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Inflammatory Bowel Disease in Children 5 Years of Age and Younger

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OBJECTIVES: Clinicians are becoming increasingly aware that inflammatory bowel disease (IBD) can affect all age groups, although it has not been well described in infants and young children. Our aim was to evaluate early onset IBD in patients 5 yr of age and younger.

METHODS: Medical records of patients diagnosed with early onset IBD at The Children's Hospital of Philadelphia between 1977 and 2000 were reviewed. Patients were divided into three categories: those with Crohn's disease (CD), those with ulcerative colitis (UC), and those with indeterminant colitis (IC).

RESULTS: A total of 82 patients fulfilled the criteria. In 12 patients (15%), the IBD diagnosis was changed during the course of illness. At the end of the follow-up period, linear growth failure was present in 10 of 35 (29%) children with CD, one of 30 (3%) with UC, and three of 17 (18%) with IC. Failure to thrive was a frequent presenting symptom in children with CD (44%) and IC (39%), whereas in all four patients with UC and failure to thrive the diagnosis was subsequently changed to CD or IC. A high proportion of patients with CD had large bowel (89%), and perianal (34%) disease. None of the tested patients were positive for anti–*Saccharomyces cerevisiae* antibody (ASCA), and 10 tested positive for perinuclear antineutrophil cytoplasmic antibody (three of five patients with CD, five of seven with UC, and two of three with IC).

CONCLUSIONS: Failure to thrive, at the time of presentation, is indicative of a final diagnosis of CD or IC, not UC. Linear growth failure is a common finding in patients with early onset CD. A high proportion of patients with CD have failure to thrive, colonic, and perianal disease. The IBD serology panel is of limited clinical relevance in providing definitive diagnostic information in this pediatric population. (Am J Gastroenterol 2002;97:2005–2010. © 2002 by Am. Coll. of Gastroenterology)

INTRODUCTION

Ulcerative colitis (UC) and Crohn's disease (CD) are chronic inflammatory bowel diseases of unclear etiology. The prevailing hypothesis regarding the pathogenesis of inflammatory bowel disease (IBD) combines both environmental factors and an altered immune response in genetically predisposed patients, which then leads to chronic inflammation of the intestinal tract (1). Recently, a mutation in the gene known as Nod2, which resides on chromosome 16 and encodes the protein recognizing lipopolysaccharides (LPS) of the bacterial outer cell wall membrane, has been identified twice as frequently in patients with CD as in the general population (2, 3). In patients with CD, the inability to recognize LPS may lead to an exaggerated inflammatory response without the innate immune system modulation. Living in a more sterile environment has been shown to delay exposure to enteric infections in early life, possibly resulting in failure of the normal maturation process necessary to develop normal intestinal tolerance (4–6).

During the last several decades, the incidence of IBD in adults is increasing (7). Pediatric epidemiological studies indicate the same patterns of increased incidence for both types of IBD (8–11). The reasons for this increase are unclear, and the contributing factors may occur early in life. Very young patients with IBD require special attention because of the potentially large impact of the disease on their growth and development.

The aim of the present study was to describe the presenting signs and symptoms along with the disease progression in children 5 yr of age and younger with early onset inflammatory bowel disease (EO-IBD). This information may help to improve care for children who present with IBD at this early age.

MATERIALS AND METHODS

A retrospective analysis of the database with all IBD patients followed at the Children's Hospital of Philadelphia between 1977 and 2000 was performed. A total of 94 patients diagnosed with EO-IBD were identified. Twelve patients were excluded from the study: three did not meet the histological criteria for IBD after review by one pathologist (P.R.), and medical records were incomplete for six patients and were not available for three. Among the six patients with incomplete records whose diagnoses could not be confirmed, four carried the diagnosis of UC and two of

