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Frequency of indeterminate colitis in children and adults with IBD — a metaanalysis

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Abstract

Background: Indeterminate colitis (IC) remains an enigmatic inflammatory bowel disease (IBD) phenotype. It is currently not clear whether it constitutes merely a problem of terminology, classification, or possibly an early stage of IBD distinct from Crohn's disease (CD) and ulcerative colitis (UC).
Methods: We analysed epidemiological data of studies comparing IC, UC and CD. We selected 14 studies investigating paediatric patients (10 prospective and 4 retrospective) and 18 studies investigating adult IBD patients (11 prospective and 7 retrospective) for this analysis.
Results: Compared to adults ($n=15{,}776$) the frequency of IC is higher in children ($n=6262$) (children 12.7% versus adults 6.0%, $p<0.0001$). This difference between children and adults has been detected irrespective whether prospective or retrospective studies were selected. In both, children and adults IC was more frequent in prospective studies compared to retrospective studies (children $p=0.0004$; adults $p=0.0024$).
Conclusions: IC has been detected in a substantial proportion of paediatric patients with IBD. IC is more frequently found in children compared to adults. Further studies are required to clarify whether IC represents an IBD phenotype associated with childhood disease onset or whether the high IC frequency is due to difficulties in establishing a UC or CD diagnosis.
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1. Introduction

30 years ago Price described a subset of patients with inflammatory bowel disease (IBD) that could not be classified as Crohn's disease (CD) or ulcerative colitis (UC).[1] This IBD phenotype termed "indeterminate colitis" (IC) still remains poorly defined and understood.[2–7] In 2007 the NASPGHAN/CCFA Working Group stated that there are not enough data in the literature for a clear definition of IC.[8] Romano et al.[9] described five major criteria to define children with IC: (1) abdominal pain, bleeding diarrhea, and weight loss, (2) endoscopic macroscopic features of erosions and ulcers of the colon, (3) pancolitis with "rectal sparing", (4) early onset, (5) diffuse, transmucosal lamina propria cell increase and patchy inflammation. Indeed, although initially strictly reserved for surgical resection specimens the term "indeterminate colitis" has been extended to clinical, endoscopic and histologic features of the disease.[5,9] IC certainly constitutes a

Abbreviations: IBD, inflammatory bowel disease; IC, indeterminate colitis; UC, ulcerative colitis; CD, Crohn's disease.

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problem of classification, since a proportion of patients can later be diagnosed as having CD or UC.[2,5] However, some patients maintain the clinical and histological picture of IC. Therefore IC might — at least in some patients — represent a third IBD phenotype distinct from the CD and the UC.[6] It is possible that IC includes several immune dysregulation disorders that exhibit a chronic colitis pheno-type distinct from the UC and the CD.

A recent review states that IC might be more frequent in children compared to adults.[5] We investigated, whether IC is indeed more frequent in children compared to adults by performing a meta-analysis including 32 studies.

2. Methods

2.1. Database search and selection criteria

We searched the NCBI Pubmed database (http://www.ncbi.nlm.nih.gov/sites/entrez?db) for original studies of IC in children, adolescents and adults. Articles published between January 1st 1990 and December 31st 2007 were selected using the term ”indeterminate colitis”. Subsequently the corresponding bibliographies were reviewed for more eligible articles. This search strategy was performed iteratively until no more relevant publications were found. Studies were selected according to the following criteria:

