

Inflammatory bowel disease in Saudi Arabia: a hospital-based clinical study of 312 patients

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Ann Saudi Med 2012; 32(3): 276-282

DOI: 10.5144/0256-4947.2012.276

BACKGROUND AND OBJECTIVES: The epidemiology, clinical characteristics, and natural course of inflammatory bowel disease (IBD) in Saudi Arabia are still largely unknown. Hence, we decided to conduct a large retrospective, cohort study to determine these features of the disease.

DESIGN AND SETTING: Retrospective study conducted in a tertiary care hospital in Riyadh from January 1970 to December 2008.

PATIENTS AND METHODS: We reviewed all the cases of IBD diagnosed and collected all data pertaining to patients with IBD.

RESULTS: A total of 312 patients with IBD were included for this analysis, including 197 (63%) patients with Crohn disease (CD) and 115 (37%) patients with ulcerative colitis (UC). The mean age (standard deviation) of patients with IBD was 25.5 (10.6) years; 152 (48.7%) were males and 160 females. The referral rate in the past 10 years was 72.1% compared with preceding 20 years, and 56% (n=178) of patients with IBD were from the central region of Saudi Arabia. The patients were followed up for a mean duration of 9.5 years; during their follow-up, 206 patients (66%) required hospital admission and 9 patients (2.9%) with UC developed colon cancer. A total of 6 patients died during the follow-up. Fifty-three percent (n=104) of the patients with CD underwent surgeries as part of their treatment, whereas only 20% (n=23) of the patients with UC underwent colectomy.

CONCLUSIONS: The incidence of IBD has been gradually increasing in Saudi Arabia over the years. Clinical features and morbidity in patients are not different from patients with IBD seen in the West.

Crohn disease (CD) and ulcerative colitis (UC) are chronic inflammatory bowel diseases (IBD), primarily affecting the small and large intestines. Although many current hypotheses implicate a combination of environmental, genetic, and immunoregulatory factors, the exact cause of these two major subtypes remains unclear. These chronic diseases are associated with increased morbidity, frequent relapses and exacerbations, and consequently a decreased quality of life.¹ Temporal changes in the incidence of IBD have been reported in different regions in the world.²⁻⁷ The incidence of IBD has either continued to increase or has stabilized at a high rate in most developed countries, whereas the incidence has continued to increase in regions where the IBD has been considered less common.

The therapeutic strategies are broadly similar in UC

and CD. The treatment choice for UC and CD depends on disease activity and extent of disease. The available medical therapies for IBD are aminosalicylates, corticosteroids, thiopurines, methotrexate, and antitumor necrosis factor.⁸ The removal of the colon and rectum cures UC. Surgery is recommended for medically refractory UC, intractable disease with impaired quality of life, and unacceptable side effects from medical therapy.⁹ Surgery plays an integral role in the treatment of CD. Greater number of patients with CD will eventually require surgery.¹⁰ Indications for surgery in CD include complications such as intra-abdominal abscess, medically intractable fistula, fibrotic stricture with obstructive symptoms, toxic megacolon, hemorrhage, and cancer.¹⁰

Before 1982, IBD was considered rare or absent in

Saudi Arabia and Morocco.¹¹ However, in a study over a period of 6 years from Kuwait, 91 patients with UC and 17 with CD were reported in 1984.¹² Between 1976 and 1994 from King Faisal Specialist Hospital and Research Center (KFSHRC), Riyadh, Saudi Arabia, 101 Arab patients were treated for IBD.¹³ In addition, a prospective hospital-based study from Saudi Arabia reported an estimated incidence of 0.5/10⁵ and prevalence of 5.0/10⁵ for IBD in children between 1993 and 2002.¹⁴ In a prospective study from Oman, 108 patients were diagnosed with UC¹⁵ in the period between 1987 and 1994 with annual incidence of 1.35/10⁵. In 2004, King Khalid University Hospital, Riyadh, Saudi Arabia, published a study describing 77 patients with CD in 20 years. The annual incidence of the disease was 0.32/10⁵ and 1.66/10⁵ over the first 10 years and the last 10 years, respectively, with a total annual incidence of 0.94/10⁵ over the past 20 years.¹⁶

From the data above, it can be noted that studies from our region on IBD epidemiology, pattern, outcome, and therapy are very few, and most of the information we currently have are obtained from the Western studies. Because of the genetic, environmental, and cultural differences, we expect that our patients will be different, and hence the importance of this study. The main objectives of this retrospective study were to review patients with IBD who have been referred to a tertiary referral center, Riyadh, Saudi Arabia, from January 1970 to December 2008 and to study the demographic characteristics, extent and pattern of diseases, and the course of the two diseases in terms of medications and surgery.