CD. In all, 82 patients were included in the study. The diagnoses were confirmed by standard endoscopic, histological, and radiographic criteria (12). The patients were divided into three categories: those with CD, those with UC, and those with indeterminant colitis (IC). The diagnosis of IC was assigned to patients with chronic inflammation limited to the large intestine for whom (on the basis of clinical, laboratory, radiological, endoscopic, or histological criteria) it was not possible to distinguish between CD and UC. All patients had colonoscopy or flexible sigmoidoscopy performed at the time of diagnosis, and all but one patient had a radiographic study during the course of the disease (upper GI series with a small bowel follow-through, or barium enema). The remaining patient had the diagnosis made at the time of surgery. The medical records and x-ray reports were reviewed by the two investigators (P.M. and G.T.) and by the patients' primary gastroenterologists. The diagnosis of the small intestinal CD was made based on the radiographic study.

The following characteristics were investigated: age, sex, diagnoses and change in diagnoses over time, length of follow-up, presenting symptoms, diagnostic time lag, medications, surgical procedures, anatomic location of the disease, growth data, family history, and results of anti–*Saccharomyces cerevisiae* antibody (ASCA) and perinuclear antineutrophil cytoplasmic antibody (p-ANCA) testing. The family history was defined as a history of IBD in parents, grandparents, aunts or uncles, and first cousins. Linear growth failure was defined as height below the fifth percentile on a height for age growth curve developed by the National Center for Health Statistics in 1979, and failure to thrive (FTT) as weight below the fifth percentile on a weight for age growth curve. Measurements of linear growth were obtained at the end of the follow-up period. Weight measurements for definition of failure to thrive were recorded at the time of diagnosis. Perianal disease was defined as perianal fistula or perianal abscess.

The association between presenting symptoms and initial diagnoses were evaluated using univariate analysis with the χ^2 test. Statistical analysis was performed using Stata version 6.0 software (Stata, College Station, TX). This study was approved by the Institutional Review Board of the Children's Hospital of Philadelphia.

RESULTS

A total of 82 patients (47 male and 35 female; sex ratio, 1.34) were diagnosed with EO-IBD. The median follow-up was 7.5 yr (range, 6 months to 23 yr). Initially, 36 children (44%) were diagnosed with UC, 27 (33%) with CD, and 19 (23%) with IC.

Figure 1 shows the changes in diagnoses. The majority of patients (nine of 12) in whom the diagnosis was changed had the initial diagnosis made before 1991. The age distribution and final diagnoses are shown in Figure 2. Only one

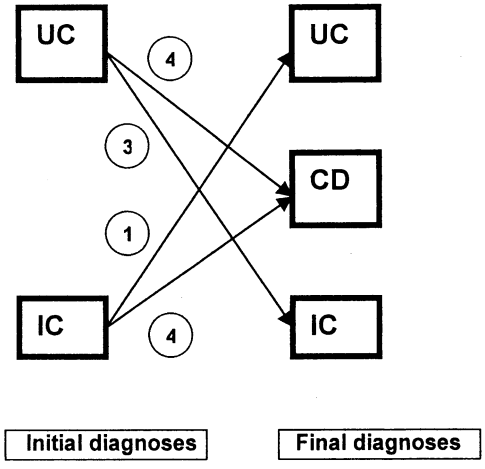

Figure 1. Changes in diagnoses among study patients over time.

of 19 patients (6%) diagnosed with EO-IBD below the age of 2 yr was diagnosed with UC.

In all, 23% of patients with CD and UC and 18% of patients with IC had a family history of IBD. When 13 patients whose family history was not available were excluded, 28% of patients with CD and UC and 20% of patients with IC had a family history of IBD. The age of onset of disease in relatives was not available.

Linear growth failure was present in 10 of 35 children (29%) with CD, one of 30 (3%) with UC, and three of 17 (18%) with IC at the end of the follow-up period.

At the time of initial diagnosis, 26% of patients with CD had inflammation in the stomach, 22% in the duodenum, 19% in the small bowel, 52% in the terminal ileum, and 89% in the large bowel. In all, 34% had perianal disease. Of the CD patients, 60% had nonstricturing nonpenetrating (inflammatory) type of the disease, 34% penetrating (fistulizing), and 6% stricturing type. Of the patients with UC, 60% had isolated left-sided colitis, and 40% had pancolitis.

