Review Article

Indian J Med Res 153, April 2021, pp 421-430
DOI: 10.4103/ijmr.IJMR_936_18

Quick Response Code:

Inflammatory bowel disease: An Indian perspective

Mayank Jain & Jayanthi Venkataraman

Department of Medical Gastroenterology, Gleneagles Global Health City, Chennai, India

Inflammatory bowel disease (IBD) in recent times is causing a significant healthcare burden as both ulcerative colitis and Crohn's disease (CD) require lifelong therapy and constant monitoring. The current review highlights the concerns in a country like India with special reference to the changing trends of IBD, risk attribution and the financial issues. Indian immigrants behave like residential Indians, whereas their children show IBD prevalence similar to the West, highlighting the role of environmental triggers. However, the environmental and genetic factors in Indians with IBD are not well understood. Men appear to be more frequently affected than women in India. The disease severity is milder in the patients, both males and females, but the risk for colorectal cancer (CRC) is similar to the West. The incidence of paediatric IBD is on the rise. The major burden of IBD in the Indian subcontinent at present is in children, adolescents and teens. Cost towards the management of complications, non-adherence to treatment, differentiating tuberculosis from CD and finally screening for CRC in patients with IBD are the points to ponder in the Indian scenario.

Key words Burden - Crohn's disease - epidemiology - inflammatory bowel disease - prevalence - ulcerative colitis

Inflammatory bowel disease (IBD) encompasses two chronic inflammatory disease entities - ulcerative colitis (UC) and Crohn's disease (CD). The diagnosis is essentially based on classical symptomatology, endoscopy and radiological and histological findings[1,2]. In 10-15 per cent of cases, it is difficult to distinguish between the two and referred to as unclassified IBD and when diagnosis is not possible even in a resected bowel specimen, this is referred to as indeterminate colitis[1,2].

IBD causes significant burden to the healthcare set up of the country as both UC and CD require long-term treatment and constant monitoring. In this review, focus is placed on the changing trends of IBD in the Indian subcontinent, risk attribution and the financial teething issues in the management of this morbid entity.

Changing epidemiological trends of inflammatory bowel disease (IBD)

IBD in migrants

IBD is a major health problem around the world. Earlier, it was reported in high proportions from northern and western Europe, North America and Australia[3,4], however, it now has a considerably wider geographic distribution, with an increasing prevalence even in countries that were initially considered as low-risk areas. In addition, there is an increase in IBD burden amongst children and adults in developing nations[5,6]. Migrant studies in the early 1990s among South Asians residing in Leicestershire, UK, showed that the standardized incidence of UC in South Asian migrants was significantly high (10.8/100,000 vs. 5.3/100,000

among locals), with the highest incidence amongst Sikhs (16.5/100,000) followed by Hindus (10.8/100,000)[7]. The same group also reported that the incidence of CD increased over time in both Europeans as well as South Asians, but was significantly low amongst South Asians[8]. Another single-centre study from England made similar observation of a high frequency of IBD amongst South Asian migrants to the UK[9]. Subsequently, an increased risk of IBD has been reported in the first- and second-generation South Asian migrants in the UK and Canada, suggesting the influence of environmental factors on the development of IBD[10-12]. The migrant study from Canada[13] in 2015 found a significantly lower incidence of 7.3/100,000 amongst migrants compared to the indigenous population (23.9/100,000). However, the incidence of IBD amongst the children of these immigrants approached that of non-immigrants. A systematic review in 2012 confirmed an increased incidence of IBD amongst migrants from Asia to the West[14]. Population-based studies in the Middle East (Kuwait and Saudi Arabia) reported an increase in the prevalence of IBD, especially amongst children[15-17].

IBD in South Asians: Epidemiological studies from China, Hong Kong, Japan, Korea, Malaysia, Singapore, Thailand, India and Sri Lanka have shown UC to be more prevalent than CD[14]. However, a trend towards an increasing incidence of CD was observed[14]. Gender wise, CD is frequent amongst men with no gender difference for UC. Extraintestinal manifestations of IBD are uncommon in Asians[14].

IBD in India: Regional differences in UC and CD have been reported from India. The first prevalence figure of 42.8/100,000 patients for UC from Haryana was reported in 1986 by Khosla *et al*[18]. Subsequently, Sood *et al*[19], in 2003, reported a similar prevalence of 44.3/100,000 while screening 51,910 people from Punjab. Both these population-based studies are, however, from select North Indian population and do not in any way represent the true burden of IBD in the Indian subcontinent. But these figures are only one-third to one-sixth of the population-based studies from Canada, North America or the UK[20-22]. In a national survey from India in 2012[23], UC was equally prevalent in the northern and southern States of the country.

Although, population-based studies for CD are lacking from India, a multicentric hospital-based study[24] from the northern and eastern States of the Indian subcontinent reported a fourfold increase in referrals for CD from the late 1990s onwards and also a higher frequency from the southern States of India[23].

Overall, hospital-based studies in the recent past have reported an increasing number of IBD cases[25]. This may be the result of increasing awareness amongst physicians, improved diagnostic techniques and enhanced access to specialized healthcare systems.

Risk attributions to IBD: Urbanization together with changes in dietary pattern *i.e.,* westernization of Indian diet, an improvement in hygienic and environmental conditions and the underlying genetic predisposition, are likely factors responsible for an increase in IBD burden[26,27].

Genetic predisposition

The results of various genetic studies from India are summarised in the Table. Transethnic studies from India, East Asian and Iranian populations in Asia[40], have shown a significant genetic heterogeneity. The nucleotide oligomerization domain (*NOD2*) variants described in Caucasians are not seen amongst Indians[41], but have been reported amongst Malaysians[42].

Environmental factors in IBD

Smoking is a factor which is consistently associated with IBD in the West, increasing the risk of CD but reducing the risk of UC[43-45]. However, this is contrary to the trend seen among Asians where despite higher smoking prevalence (65%) among men, the incidence of CD is low[46]. Some predisposing factors to IBD include food rich in animal protein[47], fats, sugar, meat[48] and excess tea and coffee[49] particularly in the West, whereas high-fibre fruits and vegetables[50] are thought to decrease the risk to IBD[51]. In a case–control, population-based study (ACCESS), 12 months of breastfeeding had a marked protective effect against IBD[52].

Rural dwelling, higher education, professionals, an annual income of ₹100,000 or more, history of appendectomy and family history of IBD are some observed risk factors for IBD in the Indian setting[50].