PATIENTS AND METHODS

This was a retrospective study of all the cases of IBD diagnosed and followed up in a tertiary care hospital in Riyadh, Saudi Arabia, from January 1970 to December 2008. We reviewed charts and electronic data for age, gender, year of presentation, number of years of follow-up in our hospital, presenting symptoms, and major clinical findings on presentation. Other data were obtained including findings on small bowel follow through, CT scans of the abdomen and pelvis, MRI scans of the abdomen and pelvis, medications, and surgical details. Our institute's ethics committee has approved our research project.

The diagnosis of CD was made based on Copenhagen diagnostic criteria of CD.¹⁷ As per criteria, after ruling out malignancy and infection, at least two of the following criteria had to be present for the diagnosis of CD. The diagnostic criteria included (1) history of abdominal pain, weight loss, and/or diarrhea for >3 months; (2) characteristic endoscopic findings of ulceration (aph-

thous lesions, and snail track ulceration), or cobblestoning, or radiological features of stricture; (3) histopathologic lesions consistent with CD (epithelioid granuloma of the Langerhans type or transmural, discontinuous focal or patchy inflammation);¹⁷ and (4) fistula and/or abscess in addition to affected bowel segments.

The diagnosis of UC was made if the patient had all the three Copenhagen diagnostic criteria for UC:¹⁷ (1) history of diarrhea and/or rectal bleeding and pus for more than 1 week or repeated episodes; (2) characteristic endoscopic findings of continuous ulceration, vulnerability, or granulated mucosa; and (3) histopathologic lesions consistent with UC (neutrophils within epithelial structures, cryptitis, crypt distortion, or crypt abscesses).¹⁸

The CD was anatomically classified into three groups: (1) small bowel CD if the disease was limited to the small bowel without spill over to the cecum, (2) colonic disease if the disease was limited to the colon, and (3) ileocolonic if the disease involved the small and large bowel. The classification of the disease behavior in CD can be inflammatory, stricturing, penetrating, or mixed.¹⁹ Inflammatory disease (nonpenetrating, nonstricturing) was defined as uncomplicated inflammatory condition without any stricturing or penetrating complications. Stricturing disease was defined as the occurrence of constant luminal narrowing demonstrated by radiological, endoscopic, or surgical examination combined with prestenotic dilation and/or obstructive signs or symptoms, but without evidence of penetrating disease. Penetrating disease was defined as the occurrence of bowel perforation, intra-abdominal fistulas, inflammatory masses, and/or abscesses during the course of the disease, but not secondary to postoperative intra-abdominal complication. Based on the predominant clinical, radiological, endoscopic, and surgical features, each individual patient was classified into one of the three patterns.

UC was anatomically classified into five groups depending on anatomic disease extension: (1) proctitis if the inflammation extended up to but not beyond 15 cm above the anorectal junction, (2) proctosigmoiditis if the inflammation involved only the rectum and sigmoid colon, (3) left-sided colitis when inflammation extended up to the splenic flexure, (4) extensive colitis if inflammation extended proximal to the splenic flexure, and (5) pancolitis if inflammation involved up to the hepatic flexure or beyond.

Anemia was diagnosed if hemoglobin in men was <130 g/L and in women <120 g/L and children less than 110 g/L; undernourishment if body mass index (BMI) was less than 18.5 and hypoalbuminemia if serum albumin was less than 31 g/L.

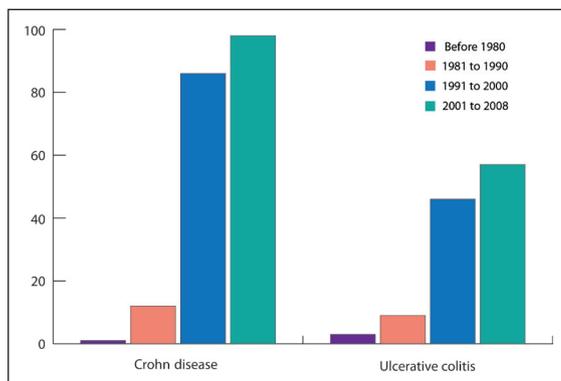


Figure 1. The bar chart shows an increase in number of patients with CD and UC in recent years.