(1) Epidemiologic studies investigating the frequency of CD, UC and IC were included.
(2) Studies were considered when published in English speaking journals.
(3) To warrant some degree of homogeneity of the study populations concerning ethnic background and life style, studies were limited to the area of Europe and Northern America.
(4) We selected studies when the diagnosis of CD, UC and IC was differentiated using established clinical criteria including endoscopy, histology and radiology.
(5) Studies that include a minimum of 50 IBD patients in total were selected.
(6) There were several studies comprising the same study cohorts or a substantial overlap (for instance follow-up studies). In this case, the largest study population was considered. This selection has been chosen to avoid a bias due to cohort overlap.
(7) Retrospective and prospective studies were analysed separately as well as combined.
(8) Paediatric patients were defined as aged less than 18 years. Some studies in the adult patient group include a minority of paediatric patients (<20%).
(9) We included studies if there was no obvious preselection in the study population (consecutive patients, all patients of a circumscribed area, and population of large IBD registries).
(10) There were epidemiological data sets provided with follow-up analysis. We used the diagnosis of the initial presentation or early analysis in order to reduce a selection bias due to different follow-up periods between children and adults.

In addition to the paediatric group including all children and adolescents (age 0 to 18 years of life), we analysed studies that described the frequency of IC in younger children with IBD (Supplemental Fig. 1).

3. Statistics

Data are presented as frequency ± 95% confidence interval according to the Wald equation. The X^2-test was calculated using GraphPad Prism 5.0 (GraphPad Software, San Diego California USA). P values ≤ 0.05 were regarded as significant.

4. Results

We selected 14 studies investigating paediatric patients (10 prospective and 4 retrospective) and 18 studies investigating adult IBD patients (11 prospective, 7 retrospective, and data of 2 studies were combined) for this analysis (Fig. 1).

In children ($n=6262$) the frequency of IC is higher compared to adults ($n=15776$) (12.7% versus 6.0%; $p<0.0001$; Fig. 2). This difference between children and adults has been detected irrespective whether prospective or retrospective studies were selected (prospective studies children 13.5% versus adults 6.2%; $p<0.0001$; retrospective studies children 10.2% versus adults 4.8%; $p<0.0001$). In both, children and adults IC was more frequent in prospective studies compared to the retrospective studies (children $p=0.0004$; adults $p=0.0024$).

To investigate whether the increased frequency of IC in paediatric patients is due to the high frequency of IC in very young patients, we analysed groups of 0 to 2 as well as 0 to 5 year old IBD patients. In the group of 0 to 2 year old children ($n=133$) 34% and in 0 to 5 year old children 21% of IBD patients were classified as IC (Supplemental Fig. 1). However it should be noted that the number of patients included into these studies are small to draw a definitive conclusion.

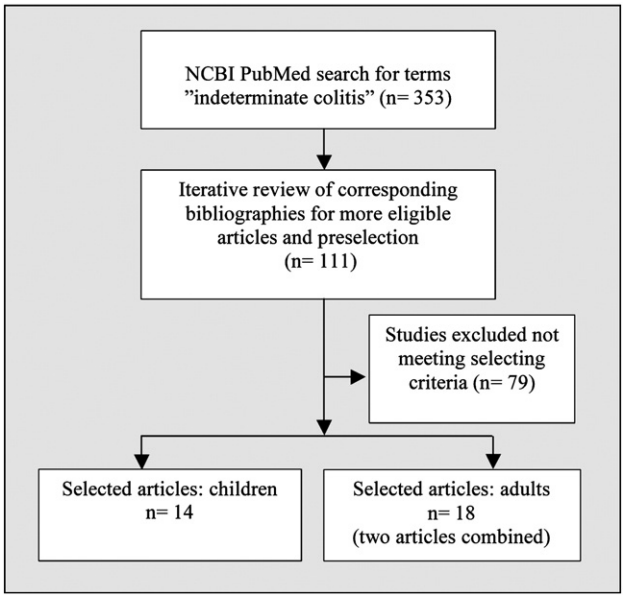

Figure 1 Data selection.