Gut microbiome and IBD

The gut microbiome and influence of antibiotics on the gut flora have been extensively deliberated in IBD. Studies from North India have shown microbiome signature in the Indian IBD population to be similar to that in the West[53,54]. Butyrate-producing bacteria such as *Clostridium coccides* and *C. leptum* were found to be significantly decreased in UC[54,55], with an increase in anaerobes and facultative aerobes (Proteobacteria), in severe UC[56]. There is a heightened mucosal adherence of *Escherichia coli* in colonic CD[57]. Organisms

Table. Genetic studies on inflammatory bowel disease (IBD) from India

Authors	Salient findings
Mahurkar *et al*[28]	NOD2 and IL23 R in CD - no association
Pugazhendhi *et al*[29,30]	rs2066842 (Pro268Ser) with UC - weak association
Juyal *et al*[31]	rs2395185 (HLA-DRA), rs3024505 (IL10), rs6426833 (RNF186), rs3763313 (BTNL2), and rs2066843 (NOD2) associated with IBD
Baskaran *et al*[32]	TNFSF15 gene polymorphisms protective in IBD
Baskaran *et al*[33]	Autophagy-related gene, the IRGM gene associated with CD
Meena *et al*[34]	TLR4 D299G polymorphism noted in UC and CD, T399I polymorphisms only in UC
Meena *et al*[35]	R392X and N592S - significant association with UC
Verma *et al*[36]	Polymorphisms of the NOD1 protein in UC patients
Juyal *et al*[37]	MDR1 (ABC B1) gene polymorphisms associated with early disease onset, left-sided disease and steroid response in UC
Ahirwar *et al*[38]	IL4 B2 carrier state was less frequently expressed in left-sided colitis and absent in colonic CD
Juyal *et al*[39]	Detection of three novel HLA-independent loci located in 3.81, BAT2, MSH5, HSPA1L, SLC44A4, CFB and NOTCH4

NOD2, nucleotide oligomerization domain 2; CD, Crohn's disease; UC, ulcerative colitis; IBD, inflammatory bowel disease; TNFSF15, tumour necrosis factor superfamily 15; IL, interleukin

such as cytomegalovirus[58], *C. difficile*[59,60], Giardia, *Strongyloides*, hookworm, herpes simplex, *Entamoeba histolytica*, *Cryptosporidium* and *Salmonella*[58,61] were also found to be associated with an exacerbation of UC. A recent Asian study reported that the use of antibiotics decreased the odds for development of both, UC and CD[49].

Indian data regarding the effect of improving hygiene standards on the prevalence of IBD have been conflicting. A study of 200 CD patients from Vellore, India, showed that regular fish consumption and rearing cattle had a protective association with CD, whereas safe drinking water was associated with greater risk for CD[62]. A study from North India showed that better toilet facilities and use of a separate beds in a household were protective, whereas owning a pet and stressful life events were found to be potential risk factors for UC[63].

Demographic profile and clinical presentation

Age: IBD in the West has a bimodal presentation with peaks at 20-39 and 60-79 yr[64]. The median age at the diagnosis of CD is a decade earlier than that of UC. The age distribution in India is similar to that of other Asian countries[65]. With the mean age at the time of diagnosis of UC and CD being closer to 40 yr[66], with no bimodal distribution[23,24]. In a multicentric study from Kerala, in adults, CD occurred at a younger age compared to UC, whereas this was reversed in children[25].

Gender: Data from the West indicate a female preponderance, more so in CD than UC[22,67], however, most studies from India have shown a male preponderance for both UC and CD[23,24,67]. However, a study from Central India showed no significant gender difference[68]. The higher prevalence in men has been ascribed to a large migration of male folks from villages to cities and more frequent visits to the hospital *vis-a-vis* lower attendance by women due to social inhibitions and genetic susceptibility.

Family history: The Indian IBD experience reportedly includes a positive family history[23,69], which is significantly lower than that reported from the West (10%-25%)[70].

Disease location: The extent of disease in 714 patients from the Indian subcontinent with UC was pancolitis in 306 (42.8%) patients, left-sided colitis in 277 (38.8%) and proctitis in 131 (18.3%) patients[23]. In a study from Central India, left-sided colitis was more common than pancolitis[68] similar to other Asian countries and the West[65].

A multicentric study on 182 patients from three centres and the IBD national survey observed near-similar disease location for CD[23,24]. In CD, the disease location was L1 (terminal ileal) in 32 and 29 per cent, L2 (colon) in 41 and 31 per cent, L3 (ileocolonic) in 23 and 40 per cent and L4 (proximal small intestinal) in 4 and 6 per cent

in these two studies[23,24]. Seventeen per cent of patients in the multicentric study had perianal disease[23]. Other studies from Mumbai (178 patients)[71] and Vellore (200 patients)[62] had similar disease locations. Uniformly, L3 appeared to be the most prevalent in the Indian subcontinent.

Disease behaviour: IBD in India is of milder phenotype compared to the West. One-third of the patients have a chronic active course; one-half, a relapsing remitting course; and four per cent require surgery. In a single-centre study from North India, out of 161 UC cases, 44 and 66 per cent were in complete remission at 1 and 3 yr, respectively. Less than 10 per cent (6.2%) required surgery in the following three years[72].

The large variations may be secondary to a referral bias or genetic variations among the populations. Most patients (76%) had an inflammatory phenotype[23]. A retrospective study from Mumbai noted an aggressive progression of IBD in 20 per cent over a 10 yr follow up[71]; the temporal progression was, however, relatively slow compared to the West.

Extraintestinal manifestations

In a questionnaire based study from India[23], the prevalence of extraintestinal manifestation (EIM) was similar to that reported from the West; 38 per cent had at least one, whereas 20 per cent had multiple EIMs. The most frequent EIM was peripheral arthritis in 33 per cent followed by ankylosing spondylitis in 18 per cent and ocular symptoms in 13 per cent. Mucocutaneous manifestations, aphthous stomatitis and pyoderma gangrenosum constituted nine per cent. These aforesaid figures may not reflect the true prevalence as no specific radiological or biochemical investigations were done to confirm the diagnosis. Female gender, Hinduism, severe disease and use of steroids were significantly associated with EIMs[73]. In a study from North India, the overall prevalence of any EIM and multiple EIMs in UC and CD was 33.2 per cent versus 38.3 per cent and 6.9 per cent versus 4.7 per cent, respectively[74]. In a large cohort from Kerala, EIMs occurred in 28 per cent cases with CD and 18 per cent cases with UC[25]. Primary sclerosing cholangitis was less frequent amongst Indians, and this may be due to the overall low prevalence of autoimmune liver disease in India[75,76].