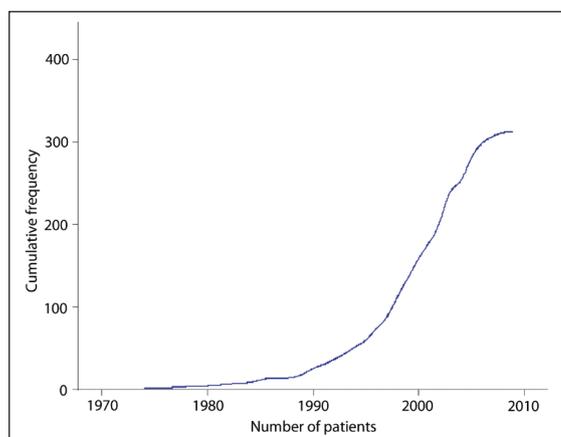


Figure 2. The line graph represents the cumulative frequency of 312 patients with IBD over the years.

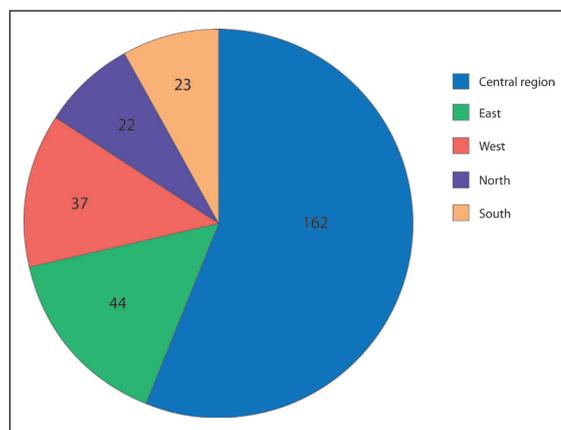


Figure 3. The number of patients from each region of Saudi Arabia (total number of Saudi patients with IBD is 288).

The data were entered to Excel and then transferred to SPSS version 16 for analysis (IBM, Armonk, NY). Frequencies such as mean, medium, and standard deviation (SD) were calculated for numerical variables, and number and percentages were calculated for categorical variables. The cumulative frequency of IBD over these years was calculated. A comparison between CD and UC was made for variables such as clinical features, medical treatment, and surgical rates.

RESULTS

Epidemiology of patients with IBD

Included in the study were 312 patients, 197 (63%) with CD and 115 (37%) with UC, followed for a median of 9.5 years (range 1 month to 35 years). The mean (SD) for the age at presentation was 25.5 (10.6) years; 152 (48.7%) were males and 160 (51.3%) females; and 288 (92.3%) were Saudis. The referral cases with IBD in the past 10 years (1998-2008) were 225 (72.1%), which was significantly higher ($P=.001$) compared with the preceding 20 years. **Figure 1** shows that the majority of cases were referred from 1991 onward. Comparing the number of newly referred cases of CD and UC during the 30-year period was not different ($P=.15$). The cumulative frequency of patients with IBD per year demonstrated a trend of an ongoing increase in the number of newly detected IBD cases (**Figure 2**). Approximately 56% of patients with IBD lived in the central region of Saudi Arabia followed by 14% from the eastern region (**Figure 3**).

Comorbidities and colon cancer in patients with IBD

A positive family history of IBD was found in 11.1%, and a history of smoking was found in 59 (18.8%) patients. Associated comorbidities were detected in 101 (32.4%), and gastrointestinal complications were found in 108 (34.6%) cases. During the follow-up, at least one hospital admission episode was required in 206 (66%) patients. Colon cancer developed in 9 (2.9%), and at least 1 IBD-related surgery was performed in 110 (35.3%). Six patients died, 8 were lost to follow-up, and 298 (95.5%) were still alive.

Age and gender distribution of patients with CD and UC

The mean age of CD patients was 23.8 years; 100 (50.8%) were males and 97 were females. The mean age of UC patients was 28.4 years; 52 (45.2%) were males and 63 (54.8%) were females (**Table 1**). Compared with patients with UC, patients with CD present signifi-

cantly at a younger age ($P=.001$). The difference in the age distribution of patients with CD and UC is given in Figure 4.

Clinical presentation of patients with CD and UC
Comparing the clinical presentation of CD and UC (Table 2), patients with CD had a significantly higher incidence of abdominal pain ($P=.04$), fever ($P=.003$), weight loss ($P=.001$), perianal symptoms ($P=.001$), strictures ($P=.001$), bowel obstruction ($P=.001$), growth retardation ($P=.003$), and mouth ulceration ($P=.02$). On the other hand, patients with UC had significantly higher incidence of bleeding per rectum ($P=.001$). Both groups had similar incidence of diarrhea and extraintestinal symptoms.