Presenting symptoms are shown in Table 1. Blood in the stool (hematochezia) was more commonly associated with UC than with IC and CD combined ($p = 0.0002$). Failure to thrive at the time of initial presentation was more common in patients with CD or IC than in those with UC ($p = 0.004$). All four patients initially diagnosed with UC who had FTT as a presenting symptom had their diagnosis changed to IC or CD ($p < 0.0001$). Chronic fever was associated with CD and not with UC or IC ($p = 0.015$). Vomiting was associated with CD or IC but not UC ($p = 0.01$). The median diagnostic lag (*i.e.*, median time between onset of symptoms and time of diagnosis) was 4.5 months for patients with CD, 2 months for UC, and 6.5 months for IC.

Serological testing for pANCA and ASCA was performed in 15 children before the age of 6 yr. All samples were tested by the Prometheus Laboratories (San Diego, CA). None of the patients had positive ASCA test results, but 10 patients had positive results for pANCA. Three of five patients (60%) with CD, five of seven (71%) with UC,

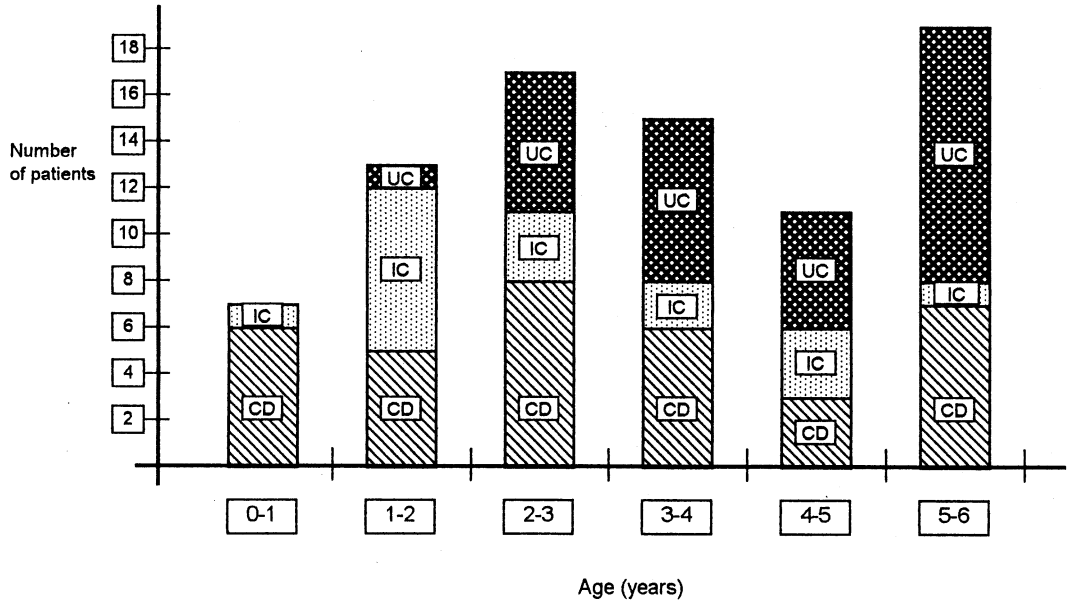

Figure 2. Age at time of diagnosis and final diagnosis.

and two of three (66%) with IC had positive pANCA results. The presence of pANCA antibodies was not significantly more prevalent in UC than in CD or IC.

Corticosteroids were used before the age of 6 yr in 67% of patients with CD, 67% of patients with UC, and 52.6% of patients with IC. 6-Mercaptopurine was used before the age of 6 yr in 22%, 11%, and 26% of patients with CD, UC, and IC, respectively.