Colorectal cancer: Earlier hospital-based studies from India found low risk of colorectal cancer (CRC) among Indian patients[77,78], however, studies from Mumbai[79] and New Delhi[80] observed that the risk rates of CRC were similar to that of the West[81]. The incidence density of IBD in Mumbai[79] was 3/1000 in the first 10 yr, 3.3/1000 at 10-20 yr and 7/1000 at >20 yr, with an overall prevalence of 2.8 per cent. Similarly, Bopanna *et al*[80] quoted an annual incidence of 0.3 per cent, with an overall prevalence of 1.9 per cent, and the cumulative probability of developing cancer was reported to be 1.5, 7.2 and 23.6 per cent in the first, second and third decades, respectively.

Treatment options in IBD: In a nationwide IBD survey, approximately two-thirds of all UC patients received steroids, a third were on azathioprine (30%) and less than one per cent received biologicals[23]. The infrequent use of biologicals in Indians may be a reflection of either a less severe disease or economic constraints. The overall colectomy rate in South Asian and Indian patients is relatively low compared to the West[14,72].

5-ASA (64%), steroids (69%) and azathioprine (63%) were the preferred medications and biologics in 2 per cent of all CD patients[23]. Two other studies reported use of biologicals in 37 per cent[24] to 55 per cent[71] respectively.

Impact of tuberculosis in the diagnosis and management of Crohn's disease (CD): Differentiation between CD and intestinal tuberculosis (TB) is important considering the risk of reactivation of latent TB, especially while initiating biologicals in severe IBD.

Despite advances in diagnostic procedures, differentiating CD and intestinal TB remains a major issue in India. Both the diseases often occur in the fourth decade and present with similar clinical features[24,82]. Systemic symptoms such as fever, anorexia and shorter duration of symptoms (less than one year) are frequent presentations of TB[24]. CD patients have longer duration of symptoms. Diarrhoea, bleeding per rectum, anaemia and EIMs are more frequent in CD patients[66,68,83].

Diagnostic tools such as erythrocyte sedimentation rate (ESR)[66] and Anti-Saccharomyces cerevisiae antibodies (ASCA)[66,84] are not always helpful in distinguishing CD from TB. ASCA has a good specificity in distinguishing CD from TB and helps in diagnosing small bowel involvement in CD[55]. The role of quantiferon TB gold remains controversial in the Indian setting[85]. At best, Mantoux and quantiferon TB gold provide supportive evidence but are not definitive for TB. Gene Xpert test is highly specific for TB, but has low sensitivity.

On computed tomography or magnetic resonance enterography, presence of lymph nodes greater than 1 cm

in size with central necrosis favours a diagnosis of TB. On the other hand, the presence of skip lesions (>3), long-segment involvement (>3 cm), comb sign, fibro-fatty proliferation, left colonic involvement and asymmetric thickening favour CD[86]. Studies have highlighted the role of visceral fat quantification as a useful marker in the differential diagnosis of CD and TB[87].

On endoscopy, involvement of the left side of the colon, involvement of multiple segments of the intestine, presence of longitudinal ulcers, isolated ileal involvement, apthous ulcers, perianal disease, long segment strictures and cobblestoning of the mucosa favour a diagnosis of CD[88,89].

Demonstration of acid-fast bacilli on histology or on culture is diagnostic of TB but is rarely documented[85]. Granulomas in TB and CD are distinctive[90,91]. They are often multiple, large, confluent and with caseating necrosis in TB. In CD, these are infrequent, small and poorly organized. TB polymerase chain reaction (PCR)[92] '*in situ* PCR'[93] and faecal sample PCR testing[94] have also been studied, but data on their role in routine screening are inconclusive.

Mycobacterium tuberculosis can be cultured from mucosal biopsies only in a third of the patients with colonic TB[92]. The isolation of *Mycobacteria* from culture can be reduced to 2-3 wk with the BACTEC, *Mycobacteria* growth indicator tube, MB/BacT mycobacterial detection system (Organon Teknika) and the ESP culture system II (ESP II; Trek Diagnostics, Inc., Westlake, USA). These tests have an additional benefit of identifying drug-resistant TB. Ultrastructural and molecular differentiation using claudin 2[95] and mesenchymal cell marker CD73[96] and increased expression of growth-related oncogene alpha mRNA in biopsy specimen and of interleukin (IL) IL-17 in peripheral blood mononuclear cells have been used as markers of intestinal TB[97]. Both TB and CD can coexist in rare situations[98].

Seven susceptibility loci for infection with *Mycobacterium leprae*, including NOD2, IL23R, RIPK2 and TNFSF15, are known to be associated with CD[99].

In 20 per cent of cases, despite all attempts, the diagnosis remains elusive. Under these circumstances, there is a role for an empirical therapeutic trial with ATT[66,100]. Those with intestinal TB are likely to show symptomatic response to antituberculous therapy (ATT) within 2-3 months of initiation of therapy; failure to do so would favour a diagnosis of CD[101].

Surgery in inflammatory bowel disease (IBD)

The surgical rates in India, in different series for UC and CD, range from 4 to 12 per cent and 19 to 100 per cent[102] respectively. Rai *et al*[103] reported that during a three year follow up of 161 patients, surgery was required in 6.2 per cent. Even though a significant number of Indians are anaemic and have low haemoglobin levels, Truelove and Witt's criteria are still viable in ascertaining the severity of colitis[104]. Surgery in CD has been reported to range from 37 to 55 per cent of cases[71].

For CD, the current indications are partial small bowel obstruction (53%), enteroenteric and enterocutaneous fistulae (10.7%), chronic gastrointestinal (GI) blood loss (7%) and protein losing enteropathy (7%). Surgical emergencies include perforation with peritonitis (14%), massive GI bleed (4%) and gastric outlet obstruction[105].

IBD in children: IBD in children and adolescents is a cause of great concern in the Indian population, more so for CD. The disease is more severe and penetrating requiring biologicals. Paediatric patients account for nearly seven per cent of new cases of IBD seen annually[106]. In a retrospective study from Chennai, ten cases of CD aged between five and 15 yr were detected over a period of eight years and 90 per cent were girls. Five had taken ATT in the past. Complications such as perianal fistulae, rectovaginal fistula, ileal and oesophageal stricture were noted separately in four children[107].

