects of nonsteroidal antiinflammatory drugs on inflammatory bowel disease: A case-control study". *American Journal of Gastroenterology* 95.8 (2000): 1949-1954.

57. Berg DJ., *et al*. "Rapid development of colitis in NSAID-treated IL-10-deficient mice". *Gastroenterology* 123.5 (2002): 1527-1542.

58. Cornish JA., *et al*. "The risk of oral contraceptives in the etiology of inflammatory bowel disease: A meta-analysis". *American Journal of Gastroenterology* 103.9 (2008): 2394-2400.

59. Timmer A., *et al*. "Oral contraceptive use and smoking are risk factors for relapse in Crohn's disease. The Canadian Mesalamine for Remission of Crohn's Disease Study Group". *Gastroenterology* 114.6 (1998): 1143-1150.

60. Reddy D., *et al*. "Possible association between isotretinoin and inflammatory bowel disease". *American Journal of Gastroenterology* 101.7 (2006): 1569-1573.

61. Crockett SD., *et al*. "Isotretinoin use and the risk of inflammatory bowel disease: A case-control study". *American Journal of Gastroenterology* 105.9 (2010): 1986-1993.

62. Bernstein CN., *et al*. "Isotretinoin is not associated with inflammatory bowel disease: A population-based case-control study". *American Journal of Gastroenterology* 104.11 (2009): 2774-2778.

63. Card T., *et al*. "Antibiotic use and the development of Crohn's disease". *Gut* 53.2 (2004): 246-250.

64. Hildebrand H., *et al*. "Early-life exposures associated with antibiotic use and risk of subsequent Crohn's disease". *Scandinavian Journal of Gastroenterology* 43.8 (2008): 961-966.

65. Hviid A., *et al*. "Antibiotic use and inflammatory bowel diseases in childhood". *Gut* 60.1 (2011): 49-54.

66. Shaw SY., *et al*. "Association between the use of antibiotics in the first year of life and pediatric inflammatory bowel disease". *American Journal of Gastroenterology* 105.12 (2010): 2687-2692.

67. Bull TJ., *et al*. "Detection and verification of Mycobacterium avium subsp. paratuberculosis in fresh ileocolonic mucosal biopsy specimens from individuals with and without Crohn's disease". *Journal of Clinical Microbiology* 41.7 (2003): 2915-2923.

68. Naser SA., *et al*. "Culture of Mycobacterium avium subspecies paratuberculosis from the blood of patients with Crohn's disease". *Lancet* 364.9439 (2004): 1039-1044.

69. Friswell M., *et al*. "The Role of Bacteria in the Pathogenesis of Inflammatory Bowel Disease". *Gut and Liver* 4.3 (2010): 295-306.

70. Podolsky DK. "Inflammatory bowel disease". *New England Journal of Medicine* 347.6 (2002): 417-429.

71. Strober W., *et al*. "The fundamental basis of inflammatory bowel disease". *Journal of Clinical Investigation* 117.3 (2007): 514-521.

72. Xavier RJ and Podolsky DK. "Unravelling the pathogenesis of inflammatory bowel disease". *Nature* 448.7152 (2007): 427-434.

73. Belkaid Y and Hand TW. "Role of the microbiota in immunity and inflammation". *Cell* 157.1 (2014): 121-141.

74. Halme L., *et al*. "Family and twin studies in inflammatory bowel disease". *World Journal of Gastroenterology* 12.23 (2006): 3668-3672.

75. Orholm M., *et al*. "Concordance of inflammatory bowel disease among Danish twins - Results of a nationwide study". *Scandinavian Journal of Gastroenterology* 35.10 (2000): 1075-1081.

76. Halfvarson J., *et al*. "Inflammatory bowel disease in a Swedish twin cohort: A long-term follow-up of concordance and clinical characteristics". *Gastroenterology* 124.7 (2003): 1767-1773.

77. Ananthakrishnan AN. "Epidemiology and risk factors for IBD". *Nature Reviews Gastroenterology and Hepatology* 12.4 (2015): 205-217.

78. Hugot JP., *et al*. "Association of NOD2Leucine-rich repeat variants with susceptibility to Crohn's disease". *Nature* 411.6837 (2001): 599-603.

79. Frank DN., *et al*. "Disease phenotype and genotype are associated with shifts in intestinal-association microbiota in inflammatory bowel diseases". *Inflammatory Bowel Diseases* 17.1 (2011): 179-184.

80. Li J., *et al*. "Functional impacts of the intestinal microbiome in the pathogenesis of inflammatory bowel disease". *Inflammatory Bowel Diseases* 21.1 (2015): 139-153.

81. Gevers D., *et al*. "The treatment-naïve microbiome in new-onset Crohn's disease". *Cell Host and Microbe* 15.3 (2014): 382-392.

82. Lupp C., *et al*. "Host-mediated inflammation disrupts the intestinal microbiota and promotes the overgrowth of Enterobacteriaceae". *Cell Host and Microbe* 2.2 (2007): 119-129.

83. Darfeuille-Michaud A., *et al*. "High prevalence of adherent-invasive Escherichia coli associated with ileal mucosa in Crohn's disease". *Gastroenterology* 127.2 (2004): 412-421.

84. Li Q., *et al*. "Dysbiosis of gut fungal microbiota is associated with mucosal inflammation in Crohn's disease". *Journal of Clinical Gastroenterology* 48.6 (2014): 513-523.

85. Lewis JD., *et al*. "Inflammation, antibiotics, and diet as environmental stressors of gut microbiome in pediatric Crohn's disease". *Cell Host and Microbe* 18.4 (2015): 489-500.

86. Annese V., *et al*. "Anti-Saccharomyces cerevisiae mannan antibodies in inflammatory bowel disease: Comparison of different assays and correlation with clinical features". *Alimentary Pharmacology and Therapeutics* 20.10 (2004): 1143-1152.

87. Hoarau G., *et al*. "Bacteriome and Mycobiome Interactions Underscore Microbial Dysbiosis in Familial Crohn's Disease". *MBio* 207.5 (2016): e01250-16.

88. Norman JM., *et al*. "Disease-specific alterations in the enteric virome in inflammatory bowel disease". *Cell* 160.3 (2015): 447-460.

89. Sales-Campos H., *et al*. "Classical and recent advances in the treatment of inflammatory bowel diseases". *Brazilian Journal of Medical and Biological Research* 48.2 (2015): 96-107.

90. Bollegala N and Nguyen GC. "Transitioning the adolescent with IBD from pediatric to adult care: A review of the literature". *Gastroenterology Research and Practice* (2015): 853530.

91. Baldassano R., *et al*. "Transition of patients with inflammatory bowel disease from paediatric to adult care: Recommendations of the North American Society of Paediatric Gastroenterology, Hepatology and Nutrition". *Journal of Pediatric Gastroenterology and Nutrition* 34.3 (2002): 245-248.

92. Hait E., *et al*. "Educate, communicate, anticipate-Practical recommendations for transitioning adolescents with IBD to adult health care". *Inflammatory Bowel Diseases* 12.1 (2006): 70-73.

93. Al-Jahdali E., *et al*. "A cross-sectional survey of Saudi gastroenterologists: Transition strategies for adolescents with inflammatory bowel disease". *Saudi Journal of Gastroenterology* 23.4 (2017): 233-237.

Volume 15 Issue 3 March 2019