During the course of their disease, 10 patients (12%) required surgical intervention: five patients (14%) with CD, four (13%) with UC, and one (6%) with IC. The patient with IC underwent colectomy because of toxic megacolon. Three patients with CD had resection of a stricture, one had a diverting colostomy secondary to severe perianal disease and stricture, and one had perforation requiring partial colectomy and recto-vaginal fistula repair. Four patients with UC had a colectomy performed: one for fulminant colitis unresponsive to *i.v.* corticosteroids and cyclosporin, and three for severe disease with failure of chronic immunomodulatory therapy.

DISCUSSION

Reports of young children with IBD have been published for several decades (13–17). Most case series have involved children of different ages, and only a few have concentrated exclusively on young children (18, 19). Recently, evidence for increased incidence of IBD not only in adults but also in children and adolescents has caused renewed interest in the younger age group (19). So far, this is the largest study of children aged 5 yr and younger who have been diagnosed with EO-IBD.

The genetic factors in the etiology of IBD are well recognized, with a high rate of concordance between monozygotic twins (44.4%) compared with dizygotic twins (3.8%) among patients with CD (20). A recent report described multiple siblings affected with CD (21). In our series, 28% of patients with CD had a family history of IBD. This correlates with the data from a combined adult and pediatric study, in which 29.9% of patients diagnosed with CD before age 20 yr had a positive family history compared with only 13.6% of patients whose diagnoses were made at a later age

Table 1. Presenting Symptoms of Study Patients

Symptom	CD (n = 27)	UC (n = 36)	IC (n = 18)
Diarrhea	81%	79%	89%
Blood in the stool*	67%	94%	67%
Abdominal pain	67%	33%	33%
Failure to thrive*	44%	11%	39%
Perianal disease	34%	0%	0%
Vomiting*	15%	0%	22%
Constipation	4%	0%	6%
Chronic fever*	11%	0%	0%

* $p < 0.05$.

(22). Genetic anticipation, which was described in parent-child pairs in Huntington's disease (23), may explain this finding. Genetic anticipation is a concept whereby the affected offspring manifest the disease at an earlier age, and sometimes in a more severe form, than does the affected parent. In the future, it will be of interest to investigate how many children with EO-IBD are positive for the recently discovered gene Nod2 associated with CD (2).

Our finding of only one patient diagnosed with UC within the first 2 yr of life differs from the report by Gryboski, in which UC was found to be more common than CD at this age (19). The reason is unclear. Of the patients with CD, 60% were diagnosed during the period between 1991–2000 in our study, whereas the study period in Gryboski's report ended in 1990. It is possible that changes in the epidemiology of the disease, as well as changes in the practice of performing full colonoscopies as opposed to flexible sigmoidoscopies, thus allowing histological sampling of the terminal ileum, contributed to the difference.

A striking number of patients with CD (29%) were noted to have linear growth failure at the final follow-up, indicating that despite early diagnosis and treatment, a significant proportion of patients are not able to achieve appropriate growth. Previous studies have reported growth failure in 7–30% of patients with CD (24). In a study by Kanof *et al.* (25), 25% of patients with CD developed severe linear growth failure (height below the fifth percentile), and in a study by McCaffery *et al.* (26), 18% of patients with IBD demonstrated height below the third percentile. Growth failure most likely occurs because of a combination of several detrimental factors: malnutrition, the effects of inflammatory cytokines, and iatrogenic causes (*e.g.*, corticosteroid therapy). Nutritional therapy has previously been shown to be beneficial in improving growth (27). However, nine of 10 patients with CD and linear growth failure in this group received either nasogastric or gastric tube feeding during the course of their illness. A new form of biological therapy directed against tumor necrosis factor–α with a potential for improved histological healing may have a beneficial effect on the final growth in patients with CD (28–32).