In a questionnaire survey across seven centres in India that included 221 children and adolescents with IBD, the mean age of presentation for UC and CD was almost similar with no gender difference. EIMs were noted in 23.6 and 36.1 per cent of UC and CD, respectively[72]. Pancolitis was predominant in UC (70.9%) and 88 per cent of the cases required steroids. Ileocolonic CD was common in three-fourths of the cases and 76.2 per cent required azathioprine for maintenance. In UC, complications such as massive haemorrhage and toxic megacolon were noted in 11.8 per cent of cases. Among the patients with CD, 27 per cent had fistulae, perianal abscess, stricture and perforation. Biologicals were used in only in a minority (0.8% of severe UC and in 12.2% of CD). In UC, 4.3 per cent of cases required surgical intervention. The authors concluded that paediatric IBD in India shares similarities with adult-onset IBD. However, growth failure and severe disease were distinctive for children[108].

Cost and adherence to treatment: Indian experience with IBD: In India, the major economic burden of disease treatment is borne by the patient and family members. Economic constraints affect not only the patient care, but also adherence to treatment. Although diagnostic and treatment expenses make up a significant portion of the cost of IBD management, other factors such as inappropriate treatment, lack of adherence to therapeutic regimens or suboptimal treatment also add to the cost burden. There is indeed a need to evolve beyond symptom control and move towards sustained control of inflammation[109]. Use of pill cards, patient information booklets and active participation by government and other public agencies can improve adherence to treatment.

The way forward: A multidisciplinary model: Integrating various disciplines in the care of IBD patients will improve patient satisfaction and decrease healthcare costs. In essence, this would mean central referral centres which cater to all aspects of patient care[110]. Such centres should include nurse practitioners, physicians, surgeons and psychologists. A model is proposed to achieve these goals (Fig. 1).

To conclude, IBD is being increasingly diagnosed in India (Fig. 2). Population-based studies from different parts of the country are the need of the hour to ascertain the magnitude of the problem of IBD in the Indian subcontinent. In the West, Indian immigrants behave like residential Indians, whereas their children show IBD prevalence similar to the West, highlighting the role of environmental triggers. However, the environmental and genetic factors amongst Indians with IBD are not well understood. IBD occurs at the same age as the West, but there is no bimodal peak. Men appear to be more frequently affected than women and disease severity is milder, but with a risk of CRC similar to the West. Paediatric IBD is increasing and would require special attention. Other issues such as cost of medication, poor adherence to treatment, problems in differentiating TB from CD and timing of screening for CRC in patients with IBD need to be addressed.

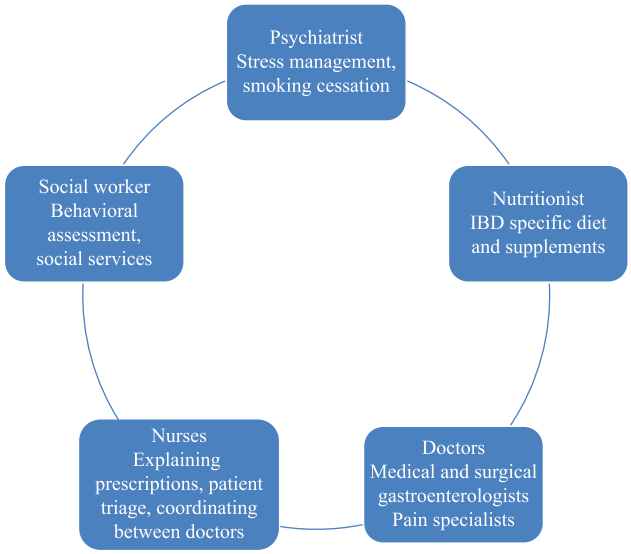

Fig. 1. Suggested multidisciplinary approach to inflammatory bowel disease care in India. *Source*: Ref 110.

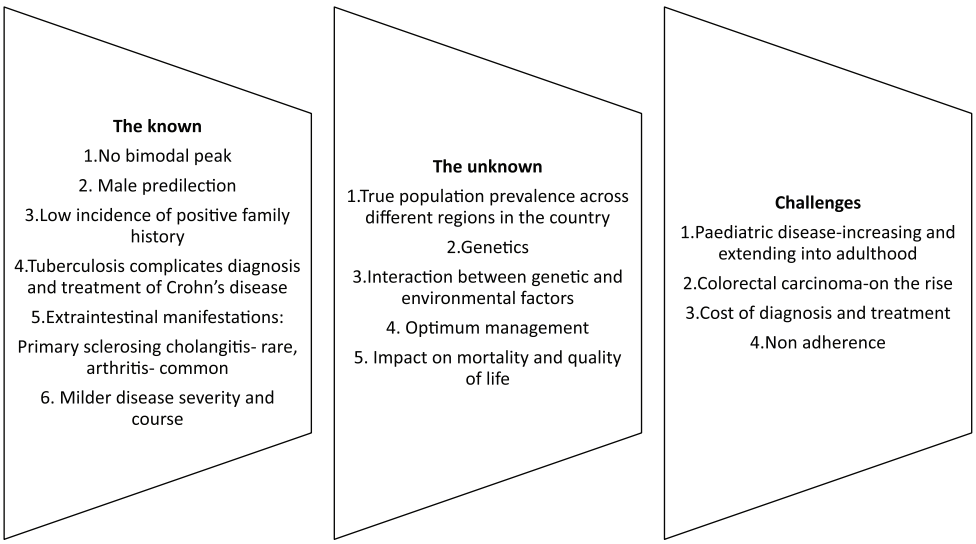

Fig. 2. Inflammatory bowel disease in India: The known, the unknown and the challenges. *Source*: Refs 23, 56-64, 68-74, 104-106

