Original Article

Natural history and outcome of inflammatory bowel diseases in children in Saudi Arabia: A single-center experience

Khalid M. Alreheili, Khalid A. Alsaleem[1], Ali I. Almehaidib[1]

Department of Pediatrics, Division of Gastroenterology, Maternity and Children's Hospital, Madinah, [1]Department of Pediatrics, Division of Gastroenterology, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia

Abstract

Background/Aim: Inflammatory bowel disease (IBD) is a chronic gastrointestinal disorder which includes ulcerative colitis (UC), Crohn's disease (CD), and indeterminate colitis (IC). The natural history of pediatric IBDs is poorly understood and generally unpredictable. We aim to study the natural history of IBD in Saudi children including the extraintestinal manifestations, changes in diagnosis, disease behavior, medical management, and surgical outcome.

Patients and Methods: A retrospective review of all the charts of children less than 14 years of age who were diagnosed as IBD and followed up in King Faisal Specialist Hospital and Research Center (KFSH and RC) from January 2001 to December 2011 was performed.

Results: Sixty-six children were diagnosed with IBD, 36 patients (54.5%) had CD, 27 patients (41%) had UC, and 3 patients (4.5%) had IC. Change in the diagnosis from UC to CD was made in 5 patients (7.6%). Extraintestinal manifestations were documented in 32% of all patients, and the most common was bone involvement (osteopenia/osteoporosis) in 16.7% of the patients. Arthritis (13.6%) was the second most common manifestation. Sclerosing cholangitis was reported in 2.8% in CD compared to 14.8% in UC. At the time of data collection, 8 patients (12%) were off therapy, 38 patients (57.6) were on 5-ASA, 31 patients (47%) were on azathioprine, and 12 patients (18.2%) were receiving anti-TNF. Of the children with CD, 10 patients (27.8%) underwent 1 or more major operations. Of the children with UC, 18.5% underwent 1 or more major intraabdominal procedures.

Conclusions: Many issues in pediatric IBD can predict the natural history of the disease including growth failure, complications, need for more aggressive medical treatment, and/or surgery. More studies are needed from the region focusing on factors that may affect the natural history and disease progression.

Keywords: Crohn's disease, extraintestinal manifestation, indeterminate colitis, inflammatory bowel disease, management, medical, natural history, outcome, Saudi Arabian children, surgical, ulcerative colitis

Address for correspondence: Dr. Khalid M. Alreheili, Department of Pediatrics, Division of Gastroenterology, Maternity and Children's Hospital, Madinah, Saudi Arabia.
E-mail: kalreheili@yahoo.com

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic gastrointestinal disorder that consists of ulcerative colitis (UC), Crohn's disease (CD), and indeterminate colitis (IC) and manifests in up to 25% of patients during childhood.

The natural history of pediatric IBDs is poorly understood and generally unpredictable and affects several aspects of

Access this article online	
Quick Response Code:	Website: www.saudijgastro.com
	DOI: 10.4103/sjg.SJG_490_17

How to cite this article: Alreheili KM, Alsaleem KA, Almehaidib AI. Natural history and outcome of inflammatory bowel diseases in children in Saudi Arabia: A single-center experience. Saudi J Gastroenterol 2018;24:171-6.

a child's health. In general, natural history can be assessed using variables including disease activity, growth failure, complications, treatment options, and outcome. At present, scanty data is available in our region. Moreover, few studies found significant variation in the demographic distribution, familial predisposition, phenotype, and outcomes of IBD between different ethnic groups, with environmental and genetic factors also playing a role. Although the incidence of IBD, especially CD, has increased in many populations, there is a paucity of studies describing different factors and their role in disease outcome. The aim of this study is to address the various factors affecting disease outcome and to compare the data with international data. Although the limitation of our study is that these variables were assessed at a single point during the disease course, it can be a base for future studies in our area with its peculiarity in ethnicity, environmental, and genetic factors in comparison with studies in European and American nations.