Pathology and laboratory findings

Patients with CD had more granuloma on histology ($P=.001$), while dysplasia and colon cancer were higher in patients with UC. Malnutrition (defined as BMI<18.5) was more common in CD than UC ($P=.01$). Anemia was seen more in male patients with CD. Hypoalbuminemia (defined as albumin <31 g/L) was more often seen in patients with CD compared with patients with UC ($P=.001$).

Disease behavior and anatomic extent of disease

The disease behavior of CD patients was equal between the inflammatory type, fistulizing, and stricturing, and many had mixed behavior. Both small and large bowel involvement was seen in 42% of patients with CD and 31% had Crohn colitis. The most common site for fistula formation was the perianal area. The distribution of 64 cases of fistula was as follows: perianal fistula in 48 cases, enterocutaneous fistula in 8, bladder in 5, vagina in 4, and enterocolic in 4. The disease extent in UC was characterized by pancolitis in 43.5%, left-sided colitis in 35.7%, proctosigmoiditis in 13.9%, and proctitis in 6.9% (Table 1).

Medical treatment

The majority of patients with CD (90%) have been treated with 5-amino salicylic acid (5-ASA), 68% with corticosteroid, 55% with azathioprine, 18% with infliximab, and 3% with adalimumab. In comparison, 86% of patients with UC received 5-ASA, 69% corticosteroid, 33% azathioprine, and 4% infliximab. Infliximab and azathioprine (Imuran) were used more often in CD ($P=.001$), while 5 ASA and corticosteroid have been used equally in CD and UC. Figure 5 shows the number and percentage of CD and UC patients treated with different regimens in our center.

Table 1. Details of demographic and clinical characteristics of 197 patients with Crohn disease and 115 patients with ulcerative colitis.

Parameter	Crohn disease (n=197)	Ulcerative colitis (n=115)	P
Gender			
Male (n, %)	100 (50.8)	52 (45.2)	
Female (n, %)	97 (49.2)	63 (54.8)	
Mean age in years (SD)	23.8 (10.2)	28.4(10.8)	.001
Median age in years	23	28	
BMI <18.5	61 (31)	20 (17.4)	.01
Hemoglobin (n, %)			
<130 g/L in male	60 (60)	21 (40)	.03
<120 g/L in female	69 (71)	39 (62)	.2
CRP above 11 mg/L	147 (74.6)	69 (60)	.008
Albumin <31 g/L	55 (28)	14 (12)	.001
Age at presentation (n,%)			
<16 years	43 (21.8)	15 (13.3)	
17 and 40 years	142 (72.1)	84 (73)	
>40 years	12 (6.1)	16 (13.9)	
Disease behavior in Crohn disease (n=197) (n,%)			
Inflammatory	70 (35.5)		
Fistulizing	64 (32.5)		
Stricturing	63 (32)		
Disease location in Crohn disease (n=160) (n,%)			
Small bowel and large intestine	67 (41.9)		
Large intestine alone	49 (30.6)		
Small bowel	44 (27.5)		
Disease location in ulcerative colitis (n=115) (n,%)			
Pancolitis		50 (43.5)	
Left sided		41 (35.7)	
Proctosigmoiditis		16 (13.9)	
Proctitis		8 (6.9)	

Surgery

Fifty-three percent of patients with CD required surgery compared with 20% of patients with UC ($P=.001$). The hospitalization rate was high in CD (76% in CD and 47% in UC; $P=.001$). Surgical procedures performed in patients with CD were as follows: ileocaecal resec-

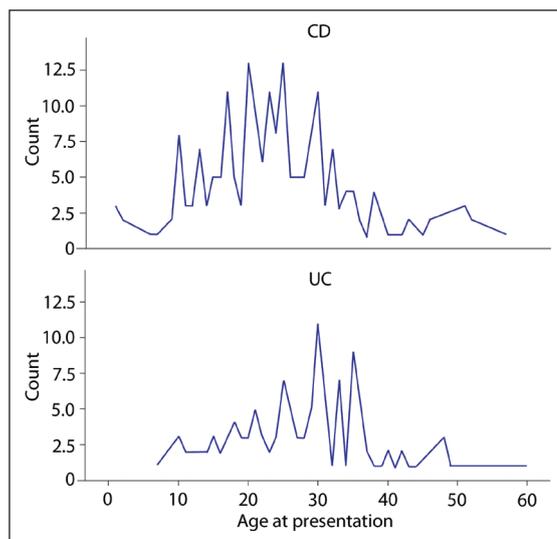


Figure 4. The line graph shows the earlier onset of Crohn disease patients in comparison with ulcerative colitis.