***Conflicts of Interest*:** None.

References

1. Geboes K, Van Eyken P. Inflammatory bowel disease unclassified and indeterminate colitis: The role of the pathologist. *J Clin Pathol* 2009; *62* : 201-5.
2. Guindi M, Riddell RH. Indeterminate colitis. *J Clin Pathol* 2004; *57* : 1233-44.
3. Crohn BB. Regional ileitis a pathologic and clinical entity. *JAMA* 1932; *99* : 1323-9.
4. Kirsner JB. Historical aspects of inflammatory bowel disease. *J Clin Gastroenterol* 1988; *10* : 286-97.
5. Benchimol EI, Fortinsky KJ, Gozdyra P, Van den Heuvel M, Van Limbergen J, Griffiths AM. Epidemiology of pediatric inflammatory bowel disease: A systematic review of international trends. *Inflamm Bowel Dis* 2011; *17* : 423-39.
6. Soon IS, Molodecky NA, Rabi DM, Ghali WA, Barkema HW, Kaplan GG. The relationship between urban environment and the inflammatory bowel diseases: A systematic review and meta-analysis. *BMC Gastroenterol* 2012; *12* : 51.
7. Probert CS, Jayanthi V, Pinder D, Wicks AC, Mayberry JF. Epidemiological study of ulcerative proctocolitis in Indian migrants and the indigenous population of Leicestershire. *Gut* 1992; *33* : 687-93.
8. Jayanthi V, Probert CS, Pinder D, Wicks AC, Mayberry JF. Epidemiology of Crohn's disease in Indian migrants and the indigenous population in Leicestershire. *Q J Med* 1992; *82* : 125-38.
9. Fellows IW, Freeman JG, Holmes GK. Crohn's disease in the city of Derby, 1951-85. *Gut* 1990; *31* : 1262-5.
10. Carr I, Mayberry JF. The effects of migration on ulcerative colitis: A three-year prospective study among Europeans and first- and second- generation South Asians in Leicester (1991-1994). *Am J Gastroenterol* 1999; *94* : 2918-22.
11. Tsironi E, Feakins RM, Probert CSJ, Roberts CSJ, Rampton DS, Phil D. Incidence of inflammatory bowel disease is rising and abdominal tuberculosis is falling in Bangladeshis in East London, United Kingdom. *Am J Gastroenterol* 2004; *99* : 1749-55.
12. Pinsk V, Lemberg DA, Grewal K, Barker CC, Schreiber RA, Jacobson K. Inflammatory bowel disease in the South Asian pediatric population of British Columbia. *Am J Gastroenterol* 2007; *102* : 1077-83.
13. Benchimol EI, Mack DR, Guttmann A, Nguyen GC, To T, Mojaverian N, *et al.* Inflammatory bowel disease in immigrants to Canada and their children: A population-based cohort study. *Am J Gastroenterol* 2015; *110* : 553-63.
14. Prideaux L, Kamm MA, De Cruz PP, Chan FK, Ng SC. Inflammatory bowel disease in Asia: A systematic review. *J Gastroenterol Hepatol* 2012; *27* : 1266-80.
15. El Mouzan MI, Al Mofarreh MA, Assiri AM, Hamid YH, Al Jebreen AM, Azzam NA. Presenting features of childhood-onset inflammatory bowel disease in the central region of Saudi Arabia. *Saudi Med J* 2012; *33* : 423-8.
16. Al-Qabandi WA, Buhamrah EK, Hamadi KA, Al-Osaimi SA, Al-Ruwayeh AA, Madda J. Inflammatory bowel disease in children, an evolving problem in Kuwait. *Saudi J Gastroenterol* 2011; *17* : 323-7.
17. Naidoo CMY, Leach ST, Day AS, Lemberg DA. Inflammatory bowel disease in children of middle Eastern descent. *Int J Pediatr* 2014; *2014* : 906128.
18. Khosla SN, Girdhar NK, Lal S, Mishra DS. Epidemiology of ulcerative colitis in hospital and select general population of Northern India. *J Assoc Physicians India* 1986; *34* : 405-7.
19. Sood A, Midha V, Sood N, Bhatia AS, Avasthi G. Incidence and prevalence of ulcerative colitis in Punjab, North India. *Gut* 2003; *52* : 1587-90.
20. Rubin GP, Hungin AP, Kelly PJ, Ling J. Inflammatory bowel disease: Epidemiology and management in an English general practice population. *Aliment Pharmacol Ther* 2000; *14* : 1553-9.
21. Loftus CG, Loftus EV Jr., Harmsen WS, Zinsmeister AR, Tremaine WJ, Melton LJ 3rd, *et al.* Update on the incidence and prevalence of Crohn's disease and ulcerative colitis in Olmsted county, Minnesota, 1940-2000. *Inflamm Bowel Dis* 2007; *13* : 254-61.
22. Bernstein CN, Wajda A, Svenson LW, MacKenzie A, Koehoorn M, Jackson M, *et al.* The epidemiology of inflammatory bowel disease in Canada: A population-based study. *Am J Gastroenterol* 2006; *101* : 1559-68.
23. Makharia GK, Ramakrishna BS, Abraham P, Choudhuri G, Misra SP, Ahuja V, *et al.* Survey of inflammatory bowel diseases in India. *Indian J Gastroenterol* 2012; *31* : 299-306.
24. Das K, Ghoshal UC, Dhali GK, Benjamin J, Ahuja V, Makharia GK. Crohn's disease in India: A multicenter study from a country where tuberculosis is endemic. *Dig Dis Sci* 2009; *54* : 1099-107.
25. Philip M, Augustine P, Thomas V, Ramesh GN, Vinayakumar KR, Ramachandran TM, *et al.* Multi-center prospective survey of inflammatory bowel diseases in Kerala: More than 2000 cases. *Indian J Gastroenterol* 2017; *36* : 459-67.
26. Desai HG, Gupte PA. Increasing incidence of Crohn's disease in India: Is it related to improved sanitation? *Indian J Gastroenterol* 2005; *24* : 23-4.
27. Pai CG, Khandige GK. Is Crohn's disease rare in India? *Indian J Gastroenterol* 2000; *19* : 17-20.
28. Mahurkar S, Banerjee R, Rani VS, Thakur N, Rao GV, Reddy DN, *et al.* Common variants in NOD2 and IL23R are not associated with inflammatory bowel disease in Indians. *J Gastroenterol Hepatol* 2011; *26* : 694-9.
29. Pugazhendhi S, Amte A, Balamurugan R, Subramanian V, Ramakrishna BS. Common NOD2 mutations are absent in patients with Crohn's disease in India. *Indian J Gastroenterol* 2008; *27* : 201-3.

30. Pugazhendhi S, Santhanam S, Venkataraman J, Creveaux I, Ramakrishna BS. NOD2 gene mutations associate weakly with ulcerative colitis but not with Crohn's disease in Indian patients with inflammatory bowel disease. *Gene* 2013; *512* : 309-13.

31. Juyal G, Prasad P, Senapati S, Midha V, Sood A, Amre D, *et al.* An investigation of genome-wide studies reported susceptibility loci for ulcerative colitis shows limited replication in North Indians. *PLoS One* 2011; *6* : e16565.