PATIENTS AND METHODS

This is a retrospective study in which the charts of all children less than 14 years of age, diagnosed as IBD and followed up in our hospital (King Faisal specialist Hospital and research center, Riyadh, Saudi Arabia) from January 2001 to December 2011 were reviewed. This study included pediatric patients less than 14 years of age at the time of diagnosis who were diagnosed with IBD confirmed by endoscopic, radiologic, and histopathologic evaluation. Variables included patient demographics (age, gender, nationality, and region), clinical presentation, duration of symptoms before diagnosis, growth, family history, diagnostic findings including laboratory, radiological endoscopic, and histopathological findings which were previously published as the first part of our work.[1] In this study, we collected information regarding the extraintestinal manifestations, behavior of IBD, changes in diagnosis, growth failure, complications, and modalities of medical and surgical management, as well as its outcome. The data were analyzed and presented in simple percentage format.

Definition and diagnostic criteria for extraintestinal symptoms

Arthritis was defined as the presence of intraarticular swelling or two or more of the following findings on joint examination: pain on motion, loss of motion, erythema, and heat. Peripheral arthritis (not spine) was mostly lower extremities including hips, knees, ankles, feet, and toes. Osteoporosis is a condition characterized by the progressive loss of bone mass and microarchitectural deterioration, leading to increased bone fragility and susceptibility to fractures. Bone mineral density (BMD) and bone mineral content was determined using dual energy X-ray absorptiometry (DXA). Low BMD is expressed as Z-score less than or equal to −2.0. Primary sclerosing cholangitis was diagnosed according to a consistent laboratory test, liver histology, endoscopic retrograde cholangiopancreatography (ERCP) findings, and magnetic resonance cholangiopancreatography (MRCP) findings. Pyoderma gangrenosum and erythema nodosum were diagnosed using characteristic clinical findings. Uveitis/episcleritis were encountered when reported by an experienced ophthalmologist.

Crohn's disease behavior assessment

We reported disease behavior in CD patient according to The Montreal Classification which defines three behaviors for CD – nonstricturing nonpenetrating disease (B1), stricturing disease (B2), and penetrating disease (B3).[2] We used clinical evaluation and different diagnostic modalities to determine the involvement and assess disease behavior including endoscopic evaluation [Ercp and capsule endoscopy, histological, and radiological tests (gastrointestinal contrast, CT scan, MRI, MRCP)].

Ethical consideration

This study was reviewed and approved by Research Ethics Committee (Research Advisory Council, Office of Research Affairs) at KFSH and RC.

RESULTS

Sixty-six patients were diagnosed with IBD from January 2001 to December 2011; 36 (54.5%) had CD, 27 (41%) had UC, and 3 (4.5%) had IC. We published the initial part of our study on the clinical presentation of IBD as a single center experience in an earlier report.[1] In this second part, we focused on the natural history assessed by growth failure, extraintestinal manifestations, CD behavior, and outcome of medical and surgical management.

Growth failure

Growth failure (defined as height and weight less than the 5th percentile). At the time of diagnosis, growth failure was reported in 17 CD patients (47%) and 5 UC patients (18.5%) while it was found in all IC patients 3 (100%) with total percentage of 37.9% (25 patients) in all IBD.

Extraintestinal manifestation

Extraintestinal manifestations were presented in 32% of all IBD patients (33.3% in both CD and UC, 66.7% in IC). The most common extraintestinal manifestation in CD was peripheral joint inflammation found in 6 (16.7%)

patients followed by osteoporosis and/or osteopenia in 5 (14%) patients whereas sclerosing cholangitis was reported in 1 (2.8%) patient. The most common extraintestinal manifestation in UC was osteoporosis and/or osteopenia in 6 (22.2%) patients followed by primary sclerosing cholangitis in 4 (15%) patients whereas peripheral joint inflammation was found in only 1 (3.7%) patient [Table 1].