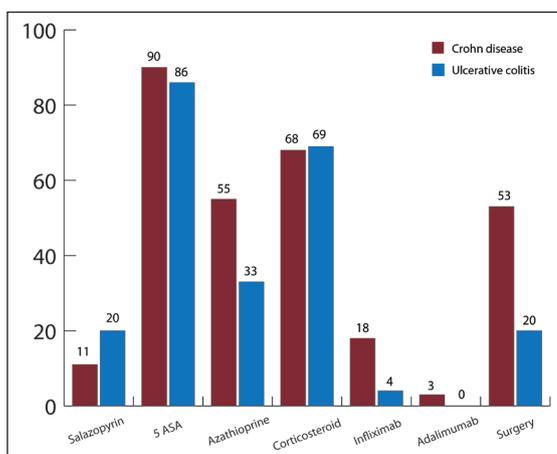


Figure 5. The bar chart demonstrates medical and surgical treatment of patients with IBD.

tion in 25 patients, right hemicolectomy in 19 patients, abscess drainage in 18 patients, small bowel resection in 14 patients, fistula repair in 10 patients, proctocolectomy in 8 patients, partial resection of colon in 8 patients, stoma formation in 5 patients, and the stricturoplasty in 3 patients. Many patients with CD had undergone more than one of the above-mentioned procedures simultaneously or as separate surgeries.

DISCUSSION

The main findings of our single-center retrospective analysis of 312 IBD cases from Saudi Arabia are as follows: (1) more patients are diagnosed with IBD every year, (2) the central region has more cases of IBD, (3)

patients with CD outnumbered patients with UC, (4) CD and UC are equal among both genders, (5) CD patients compared with UC were younger and malnourished, and had more perianal disease, strictures, and complications such as intestinal obstruction and abscess, (6) patients with CD required more surgeries and hospitalizations, (7) involvement of both the small and large bowel was seen in the majority of CD cases, (8) penetrating and stricturing disease were common in CD, and (9) most of our patients with UC had either pancolitis or left-sided colitis.

The reasonable implications of our findings are many. The observation of an increase in the referred cases of IBD in the last 10 years is an important finding; the increase was noted for both CD and UC. We believe that the increased flow of IBD cases to our center reflects a real increase in the incidence of IBD cases at the community level. Two decades ago, IBD was considered rare in the Middle East; but many reports from different centers in Saudi Arabia and from other Gulf region countries along with our study suggest that IBD is becoming a common disease.^{13,14,16,20-27}

Our data show that 56% of the patients were referred from the central region of Saudi Arabia. Several studies have described the relationship between the increased incidences of IBD in recent years and the socioeconomic status of a country. Changes in dietary habits, industrialization, improvement in hygiene, etc., have been linked to the pathogenesis of IBD.²⁸ IBD patients tend to cluster among urban, well-educated, affluent communities.²⁹ We feel several of the above factors may play a role in the increase in incidence of IBD in Saudi Arabia and particularly in the more urbanized central region.

In this study, the median age at presentation of CD was 23 years; our patients were younger than patients from the West. In contrast, the population-based studies from Western countries have shown the median age of diagnosis of CD to be approximately 30 years.^{30,31} The presenting symptoms of our CD patients were dominated by abdominal pain, weight loss, and diarrhea. The phenotypic nature of our CD patients was characterized by involvement of the small and large bowel in 42%, the large intestine alone in 31%, and the small bowel alone in 27%. This distribution is like that reported from the West.³² In a previous study from Saudi Arabia by Al-Ghamdi et al, the incidence of colonic CD was low (6%), but in that study the total number of patients was 77 with CD, low compared with our study.¹⁶ Another notable finding of our study was the higher incidence of penetrating and stricturing disease in more than 50% of our patients. Similar findings were observed in studies from different parts of the world in-

cluding Belgium and India.^{32,33} With regard to the location of the fistula in patients with CD, the most affected area was the perianal region.