32. Baskaran K, Pugazhendhi S, Ramakrishna BS. Protective association of tumor necrosis factor superfamily 15 (TNFSF15) polymorphic haplotype with ulcerative colitis and Crohn's disease in an Indian population. *PLoS One* 2014; *9* : e114665.

33. Baskaran K, Pugazhendhi S, Ramakrishna BS. Association of IRGM gene mutations with inflammatory bowel disease in the Indian population. *PLoS One* 2014; *9* : e106863.

34. Meena NK, Verma R, Verma N, Ahuja V, Paul J. TLR4 D299G polymorphism modulates cytokine expression in ulcerative colitis. *J Clin Gastroenterol* 2013; *47* : 773-80.

35. Meena NK, Ahuja V, Meena K, Paul J. Association of TLR5 gene polymorphisms in ulcerative colitis patients of North India and their role in cytokine homeostasis. *PLoS One* 2015; *10* : e0120697.

36. Verma R, Ahuja V, Paul J. Detection of single-nucleotide polymorphisms in the intron 9 region of the nucleotide oligomerization domain-1 gene in ulcerative colitis patients of North India. *J Gastroenterol Hepatol* 2012; *27* : 96-103.

37. Juyal G, Midha V, Amre D, Sood A, Seidman E, Thelma BK. Associations between common variants in the MDR1 (ABCB1) gene and ulcerative colitis among North Indians. *Pharmacogenet Genomics* 2009; *19* : 77-85.

38. Ahirwar DK, Kesarwani P, Singh R, Ghoshal UC, Mittal RD. Role of tumor necrosis factor-alpha (C-863A) polymorphism in pathogenesis of inflammatory bowel disease in Northern India. *J Gastrointest Cancer* 2012; *43* : 196-204.

39. Juyal G, Negi S, Sood A, Gupta A, Prasad P, Senapati S, *et al.* Genome-wide association scan in North Indians reveals three novel HLA-independent risk loci for ulcerative colitis. *Gut* 2015; *64* : 571-9.

40. Liu JZ, van Sommeren S, Huang H, Ng SC, Alberts R, Takahashi A, *et al.* Association analyses identify 38 susceptibility loci for inflammatory bowel disease and highlight shared genetic risk across populations. *Nat Genet* 2015; *47* : 979-86.

41. Ng SC, Tsoi KK, Kamm MA, Xia B, Wu J, Chan FK, *et al.* Genetics of inflammatory bowel disease in Asia: Systematic review and meta-analysis. *Inflamm Bowel Dis* 2012; *18* : 1164-76.

42. Chua KH, Hilmi I, Ng CC, Eng TL, Palaniappan S, Lee WS, *et al*. JW1 mutation and Han Chinese and Indians (P268S mutation) Identification of NOD2/CARD15 mutations in Malaysian patients with Crohn's disease. *J Dig Dis* 2009; *10* : 124-30.

43. Sutherland LR, Ramcharan S, Bryant H, Fick G. Effect of cigarette smoking on recurrence of Crohn's disease. *Gastroenterology* 1990; *98* : 1123-8.

44. Cosnes J, Beaugerie L, Carbonnel F, Gendre JP. Smoking cessation and the course of Crohn's disease: An intervention study. *Gastroenterology* 2001; *120* : 1093-9.

45. van der Heide F, Dijkstra A, Weersma RK, Albersnagel FA, van der Logt EM, Faber KN, *et al.* Effects of active and passive smoking on disease course of Crohn's disease and ulcerative colitis. *Inflamm Bowel Dis* 2009; *15* : 1199-207.

46. Prideaux L, Kamm MA, De Cruz P, Williams J, Bell SJ, Connell WR, *et al.* Comparison of clinical characteristics and management of inflammatory bowel disease in Hong Kong versus Melbourne. *J Gastroenterol Hepatol* 2012; *27* : 919-27.

47. Jantchou P, Morois S, Clavel-Chapelon F, Boutron-Ruault MC, Carbonnel F. Animal protein intake and risk of inflammatory bowel disease: The E3N prospective study. *Am J Gastroenterol* 2010; *105* : 2195-201.

48. Jowett SL, Seal CJ, Pearce MS, Phillips E, Gregory W, Barton JR, *et al.* Influence of dietary factors on the clinical course of ulcerative colitis: A prospective cohort study. *Gut* 2004; *53* : 1479-84.

49. Ng SC, Tang W, Leong RW, Chen M, Ko Y, Studd C, *et al.* Environmental risk factors in inflammatory bowel disease: A population-based case-control study in Asia-Pacific. *Gut* 2015; *64* : 1063-71.

50. Amarapurkar AD, Amarapurkar DN, Rathi P, Sawant P, Patel N, Kamani P, *et al.* Risk factors for inflammatory bowel disease: A prospective multi-center study. *Indian J Gastroenterol* 2018 ; *37* : 189-95.

51. 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* 2011; *106* : 563-73.

52. Ng SC, Tang W, Ching JY, Wong M, Chow CM, Hui AJ, *et al*. Incidence and phenotype of inflammatory bowel disease based on results from the Asia-pacific Crohn's and colitis epidemiology study. *Gastroenterology* 2013; *145* : 158-65.

53. Verma R, Verma AK, Ahuja V, Paul J. Real-time analysis of mucosal flora in patients with inflammatory bowel disease in India. *J Clin Microbiol* 2010; *48* : 4279-82.

54. Kumari R, Ahuja V, Paul J. Fluctuations in butyrate-producing bacteria in ulcerative colitis patients of North India. *World J Gastroenterol* 2013; *19* : 3404-14.

55. Kabeerdoss J, Sankaran V, Pugazhendhi S, Ramakrishna BS. Clostridium leptum group bacteria abundance and diversity in the fecal microbiota of patients with inflammatory bowel disease: A case-control study in India. *BMC Gastroenterol* 2013; *13* : 20.

56. Walujkar SA, Dhotre DP, Marathe NP, Lawate PS, Bharadwaj RS, Shouche YS. Characterization of bacterial community shift in human ulcerative colitis patients revealed by Illumina based 16S rRNA gene amplicon sequencing. *Gut Pathog* 2014; *6* : 22.

57. Patra S, Samal SC, Kang G, Pulimood A, Mathan M, Ramakrishna BS. Adherent *Escherichia coli* in colorectal

mucosal biopsies: A histological and ultrastructural evaluation. *Indian J Pathol Microbiol* 2012; *55* : 485-9.