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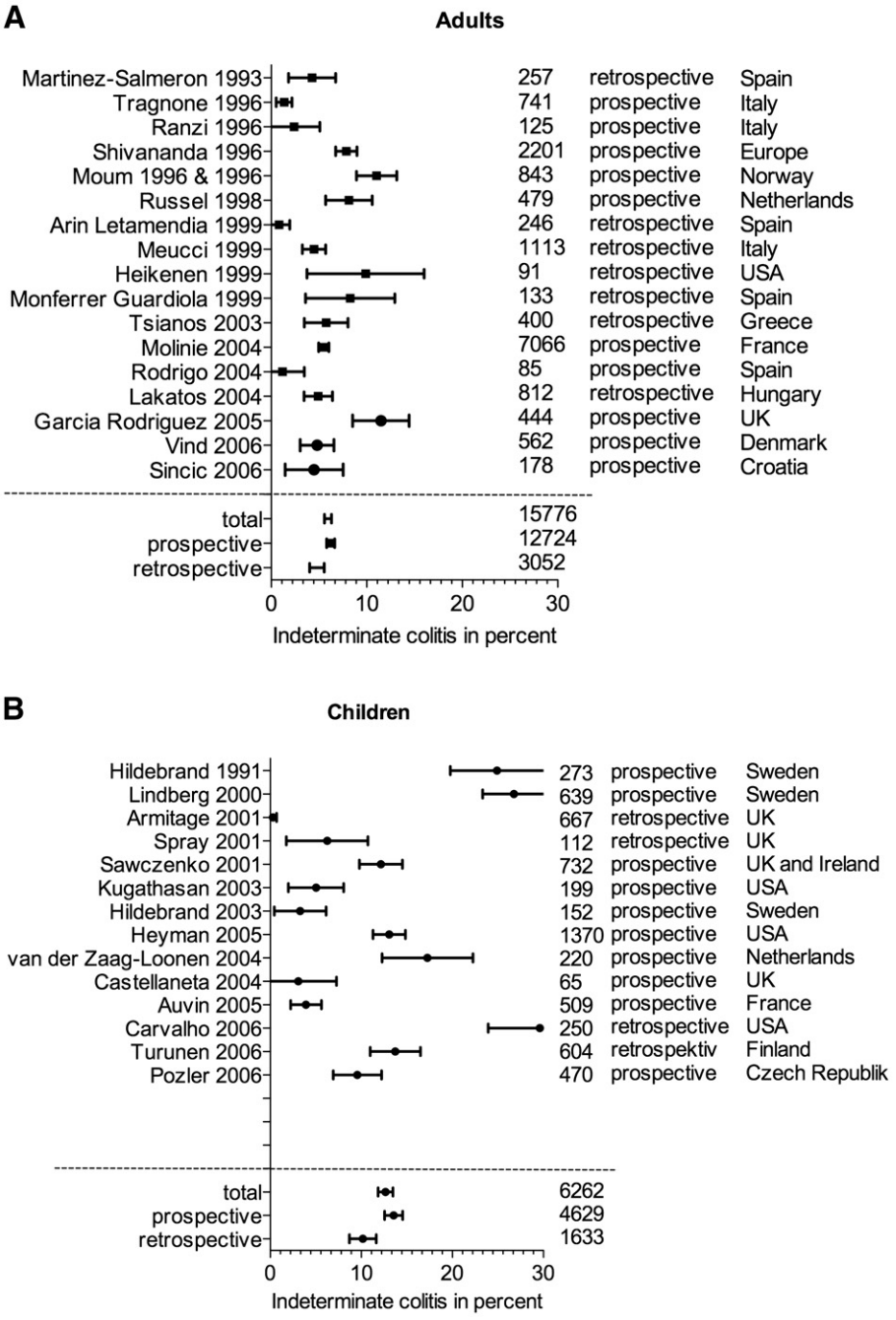

Figure 2 Increased frequency of IC in paediatric patients compared to adults. A: 18 studies on adult patients including 15776 IBD patients were analysed.[24–41] B: 14 studies on paediatric patients including 6262 IBD patients were selected.[11,42–54] *Data of the studies of Moum were analysed combined.[40,41] The frequency of IC among all IBD patients was calculated for all individual studies separately and for the sum of all patients per group.