Table 1: Extraintestinal manifestation

Manifestation	CD	UC	IC	Total
Sacroiliitis	2 (5.6%)			2 (3%)
Osteoporosis/Oseopenia	5 (13.9%)	6 (22.2%)		11 (16.7%)
Peripheral Joint inflammation	6 (16.7%)	1 (3.7%)	2 (66.7%)	9 (13.6%)
Primary Sclerosing Cholangitis	1 (2.8%)	4 (14.8%)		5 (7.6%)
Erythema Nodosum	2 (5.6%)			2 (3%)
Pyoderma Gangrenosum	1 (2.8%)			1 (1.5%)
Uveitis/Episcleritis	1 (2.8%)			1 (1.5%)
Ankylosing Spondylitis	2 (5.6%)			2 (3%)
Total number with EIM	12 (33.3%)	9 (33.3%)	2 (66.7%)	21 (31.8%)
Total number of patients	36	27	3	66

EIM: Extraintestinal manifestation, CD: Crohn's disease, UC: Ulcerative colitis, IC: Indeterminate colitis

Crohn's disease behavior

We reported disease behavior in CD patients according to The Montreal Classification which defines three behaviors for CD: nonstricturing nonpenetrating disease (B1), stricturing disease (B2), penetrating disease (B3). Nonstricturing nonpenetrating disease (B1) was found in 25 (69.5%) patients, stricturing disease (B2) in 3 (8.3%) patients, whereas penetrating disease (B3) was found in 8 (22.2%) patients.

Change in diagnosis

Change in diagnosis from UC to CD was noted in 5 patients (7.6%). Confirmed diagnosis was made post colectomy and examination of resected tissue or small intestine studies by capsule endoscopy.

Malignancy

No incidence of cancer was reported in our patients either from the disease itself or due to medications till the end of pediatric follow-up age at 14 years.

Outcome of management

Medical management

Among 66 IBD patients, 8 (12%) were off therapy.UC patients were more often off therapy than those with CD (22.2% vs 5.6%). A total of 14 patients out of 66 (21.1%) were steroid dependent. Among those 6 were CD (16.7%), 6 (22.2%) were UC, and 2 (66.7%) were IC. A total of 38 patients received 5-Aminosalicylic acid (5-ASA) (52.8% in CD vs 63% in UC). Administration of immunosuppressants (azathioprine) was reported in a total of 31 (47%) patients, 19 (52.8%) in CD vs 9 (33.3%) in UC. A total of 12 patients (18.2%) received biological agents (infliximab); 10 (27.8%) patients with CD and 2 (7.4%) patients with UC [Table 2].

Table 2: Management protocol at the time of the review

Outcome	CD	UC	IC	Total
Off therapy	2 (5.6%)	6 (22.2%)	N/A	8 (12%)
Steroid dependent	6 (16.7%)	6 (22.2%)	2 (66.7%)	14 (21.1%)
5 ASA	19 (52.8%)	17 (63%)	2 (66.7%)	38 (57.6%)
Azathioprine	19 (52.8%)	9 (33.3%)	3 (100%)	31 (47%)
Anti-TNF	10 (27.8%)	2 (7.4%)	N/A	12 (18.2%)
Surgery	10 (27.8%)	5 (18.5%)	N/A	15 (22.7%)

N/A: Nonapplicable, CD: Crohn's disease, UC: Ulcerative colitis, IC: Indeterminate colitis

Surgical management

A total of 15 (22.7%) IBD patients underwent surgical management. Of the children with CD, 10 (27.8%) underwent 1 or more major operations. Of children with UC, 5 (18.5%) underwent 1 or more major intraabdominal procedures, as shown in Table 2. CD patients underwent various surgical procedures including proctocolectomy with end-ileostomy (4 patients), subtotal colectomy with ileorectal anastomosis (IRA) (2 patients), total colectomy with ileal pouch-anal anastomosis (IPAA) (1 patient), right hemicolectomy (1 patient), and bowel diversion with ilieostomy (1 patient). The duration between the age of diagnosis and the time of surgery ranged from 1 year to12 years. Table 3 lists the characteristics and indication of operated CD patients. UC patients underwent either total colectomy with IPAA or proctocolectomy with end ileostomy. Indication of surgery were failure of medical therapy, complication from disease or medication and poor compliance. The duration between the age at diagnosis and time of surgery ranged from 4 years to 10 years and 8 months [Table 4].