58. Iyer VH, Augustine J, Pulimood AB, Ajjampur SS, Ramakrishna BS. Correlation between coinfection with parasites, cytomegalovirus, and *Clostridium difficile* and disease severity in patients with ulcerative colitis. *Indian J Gastroenterol* 2013; *32* : 115-8.
59. Balamurugan R, Balaji V, Ramakrishna BS. Estimation of faecal carriage of *Clostridium difficile* in patients with ulcerative colitis using real time polymerase chain reaction. *Indian J Med Res* 2008; *127* : 472-7.
60. Vaishnavi C, Kochhar R, Bhasin D, Thennarasu K, Singh K. Simultaneous assays for *Clostridium difficile* and faecal lactoferrin in ulcerative colitis. *Trop Gastroenterol* 2003; *24* : 13-6.
61. Banerjee D, Deb R, Dar L, Mirdha BR, Pati SK, Thareja S, *et al.* High frequency of parasitic and viral stool pathogens in patients with active ulcerative colitis: Report from a tropical country. *Scand J Gastroenterol* 2009; *44* : 325-31.
62. Pugazhendhi S, Sahu MK, Subramanian V, Pulimood A, Ramakrishna BS. Environmental factors associated with Crohn's disease in India. *Indian J Gastroenterol* 2011; *30* : 264-9.
63. Sood A, Amre D, Midha V, Sharma S, Sood N, Thara A, *et al.* Low hygiene and exposure to infections may be associated with increased risk for ulcerative colitis in a North Indian population. *Ann Gastroenterol* 2014; *27* : 219-23.
64. Loftus EV Jr., Sandborn WJ. Epidemiology of inflammatory bowel disease. *Gastroenterol Clin North Am* 2002; *31* : 1-20.
65. Wang YF, Zhang H, Ouyang Q. Clinical manifestations of inflammatory bowel disease: East and West differences. *J Dig Dis* 2007; *8* : 121-7.
66. Makharia GK, Sachdev V, Gupta R, Lal S, Pandey RM. Anti-*Saccharomyces* cerevisiae antibody does not differentiate between Crohn's disease and intestinal tuberculosis. *Dig Dis Sci* 2007; *52* : 33-9.
67. Vind I, Riis L, Jess T, Knudsen E, Pedersen N, Elkjaer M, *et al.* Increasing incidences of inflammatory bowel disease and decreasing surgery rates in Copenhagen city and county, 2003-2005: A population-based study from the Danish Crohn colitis database. *Am J Gastroenterol* 2006; *101* : 1274-82.
68. Jain AK, Sircar S, Jain M, Adkar S, Waghmare CS. Inflammatory bowel disease in central India: A single centre experience over five years. *Trop Doct* 2012; *42* : 198-9.
69. Gupta A, Bopanna S, Kedia S, Yadav DP, Goyal S, Jain S, *et al.* Familial aggregation of inflammatory bowel disease in patients with ulcerative colitis. *Intest Res* 2017; *15* : 388-94.
70. Roth MP, Petersen GM, McElree C, Vadheim CM, Panish JF, Rotter JI. Familial empiric risk estimates of inflammatory bowel disease in Ashkenazi Jews. *Gastroenterology* 1989; *96* : 1016-20**.**
71. Kalaria R, Desai D, Abraham P, Joshi A, Gupta T, Shah S. Temporal change in phenotypic behaviour in patients with Crohn's disease: Do Indian patients behave differently from Western and other Asian patients? *J Crohns Colitis* 2016; *10* : 255-61.
72. Kedia S, Ahuja V. Epidemiology of inflammatory bowel disease in India: The great shift East. *Inflamm Intest Dis* 2017; *2* : 102-15.
73. Bandyopadhyay D, Bandyopadhyay S, Ghosh P, De A, Bhattacharya A, Dhali GK, *et al.* Extraintestinal manifestations in inflammatory bowel disease: Prevalence and predictors in Indian patients. *Indian J Gastroenterol* 2015; *34* : 387-94.
74. Singh B, Kedia S, Konijeti G, Mouli VP, Dhingra R, Kurrey L, *et al.* Extraintestinal manifestations of inflammatory bowel disease and intestinal tuberculosis: Frequency and relation with disease phenotype. *Indian J Gastroenterol* 2015; *34* : 43-50.
75. Amarapurkar DN, Patel ND. Spectrum of autoimmune liver diseases in Western India. *J Gastroenterol Hepatol* 2007; *22* : 2112-7.
76. Gupta R, Agarwal SR, Jain M, Malhotra V, Sarin SK. Autoimmune hepatitis in the Indian subcontinent: 7 years experience. *J Gastroenterol Hepatol* 2001; *16* :1144-8.
77. Kochhar R, Goenka MK, Kaushik SP, Gupta NM, Nagi B, Mehta SK. Colorectal carcinoma in Indian patients with idiopathic ulcerative colitis. *Eur J Cancer Prev* 1992; *1* : 293-6.
78. Venkataraman S, Mohan V, Ramakrishna BS, Peter S, Chacko A, Chandy G, *et al.* Risk of colorectal cancer in ulcerative colitis in India. *J Gastroenterol Hepatol* 2005; *20* : 705-9.
79. Desai D, Shah S, Deshmukh A, Abraham P, Joshi A, Gupta T, *et al.* Colorectal cancers in ulcerative colitis from a low-prevalence area for colon cancer. *World J Gastroenterol* 2015; *21* : 3644-9.
80. Bopanna S, Kedia S, Das P, Dattagupta S, Sreenivas V, Mouli VP, *et al.* Long-term follow-up reveals high incidence of colorectal cancer in Indian patients with inflammatory bowel disease. *United European Gastroenterol J* 2017; *5* : 708-14.
81. Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: A meta-analysis. *Gut* 2001; *48* : 526-35.
82. Amarapurkar DN, Patel ND, Rane PS. Diagnosis of Crohn's disease in India where tuberculosis is widely prevalent. *World J Gastroenterol* 2008; *14* : 741-6.
83. Sharma R, Madhusudhan KS, Ahuja V. Intestinal tuberculosis versus Crohn's disease: Clinical and radiological recommendations. *Indian J Radiol Imaging* 2016 ; *26* : 161-72.
84. Ghoshal UC,w Ghoshal U, Singh H, Tiwari S. Anti-*Saccharomyces* cerevisiae antibody is not useful to differentiate between Crohn's disease and intestinal tuberculosis in India. *J Postgrad Med* 2007; *53* : 166-70.
85. Pulimood AB, Amarapurkar DN, Ghoshal U, Phillip M, Pai CG, Reddy DN, *et al.* Differentiation of Crohn's disease

from intestinal tuberculosis in India in 2010. *World J Gastroenterol* 2011; *17* : 433-43.