The preliminary analysis suggests that there is a direct correlation between the age of the patients and the frequency of IC.

5. Discussion

IC is significantly associated with childhood onset of IBD. Our meta-analysis shows that 13% of children and 6% of adults with IBD are classified as IC. Recent studies showed that among paediatric patients the frequency of IC is highest in younger age groups.[10–12] Indeed, up to one third of children younger than 2 years and one fifth of children between 0 and 5 years were classified as IC phenotype.[11] Although only a restricted number of studies are available in the very young age groups, the meta-analysis supports the finding of high IC frequency in young IBD patients.

The high frequency of IC in children may be due to difficulties in classifying IBD in young children per se. This is most likely not due to technical difficulties in paediatrics but due to specific immune reactions in childhood. The hypothesis of specific intestinal immune mechanisms in

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early childhood is supported by the fact that the pattern of CD in young children is also different from adult patients. Young patients with CD frequently present as a colitis phenotype.[13] Polymorphism in the TNF-alpha promotor gene is associated with paediatric onset of colonic CD.[14] Young children without NOD2/CARD15 mutations show an isolated colonic disease.[15] It should be noted that in particular in very young patients immune deficiency disorders may present phenotypically as chronic intestinal inflammation. Among those immune deficiency disorders with early onset of intestinal inflammation are chronic granulomatous disease, Wiskott Aldrich syndrome, common variable immunodeficiency disease (CVID), immunodysregulation polyendocrinopathy enteropathy X-linked syndrome (IPEX), or glycogenosis type 1b.[16–20]

Our study has several limitations: (1) The term IC is not clearly defined. We refer to the clinical diagnosis of patients that cannot be classified as UC or CD. The application of the term IC might vary among the studies selected. (2) Since we only considered studies in English there is a selection bias. (3) There is a heterogeneity of the study population among different studies. (4) The differentiation of CD, UC and IC has been performed similarly, but is not based on the identical selection criteria among different studies. The heterogeneity in the frequency of IC in children may be influenced by factors such as the ones mentioned above.

Whereas the understanding of the molecular processes involved in the pathogenesis of CD and UC[21,22] and specific phenotypes in paediatric patients are currently emerging,[13,14] the immunological mechanisms underlying IC remain unsolved. Obviously, better biomarkers are needed that predict the childhood development of CD or UC as well as IC. The absence of the CD specific ASCA and UC associated ANCA antibodies correlate with the IC pheno-type.[23] Further studies are needed to clarify the immunopathogenesis of the patients that we currently classify as IC.

The analysis of current data on childhood IC suggests the following aspects of future research: (1) Careful prospective studies are needed to investigate the occurrence of IC in pediatric patients, in particular in patients below 5 years of age. (2) Epidemiologic studies should aim to apply a positive definition of IC. For instance, authors might apply the definition of Romano et al. (3) Reference pathologists should reinvestigate all cases of IC in order to avoid misclassification. (4) Epidemiological studies of IBD in young children should include a structured prospective work-up to avoid initial misclassification of immunodeficiencies as IC. (5) Genetical studies such as genome wide association studies of IC patients are needed to better understand the pathogenesis of IC.

Conflict of interest

No conflict of interest has been declared.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.crohns.2009.07.001.