DISCUSSION

The natural history of pediatric IBDs is poorly understood and generally unpredictable and affects several aspects of a child's health. Growth failure in our patients was evaluated using height and weight below the 5th percentile. Growth was more affected in CD patients than UC patients (47% vs 18.5%) in our cohort. Such a finding was reported for CD in different international studies. Growth failure at the time of diagnosis of CD ranged between 10% and 56%.[3-11] In UC, growth failure at diagnosis ranged from 0% to 10%.[5,6,12] Our UC patients had higher growth failure in comparison to the international data while it was less in comparison to recent national data.[13]

At least one extraintestinal manifestation is seen in approximately 25–47% of adult patients with IBD.[14-16] In recent studies, extraintestinal manifestations were reported in 2–29% of pediatric patients.[17] The rate was

Table 3: Characteristics of operated CD patients

Operation	Indication	Sex	Age at Dx (years)	Age at operation (years)	Other surgery (age at operation in years)
Bowel diversion with ileostomy	Severe perianal disease	F	0.75	2	Bowel perforation post colonoscopy (6) Central for TPN (8)
Ileocecal resection	TI stricture	M	13.33	17.6	N/A
Subtotal colectomy with IRA	Failure of Medical Rx Steroid Dependent	F	6.08	18.25	
	Fistulizing Disease			20.33	Repair of gastric fistula (11.4)
	Failure of medical treatment	F	11.4		
Proctocolectomy with end-ileostomy	Failure of medical treatment	F	8.08	23.17	
	Fistulizing disease Defunctioning ileostomy	F	5	13.4	Diversion ileostomy (11.33)
	Extensive perianal disease Failure of medical treatment	M	10	13	
	Extensive perianal disease Failure of medical treatment	F	12.5	15.8	Aspiration of coccygeal abscess (12.5)
Total colectomy with IPAA	Failure of medical treatment	M	10.33	14.25	N/A
Rt Hemicolectomy	Failure of medical treatment	M	13.33	14.33	Appendectomy

Dx: Diagnosis, N/A: Nonapplicable, IPAA: Ileal pouch-anal anastomosis, IRA: Ileorectal anastomosis, TPN: Total parenteral nutrition, TI: Terminal ileum

Table 4: Characteristics of operated UC patients

Sex	Age at Dx	surgery	indication	Age at surgery	Other surgery	Complication
M	7 y 4 m	Total colectomy with IPAA	Failure of medical treatment	12 y 2 m	N/A	Growth failure osteopenia
Fe	3 y 6 m	Total colectomy with IPAA	Sever UC Steroid dependent Poor compliance	14 y 2 m	N/A	Growth failure
Fe	8 y 2 m	Total colectomy with IPAA	Failure of medical treatment Poor compliance Experience of family with another sibling	14 y 3 m	N/A	Growth failure
M	8 y 2 m	Total colectomy with IPAA	N/A	12 y 2 m	Reduction of intussusceptions, resection of distal AC, TC, and colostomy	Intussusceptions
Fe	8 y	Proctocolectomy with end ileostomy	N/A	14 y 4 m	Adhesiolysis (8 m and 3 y postsurgery) Anal dilatation (3 y postsurgery)	Short stature Intestinal obstruction

Dx: Diagnosis, AC: Ascending colon, TC: Transverse colon, N/A: Nonapplicable, IPAA: Ileal pouch-anal anastomosis, UC: Ulcerative colitis

higher when osteopenia and growth delay were included as an extraintestinal manifestation.[18,19] Extraintestinal symptoms were more frequent in CD than in UC. Our data is not different from international data, although we report similar rate of extraintestinal manifestations in both CD and UC (33%) taking into account that osteopenia was considered an extraintestinal manifestation. If this were to be excluded then the rate of extraintestinal manifestations would be 19.4% and 11.1% for CD and UC, respectively, which is comparable to international data.