86. Kedia S, Sharma R, Makharia GK, Ahuja V, Desai D, Kandasamy D, *et al.* Imaging of the small intestine in Crohn's disease: Joint position statement of the Indian society of gastroenterology and Indian radiological and imaging association. *Indian J Gastroenterol* 2017; *36* : 487-508.
87. Yadav DP, Madhusudhan KS, Kedia S, Sharma R, Pratap Mouli V, Bopanna S, *et al.* Development and validation of visceral fat quantification as a surrogate marker for differentiation of Crohn's disease and intestinal tuberculosis. *J Gastroenterol Hepatol* 2017; *32* : 420-6.
88. Moka P, Ahuja V, Makharia GK. Endoscopic features of gastrointestinal tuberculosis and Crohn's disease. *J Dig Endosc* 2017; *8* : 1-11.
89. Prabhu PR, Jain M, Bawane P, Varghese J, Venkataraman J. Role of colonoscopy in differentiating intestinal tuberculosis from Crohn's disease. *J Dig Endosc* 2017; *8* : 72-7.
90. Pulimood AB, Ramakrishna BS, Kurian G, Peter S, Patra S, Mathan VI, *et al.* Endoscopic mucosal biopsies are useful in distinguishing granulomatous colitis due to Crohn's disease from tuberculosis. *Gut* 1999; *45* : 537-41.
91. Pulimood AB, Peter S, Ramakrishna B, Chacko A, Jeyamani R, Jeyaseelan L, *et al.* Segmental colonoscopic biopsies in the differentiation of ileocolic tuberculosis from Crohn's disease. *J Gastroenterol Hepatol* 2005; *20* : 688-96.
92. Amarapurkar DN, Patel ND, Amarapurkar AD, Agal S, Baigal R, Gupte P. Tissue polymerase chain reaction in diagnosis of intestinal tuberculosis and Crohn's disease. *J Assoc Physicians India* 2004; *52* : 863-7.
93. Pulimood AB, Peter S, Rook GW, Donoghue HD. *In situ* PCR for *Mycobacterium tuberculosis* in endoscopic mucosal biopsy specimens of intestinal tuberculosis and Crohn disease. *Am J Clin Pathol* 2008; *129* : 846-51.
94. Balamurugan R, Venkataraman S, John KR, Ramakrishna BS. PCR amplification of the IS6110 insertion element of *Mycobacterium tuberculosis* in fecal samples from patients with intestinal tuberculosis. *J Clin Microbiol* 2006; *44* : 1884-6.
95. Das P, Goswami P, Das TK, Nag T, Sreenivas V, Ahuja V, *et al.* Comparative tight junction protein expressions in colonic Crohn's disease, ulcerative colitis, and tuberculosis: A new perspective. *Virchows Arch* 2012; *460* : 261-70.
96. Banerjee R, Balaji M, Sasikala M, Anuradha S, Rao GV, Nageshwar Reddy D. Granulomas of intestinal tuberculosis and Crohn's disease can be differentiated by CD73 cell surface marker expression: A pilot study. *Dig Dis Sci* 2013; *58* : 2301-7.
97. Pugazhendhi S, Jayakanthan K, Pulimood AB, Ramakrishna BS. Cytokine gene expression in intestinal tuberculosis and Crohn's disease. *Int J Tuberc Lung Dis* 2013; *17* : 662-8.
98. Baijal R, Chogle A, Kumar P, Shah N, Kulkarni S, Doshi S, *et al.* A case of tuberculous colitis with associated Takayasu's Arteritis. *J Assoc Physicians India* 2015; *63* : 62-5.
99. Ek WE, D'Amato M, Halfvarson J. The history of genetics in inflammatory bowel disease. *Ann Gastroenterol* 2014; *27* : 294-303.
100. Sood A, Midha V, Singh A. Differential diagnosis of Crohn's disease versus ileal tuberculosis. *Curr Gastroenterol Rep* 2014; *16* : 418.
101. Pratap Mouli V, Munot K, Ananthakrishnan A, Kedia S, Addagalla S, Garg SK, *et al.* Endoscopic and clinical responses to anti-tubercular therapy can differentiate intestinal tuberculosis from Crohn's disease. *Aliment Pharmacol Ther* 2017; *45* : 27-36.
102. Ray G. Inflammatory bowel disease in India – Changing paradigms. *Int J Colorectal Dis* 2011; *26* : 635-44.
103. Rai T, Choudhury BN, Kedia S, Bopanna S, Venigalla PM, Garg SK, *et al.* Short-term clinical response to corticosteroids can predict long-term natural history of ulcerative colitis: Prospective study experience. *Dig Dis Sci* 2017; *62* : 1025-34.
104. Jain S, Kedia S, Bopanna S, Yadav DP, Goyal S, Sahni P, *et al.* Are Truelove and Witts criteria for diagnosing acute severe colitis relevant for the Indian population? A prospective study. *Intest Res* 2018; *16* : 69-74.
105. Prakash K, Varma D, Mahadevan P, Narayanan RG, Philip M. Surgical treatment for small bowel Crohn's disease: An experience of 28 cases. *Indian J Gastroenterol* 2008; *27* : 12-5.
106. Avinash B, Dutta AK, Chacko A. Pediatric inflammatory bowel disease in South India. *Indian Pediatr* 2009; *46* : 639-40.
107. Sathiyasekaran M, Raju BB, Shivbalan S, Rajarajan K. Pediatric Crohn's disease in South India. *Indian Pediatr* 2005; *42* : 459-63.
108. Sathiyasekaran M, Bavanandam S, Sankaranarayanan S, Mohan N, Geetha M, Wadhwa N, *et al.* A questionnaire survey of pediatric inflammatory bowel disease in India. *Indian J Gastroenterol* 2014; *33* : 543-9.
109. Mehta F. Report: Economic implications of inflammatory bowel disease and its management. *Am J Manag Care* 2016; *22* : s51-60.
110. Lee CK, Melmed GY. Multidisciplinary Team-Based Approaches to IBD Management: How Might "One-Stop Shopping" Work for Complex IBD Care? *Am J Gastroenterol* 2017; *112* : 825-7.

For correspondence: Dr Mayank Jain, Department of Medical Gastroenterology, Gleneagles Global Health City, Chennai 600 100, Tamil Nadu, India
e-mail: mayank4670@rediffmail.com