Most of our patients with CD received 5-ASA preparations; 68% patients received steroids at some point of their course of disease and 55% received azathioprine. By the end of 2008, the antitumor necrosis factor infliximab and adalimumab were used in 18% and in 4% of our patients with CD, respectively. The efficacy of 5-ASA in inducing remission and maintenance of disease activity has been questioned in the management of CD.⁸ Steroids are effective for short control of symptoms of CD, but they are not effective as a maintenance therapy for CD.³⁴ Azathioprine has been found effective in inducing remission, maintaining remission, fistula healing, and preventing postsurgical relapse of CD. Similarly, antitumor necrosis factors infliximab and adalimumab have been found effective for inducing remission, maintenance therapy, fistula healing, and preventing postoperative recurrence of CD.⁸ Fifty-three percent of our patients with CD underwent surgery, which is comparable to reports from other parts of the world, including one study from Iran.³⁵ However, the previous study from Saudi Arabia by Al-Ghamdi et al showed a lower rate of surgery.¹⁶

In this study, the median age of UC patients was 28 years, which is similar to that in other studies. The peak incidence of UC occurs in the second and third decades of life, but some studies have reported a second peak between 60 and 70 years.¹ In our study, we did not observe a second peak in the elderly. In agreement with the observations from other centers, the male-to-female ratio in UC was 1:1. The patients with UC were equally distributed between both sexes in our study. Diarrhea and bleeding per rectum were a common presentation in UC. At the time of presentation, pancolitis was seen in 43.5%, left-sided colitis in 35.7%, proctosigmoiditis in 13.9%, and proctitis in 6.9%. This observation is different from reports from other studies. From the West it has been reported that approximately 45% of patients with UC have rectosigmoiditis, 35% extends beyond the sigmoid colon, and 20% of patients have pancolitis.³⁶ The higher rate of pancolitis in our series might be because of referral and acceptance bias as our center accepts mostly refractory and difficult patients for treatment.

Most of our patients with UC were treated with 5-ASA preparations; two-thirds of patients received steroids and one-third patients received azathioprine. The accepted therapeutic agents for inducing remission of mild-to-moderate UC are 5-ASA preparations (both oral and topical preparations), steroids, and aza-

Table 2. Comparison of clinical presentation of 197 Crohn disease and 115 ulcerative colitis patients.

Clinical feature	Crohn disease (n=197) (%)	Ulcerative colitis (n=115) (%)	P
Abdominal pain	180 (92)	96 (84)	.04
Diarrhea	166 (85)	105 (91)	.2
Weight loss	50 (77)	44 (38)	.001
Bleeding per rectum	84 (43)	107 (93)	.001
Fistula	76 (39.2)	0	.001
Fever	63 (32)	19 (16.5)	.003
Abscess	48 (25)	3 (6)	.001
Anorexia	45 (23)	10 (8.7)	.001
Perianal symptoms	42 (21.4)	5 (4.3)	.001
Abdominal mass	34(17.5)	0	.001
Mouth ulcer	30 (15.3)	7(6.1)	.02
Intestinal obstruction	19(9.7)	0	.001
Perforation	10 (5.1)	1(0.9)	.06
Extraintestinal manifestations			
Joint pain	45 (23)	24 (21)	.78
Back pain	15 (7.7)	11 (9.6)	.67
Skin	7 (3.6)	2 (1.8)	.5
Eye	4 (2)	2 (1.7)	.1

thioprine. For severe UC, intravenous (IV) steroids, or IV cyclosporine, or infliximab are recommended for inducing remission. For maintenance of remission, 5-ASA oral and or topical, azathioprine, and infliximab have been recommended.⁸ In this study, 20% of patients with UC underwent colectomy during the mean follow-up of 9.5 years. The rate of colectomy is similar to that reported in studies from Europe. In a retrospective population-based series of 1586 patients with UC, in Stockholm County during 1955-1984, during a median period of observation of 13 years, 514 (32.4%) patients were treated by colectomy.³⁷

The limitations of our article are many, including that this analysis is a retrospective study representing experience from a single center. We tried to analyze many aspects of CD and UC at the cost of losing many minor details. On the other hand, the main strength of our study is that we analyzed a large number of patients with IBD which is the largest series from Saudi Arabia so far with a long follow-up. This study is an overview

of different aspects of IBD from Saudi Arabia; further studies are needed to address various other aspects of IBD in this region. In conclusion, from the discussion above we can conclude that IBD is a common medical

problem in Saudi Arabia; patients with IBD are increasing, our cases are not different from patients from the rest of the world in terms of clinical presentation, management, morbidities, and mortalities.

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