Change in diagnosis from UC to CD has been reported in many studies.[3] This was attributed to multiple reasons including improvement in the diagnosis of CD over time as a result of new modalities such as capsule endoscopy, progression of disease during follow-up, and confirmation of histopathology of resected bowel. In our study, change in diagnosis from UC to CD was found in 5 patients (7.6%). Although we had small number of IC patients, none of them were reclassified during follow-up. Mamula *et al.* demonstrated that in 15% of patients the IBD diagnosis was changed during the course of the illness.[20] Other studies have also reported reclassification from IC.[21,22]

Steroid dependency in our studies was 21% which is almost similar to those reported in pediatric patients in other studies.[23,24] 5-ASA is the most common drug therapy used in UC patients (63%) and in 52.8% of CD patients. Treatment with immunomodulator agents (azathioprine) was reported in 52.8% of CD patients and 33.3% of UC patients. Vernier-Massouille *et al.* reported similar rate for CD (61%).[24] Hasosah *et al.* described in a recent local study a similar rate for CD (59%) but higher than ours for UC (51%).[25] Use of biological medication was reported in 27.8% and 7.4% for CD and UC patients, respectively, which is almost the same rate as that of a local study (28% and 8%)[25] and other international studies for CD,[26] although its use for UC has been reported to be higher.[26]

There are no clear universal guidelines for medication withdrawal in IBD patients. Therefore, it is essential to identify patient groups where the maintenance therapy

can be discontinued without a high risk of relapse. The discontinuation of therapy should be considered only in patients who have a milder disease course and who are in a complete remission with no alterations in laboratory parameters and with a negative colonoscopy.[27-29] Taking this into consideration, we were able to discontinue medication in 12% of our IBD patients.

Surgery plays an important role in the management of pediatric IBD patients. The most common indication of surgery in the pediatric age group is failure of medical therapy to control the disease activity, Other indications include complication of the disease such as obstruction or fistulas, unacceptable side effects of medication, and growth failure. Cancer is a rare indication in children.[30] The aim of surgery is to control disease progression, manage complication, and improve growth and nutrition. Although some extraintestinal manifestations are improved by surgery, some are not.[31] Colectomy rates in UC at five years from diagnosis range between 14%[32] and 24%[33-35] in children. Surgical resection requirement in CD was 34%–50% at 5 years from diagnosis in pediatric age group.[36,37] IPAA is now the gold standard surgery in UC,[38] while in CD the golden rule is to resect only symptomatic macroscopic disease.[39] Our study is not different from international data where the rate of surgery was 22.7% (27.8% in CD vs 18.5% in UC). The most common indication was failure of medical treatment to control disease activity. IPAA was the most common procedure in UC whereas proctocolectomy with end-ileostomy is the most common in CD.