The anatomic distribution of the disease in this group of patients with CD is different from that in previously published studies in older children and adolescents (33). In our study, isolated small bowel disease was seen in only 11% of patients, isolated large bowel disease in 30%, and small and large bowel disease in 59%, resulting in a total of 89% of patients with large bowel disease. Pooled data of 14 pediatric studies involving a total of 1153 older children revealed that only 58% of patients had large bowel disease (34). Another study reported that patients younger than 20 yr were more likely to have small intestinal disease when compared with patients 40 yr and older (22). The reasons for the noted difference are unclear. However, patients with CD diagnosed at a very early age may represent a new subgroup with a distinct anatomic disease distribution.

Presenting symptoms can be helpful in differentiating between CD and UC. Hematochezia was more common in UC than in CD or IC. Vomiting was associated with CD and IC, and chronic fever was associated exclusively with CD. Most importantly, in this cohort with early onset CD and IC, failure to thrive (FTT) as a presenting symptom was present in 44% and 39% of patients, respectively. Four patients (12%) initially diagnosed with UC had FTT as a presenting symptom. Interestingly, all four patients had their diagnosis subsequently changed from UC to IC or CD. One of these patients was subsequently found to have granulomas in the large intestine, one had severe inflammation of the terminal ileum on a repeat colonoscopy, one had persistent inflammation of the ileum after the colectomy, and one was found to have patchy inflammation on subsequent colonoscopies. At the same time, none of the remaining 32 patients initially diagnosed with UC had FTT. We therefore conclude that failure to thrive is a presenting symptom that is predictive of CD or IC and not UC. The only other available study that examined FTT as one of the symptoms of IBD (33) described it in 25% of patients with CD, which is less than in our series, and in none in UC, which corresponds to our results. This may possibly be due to more severe disease at the time of diagnosis in our group of patients with CD.

More than 20% of patients with EO-IBD had the diagnosis of indeterminant colitis. In a large, multicenter study of European adults, 5% of newly diagnosed patients were diagnosed with IC (35). The large proportion of children with large bowel involvement could possibly explain this difference. In pediatric series of older children, 14–23% were diagnosed with IC (8), which is similar to our results. Changes in diagnoses occurred more frequently in patients whose diagnoses were made before 1990. This could be explained both by the longer duration of follow-up, allowing the establishment of correct diagnosis, or by improvements in the technical aspects of pediatric colonoscopy during the last decade, allowing better visualization and tissue sampling of the terminal ileum.

Serological assay is a potentially important addition to the diagnostic armamentarium in IBD. Combined measurement of pANCA and ASCA has been advocated as a valuable diagnostic approach in older children and adults. The combination of positive pANCA and negative ASCA had 57% sensitivity and 97% specificity for the diagnosis of UC, and the combination of positive ASCA and negative pANCA had 47% sensitivity and 97% specificity for the diagnosis of CD (36). No study with long term follow-up has been performed to validate the use of these tests to differentiate between UC and CD in a setting of indeterminate colitis (37). In a study of older children, Ruemmele *et al.* reported that the combined test had 57% sensitivity and 92% specificity for UC, and 55% sensitivity and 95% specificity for CD (38). None of the patients with EO-IBD in our study had a positive ASCA. One can postulate that several years of exposure to *Saccharomyces cerevisiae* in an individual with increased intestinal permeability are necessary to produce

detectable ASCA levels (38). The percentage of positive pANCA was similar among UC and CD patients. Because only 15 patients had testing performed before the age of 6 yr, the sample size may be too small to draw reliable conclusions. A larger study is necessary to confirm these important findings.

Finally, surgery was performed in 12.2% of patients during the course of their disease, a higher proportion than the 5% of patients reported in a pediatric series of patients under 10 yr of age (19). Another study of Crohn's disease in children reported 50% and 70% of patients requiring surgery within the first 10 and 15 yr of diagnosis, respectively (39). Among adult patients with UC, almost one half will undergo surgery within the first 10 yr of their illness, and more than 75% of patients with CD will have surgery during the first 20 yr of the disease (40). Length of the follow-up is most likely the reason for the small proportion of children requiring surgery in our series. Continued follow-up may provide further information. Also, a small number of patients in this group were found to have small intestinal CD, which may be associated with a greater need for surgery because of stricturing disease.