CONCLUSION

Many issues in pediatric IBD can directly or indirectly affect the natural history of diseases. Although our study is similar to international studies, the timing was specific, at initial presentation or at the time of data collection. Hence, more studies are needed in our area focusing on multiple factors affecting the natural history and disease progression as well as the change in these factors during the disease course.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Alreheili K, Almehaidib A, Banemi M, Aldekhail W, Alsaleem K. Clinical presentation of inflammatory bowel disease in Saudi children (Single centre experience). Int J Pediatr Adolesc Med 2016;3:175-9.
2. Silverberg MS, Satsangi J, Ahmad T, Arnott ID, Bernstein CN, Brant SR, *et al*. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. Can J Gastroenterol 2005;19 (Suppl A):5-36.
3. Abraham BP, Mehta S, El-Serag HB. Natural history of pediatric-onset inflammatory bowel disease: A systematic review. J Clin Gastroenterol 2012;46:581-9.
4. Puntis J, McNeish AS, Allan RN. Long-term prognosis of Crohn's disease with onset in childhood and adolescence. Gut 1984;25:329-36.
5. Langholz E, Munkholm P, Krasilnikoff PA, Binder V. Inflammatory bowel diseases with onset in childhood: clinical features, morbidity, and mortality in a regional cohort. Scand J Gastroenterol 1997;32:139-47.
6. Bland RM, Evans TJ, Raine P, Weaver LT. Inflammatory bowel disease in Scottish children. Health Bull (Edinb) 1999;57:365-73.
7. Homer DR, Grand RJ, Colodny AH. Growth, course, and prognosis after surgery for Crohn's disease in children and adolescents. Pediatrics 1977;59:717-25.
8. Gryboski JD, Spiro HM. Prognosis in children with Crohn's disease. Gastroenterology 1978;74:807-17.
9. Gryboski JD. Crohn's disease in children 10 years old and younger: Comparison with ulcerative colitis. J Pediatr Gastroenterol Nutr 1994;18:174-82.
10. Vasseur F, Gower-Rousseau C, Vernier-Massouille G, Dupas JL, Merle V, Merlin B, *et al*. Nutritional status and growth in pediatric Crohn's disease: A population-based study. Am J Gastroenterol 2010;105:1893-900.
11. Mesker T, van Rheenen PF, Norbruis OF, Uitentuis J, Waalkens HJ, Gonera G, *et al*. Pediatric Crohn's disease activity at diagnosis, its influence on pediatrician's prescribing behavior, and clinical outcome 5 years later. Inflamm Bowel Dis 2009;115:1670-7.
12. Gryboski JD. Ulcerative colitis in children 10 years old or younger. J Pediatr Gastroenterol Nutr 1993;17:24-31.
13. El Mouzan MI, Al Mofarreh MA, Saadah OI, Al-Hussaini AA, Al-Saleem KA, Al Mehaidib AI. Impact of pediatric inflammatory bowel disease on linear growth: Data from a national cohort study in Saudi Arabia. Saudi J Gastroenterol 2016;22:106-8.
14. Greenstein AJ, Janowitz HD, Sachar DB. The extraintestinal complications of Crohn's disease and ulcerative colitis: A study of 700 patients. Medicine 1979;55:410-2.
15. Bernstein CN, Blanchard JF, Rawsthorne P, Yu N. The prevalence of extraintestinal diseases in inflammatory bowel disease: A population-based study. Am J Gastroenterol 2001;96:1116-22.
16. Mendoza JL, Lana R, Taxonera C, Alba C, Izquierdo S, Díaz-Rubio M. Extraintestinal manifestations in inflammatory bowel disease: differences between Crohn's disease and ulcerative colitis. Med Clin (Barc) 2005;125:297-300.
17. Jose FA, Garnett EA, Vittinghoff E, Ferry GD, Winter HS, Baldassano RN, *et al*. Development of Extraintestinal Manifestations in Pediatric Patients with Inflammatory Bowel Disease. Inflamm Bowel Dis 2009;15:63-8.
18. Grossman BJ, DeBenedetti CD. Extraintestinal manifestations of chronic inflammatory bowel disease in children. Proc Inst Med Chic 1970;28:119.
19. Stawarski A, Iwanczak B, Krzesiek E, Iwanczak F. Intestinal complications and extraintestinal manifestations in children with inflammatory bowel disease. Pol Merkur Lekarski 2006;20:22-5.
20. Mamula P, Telega GW, Markowitz JE, Brown KA, Russo PA, Piccoli DA, *et al*. Inflammatory bowel disease in children 5 years of age and younger. Am J Gastroenterol 2002;97:2005-10.
21. Hildebrand H, Finkel Y, Grahnquist L, Lindholm J, Ekbom A, Askling J. Changing pattern of paediatric inflammatory bowel disease in northern Stockholm 1990–2001. Gut 2003;52:1432-4.
22. Carvalho RS, Abadom V, Dilworth HP, Thompson R, Oliva-Hemker M, Cuffari C. Indeterminate colitis: A significant subgroup of pediatric IBD. Inflamm Bowel Dis 2006;12:258-62.

23. Markowitz J, Hyams J, Mack D, Leleiko N, Evans J, Kugathasan S, *et al*. Corticosteroid therapy in the age of infliximab: Acute and 1-year outcomes in newly diagnosed children with Crohn's disease. Clin Gastroenterol Hepatol 2006;4:1124-9.
24. Vernier-Massouille G, Balde M, Salleron J, Turck D, Dupas JL, Mouterde O, *et al*. Natural history of pediatric Crohn's disease: A population-based cohort study. Gastroenterology 2008;135:1106-13.
25. Hasosah M, El Mouzan M, Saadah O, Al-Saleem K, Al-Hussaini A, Al Mehaidib A, *et al*. Treatment Profile of Pediatric Inflammatory Bowel Disease in Saudi Arabia: Issues in Treatment Adherence. Adv Pharmacol Pharm 2015;3:82-6.
26. Adamiak T, Walkiewicz-Jedrzejczak D, Fish D, Brown C, Tung J, Khan K, *et al*. Incidence, clinical characteristics, and natural history of pediatric IBD in Wisconsin: A population-based epidemiological study. Inflamm Bowel Dis 2013;19:1218-23.
27. Annaházi A, Molnár T. Optimal Endpoint of Therapy in IBD: An Update on Factors Determining a Successful Drug Withdrawal. Gastroenterol Res Pract 2015;2015:832395.
28. Ardizzone S, Petrillo M, Imbesi V, Cerutti R, Bollani S, Bianchi Porro G. Is maintenance therapy always necessary for patients with ulcerative colitis in remission? Aliment Pharmacol Ther 1999;13:373-9.
29. Lémann M, Mary JY, Colombel JF, Duclos B, Soule JC, Lerebours E, *et al*. A randomized, double-blind, controlled withdrawal trial in Crohn's disease patients in long-term remission on azathioprine. Gastroenterology 2005;128:1812-18.
30. Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: A meta-analysis. Gut 2001;48:526-35.
31. Goudet P, Dozois RR, Kelly KA, Ilstrup DM, Phillips SF. Characteristics and evolution of extraintestinal manifestations associated with ulcerative colitis after proctocolectomy. Dig Surg 2001;18:51-5.
32. Malaty HM, Abraham BP, Mehta S, Garnett EA, Ferry GD. The natural history of ulcerative colitis in a pediatric population: A follow-up population-based cohort study. Clin Exp Gastroenterol 2013;6:77-83.
33. Hyams JS, Davis P, Grancher K, Lerer T, Justinich CJ, Markowitz J. Clinical outcome of ulcerative colitis in children. J Pediatr 1996;129:81-8.
34. Gower-Rousseau C, Dauchet L, Vernier-Massouille G, Tilloy E, Brazier F, Merle V, *et al*. The natural history of pediatric ulcerative colitis: A population-based cohort study. Am J Gastroenterol 2009;104:2080-8.
35. Baillie CT, Smith JA. Surgical strategies in paediatric inflammatory bowel disease. World J Gastroenterol 2015;21:6101-16.
36. Vernier-Massouille G, Balde M, Salleron J, Turck D, Dupas JL, Mouterde O, *et al*. Natural history of pediatric Crohn's disease: A population-based cohort study. Gastroenterology 2008;135:1106-13.
37. Sedgwick DM, Barton JR, Hamer-Hodges DW, Nixon SJ, Ferguson A. Population-based study of surgery in juvenile onset Crohn's disease. Br J Surg 1991;78:171-5.
38. Parks AG, Nicholls RJ. Proctocolectomy without ileostomy for ulcerative colitis. Br Med J 1978;2:85-8.
39. Alexander-Williams J, Haynes IG. Up-to-date management of small-bowel Crohn's disease. Adv Surg 1987;20:245-64.