In summary, we describe a unique subgroup of young patients with EO-IBD. Accurate differentiation between CD and UC in this age group is very difficult. We noted a high proportion of patients with Crohn's disease with linear growth failure and large bowel disease. Failure to thrive at the time of presentation was predictive of a final diagnosis of CD or IC and not UC. The combined testing of pANCA and ASCA is of limited clinical use for differentiating between CD and UC in children 5 yr of age or younger.

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REFERENCES

1. Papadakis KA, Targan SR. Current theories on the causes of inflammatory bowel disease. Gastroenterol Clin North Am 1999;28:283–96.
2. Ogura Y, Bonen DK, Inohara N, et al. A frameshift mutation in NOD2 associated with susceptibility to Crohn's disease. Nature 2001;411:603–6.
3. Hugot J-P, Chamaillard M, Zouali H, et al. Association of NOD2 leucine-rich repeat variants with susceptibility to Crohn's disease. Nature 2001;411:599–603.
4. Gent AE, Hellier MD, Grace RH, et al. Inflammatory bowel disease and domestic hygiene in infancy. Lancet 1994;343: 766–7.
5. Montgomery SM, Pounder RE, Wakefield AJ. Infant mortality and the incidence of inflammatory bowel disease. Lancet 1997;349:472–3.
6. Duggan AE, Usmani I, Neal KR, et al. Appendicectomy, childhood hygiene, Helicobacter pylori status, and risk of inflammatory bowel disease: A case control study. Gut 1998; 43:494–8.
7. Logan RF. Inflammatory bowel disease incidence: Up, down or unchanged? Gut 1998;42:309–11.
8. Hildebrand H, Fredrikzon B, Holmquist L, et al. Chronic inflammatory bowel disease in children and adolescents in Sweden. J Pediatr Gastroenterol Nutr 1991;13:293–7.
9. Cosgrove M, Al-Atia RF, Jenkins HR. The epidemiology of paediatric inflammatory bowel disease. Arch Dis Child 1996; 74:460–1.
10. Barton JR, Gillon S, Ferguson A. Incidence of inflammatory bowel disease in Scottish children between 1968 and 1983; marginal fall in ulcerative colitis; three-fold rise in Crohn's disease. Gut 1989;30:618–22.
11. Askling J, Grahnquist L, Ekbom A, et al. Incidence of paediatric Crohn's disease in Stockholm, Sweden. Lancet 1999;354: 1179.
12. Ogorek CP, Fisher RS. Differentiation between Crohn's disease and ulcerative colitis. Med Clin North Am 1994;78: 1249–58.
13. Farmer RG, Michener WM. Prognosis of Crohn's disease with onset in childhood or adolescence. Dig Dis Sci 1979;24: 752–7.
14. Ein SH, Lynch MJ, Stephens CA. Ulcerative colitis in children under one year: A twenty-year review. J Pediatr Surg 1971; 6:264–71.
15. Guttman FM. Granulomatous enterocolitis in childhood and adolescence. J Pediatr Surg 1974;9:115–21.
16. Miller RC, Larsen E. Regional enteritis in early infancy. Am J Dis Child 1971;122:301–11.
17. O'Donoghue DP, Dawson AM. Crohn's disease in childhood. Arch Dis Child 1977;52:627–32.
18. Gryboski JD. Ulcerative colitis in children 10 years old or younger. J Pediatr Gastroenterol Nutr 1993;17:24–31.
19. Gryboski JD. Crohn's disease in children 10 years old and younger: Comparison with ulcerative colitis. J Pediatr Gastroenterol Nutr 1994;18:174–82.
20. Tysk C, Lindberg E, Jarnerot G, et al. Ulcerative colitis and Crohn's disease in an unselected population of monozygotic and dizygotic twins. A study of heritability and the influence of smoking. Gut 1988;29:990–6.
21. Cohen Z, Weizman Z, Kurtzbart E, et al. Infantile colonic Crohn's disease: A report of four cases in one family. J Pediatr Gastroenterol Nutr 2000;30:461–3.
22. Polito JM II, Childs B, Mellits ED, et al. Crohn's disease: Influence of age at diagnosis on site and clinical type of disease. Gastroenterology 1996;111:580–6.
23. Snell RG, MacMillan JC, Cheadle JP, et al. Relationship between trinucleotide repeat expansion and phenotypic variation in Huntington's disease. Nat Genet 1993;4:393–7.
24. Ballinger AB, Camacho-Hubner C, Croft NM. Growth failure and intestinal inflammation. Q J Med 2001;94:121–5.
25. Kanof ME, Lake AM, Bayless TM. Decreased height velocity in children and adolescents before the diagnosis of Crohn's disease. Gastroenterology 1988;95:1523–7.
26. McCaffery TD, Nasr K, Lawrence AM, et al. Severe growth retardation in children with inflammatory bowel disease. Pediatrics 1970;45:386–93.
27. Polk DB, Hattner JA, Kerner JA Jr. Improved growth and disease activity after intermittent administration of a defined formula diet in children with Crohn's disease. JPN 1992;16: 499–504.
28. Baldassano RN, Vasiliauskas E, Braegger CP, et al. A multicenter study of infliximab (anti-TNF alpha antibody) in the treatment of children with active Crohn's disease. Gastroenterology 1999;116:A665.
29. Kugathasan S, Werlin SL, Martinez A, et al. Prolonged duration of response to infliximab in early but not late pediatric Crohn's disease. Am J Gastroenterol 2000;95:3189–94.

30. Hyams JS, Markowitz J, Wyllie R. Use of infliximab in the treatment of Crohn's disease in children and adolescents. J Pediatr 2000;137:192–6.
31. D'Haens G, Van Deventer S, Van Hogezand R, et al. Endoscopic and histological healing with infliximab anti-tumor necrosis factor antibodies in Crohn's disease: A European multicenter trial. Gastroenterology 1999;116:1029–34.
32. Murch SH, Lamkin VA, Savage MO, et al. Serum concentrations of tumour necrosis factor alpha in childhood chronic inflammatory bowel disease. Gut 1991;32:913–7.
33. Krebs C, Nixon HH. Inflammatory bowel disease in childhood. Presentation and diagnosis. Z Kinderchir 1983;38:387–91.
34. Barton JR, Ferguson A. Clinical features, morbidity and mortality of Scottish children with inflammatory bowel disease. Q J Med 1990;75:423–39.
35. Shivananda S, Lennard-Jones J, Logan R, et al. Incidence of inflammatory bowel disease across Europe: Is there a difference between north and south? Results of the European Collaborative Study on Inflammatory Bowel Disease (EC-IBD). Gut 1996;39:690–7.
36. Quinton JF, Sendid B, Reumaux D, et al. Anti-Saccharomyces cerevisiae mannan antibodies combined with antineutrophil cytoplasmic autoantibodies in inflammatory bowel disease: Prevalence and diagnostic role. Gut 1998;42:788–91.
37. Moum B, Ekbom A, Vatn MH, et al. Inflammatory bowel disease: Re-evaluation of the diagnosis in a prospective population based study in south eastern Norway. Gut 1997;40:328–32.
38. Ruemmele FM, Targan SR, Levy G, et al. Diagnostic accuracy of serological assays in pediatric inflammatory bowel disease. Gastroenterology 1998;115:822–9.
39. Davies G, Evans CM, Shand WS, et al. Surgery for Crohn's disease in childhood: Influence of site of disease and operative procedure on outcome. Br J Surg 1990;77:891–4.
40. Becker JM. Surgical therapy for ulcerative colitis and Crohn's disease. Gastroenterol Clin North Am 1999;28:371–90, viii-ix.