References

1. Price AB. Overlap in the spectrum of non-specific inflammatory disease—"colitis indeterminate". *J Clin Pathol* 1978;**31**(6): 567–77.
2. Guindi M, Riddell RH. Indeterminate colitis. *J Clin Pathol* 2004;**57**(12): 1233–44.
3. Odze RD. Pathology of indeterminate colitis. *J Clin Gastroenterol* 2004;**38**(5 Suppl):S36–40.
4. Geboes K. Crohn's disease, ulcerative colitis or indeterminate colitis—how important is it to differentiate? *Acta Gastroenterol Belg* 2001;**64**(2):197–200.
5. Geboes K, Colombel JF, Greenstein A, et al. Indeterminate colitis: a review of the concept—what's in a name? *Inflamm Bowel Dis* 2008;**14**(6):850–7.
6. Tremaine WJ. Review article: indeterminate colitis—definition, diagnosis and management. *Aliment Pharmacol Ther* 2007;**25** (1): 13–7.
7. Martland GT, Shepherd NA. Indeterminate colitis: definition, diagnosis, implications and a plea for nosological sanity. *Histopathology* 2007;**50**(1):83–96.
8. Bousvaros A, Antonioli DA, Colletti RB, et al. Differentiating ulcerative colitis from Crohn disease in children and young adults: report of a working group of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the Crohn's and Colitis Foundation of America. *J Pediatr Gastroenterol Nutr* 2007;**44**(5):653–74.
9. Romano C, Famiani A, Gallizzi R, Comito D, Ferrau V, Rossi P. Indeterminate colitis: a distinctive clinical pattern of inflammatory bowel disease in children. *Pediatrics* 2008;**122**(6):e1278–81.
10. Mamula P, Telega GW, Markowitz JE, et al. Inflammatory bowel disease in children 5 years of age and younger. *Am J Gastroenterol* 2002;**97**(8):2005–10.
11. Heyman MB, Kirschner BS, Gold BD, et al. Children with early-onset inflammatory bowel disease (IBD): analysis of a pediatric IBD consortium registry. *J Pediatr* 2005;**146**(1):35–40.
12. Ruemmele FM, El Khoury MG, Talbotec C, et al. Characteristics of inflammatory bowel disease with onset during the first year of life. *J Pediatr Gastroenterol Nutr* 2006;**43**(5):603–9.
13. Meinzer U, Idestrom M, Alberti C, et al. Ileal involvement is age dependent in pediatric Crohn's disease. *Inflamm Bowel Dis* 2005;**11**(7):639–44.
14. Levine A, Karban A, Eliakim R, et al. A polymorphism in the TNF-alpha promoter gene is associated with pediatric onset and colonic location of Crohn's disease. *Am J Gastroenterol* 2005;**100**(2): 407–13.
15. Levine A, Kugathasan S, Annese V, et al. Pediatric onset Crohn's colitis is characterized by genotype-dependent age-related susceptibility. *Inflamm Bowel Dis* 2007;**13**(12):1509–15.
16. Thapar N, Shah N, Ramsay AD, Lindley KJ, Milla PJ. Long-term outcome of intractable ulcerating enterocolitis of infancy. *J Pediatr Gastroenterol Nutr* 2005;**40**(5):582–8.
17. Ruemmele FM, Moes N, de Serre NP, Rieux-Laucat F, Goulet O. Clinical and molecular aspects of autoimmune enteropathy and immune dysregulation, polyendocrinopathy autoimmune enteropathy X-linked syndrome. *Curr Opin Gastroenterol* 2008;**24**(6): 742–8.
18. Daniels JA, Lederman HM, Maitra A, Montgomery EA. Gastrointestinal tract pathology in patients with common variable immunodeficiency (CVID): a clinicopathologic study and review. *Am J Surg Pathol* 2007;**31**(12):1800–12.
19. Cannioto Z, Berti I, Martelossi S, et al. IBD and IBD mimicking enterocolitis in children younger than 2 years of age. *Eur J Pediatr* 2009;**168**(2):149–55.
20. Dieckgraefe BK, Korzenik JR, Husain A, Dieruf L. Association of glycogen storage disease 1b and Crohn disease: results of a North American survey. *Eur J Pediatr* 2002;**161**(Suppl 1):S88–92.
21. Xavier RJ, Podolsky DK. Unravelling the pathogenesis of inflammatory bowel disease. *Nature* 2007;**448**(7152): 427–34.

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22. Cho JH. The genetics and immunopathogenesis of inflammatory bowel disease. *Nat Rev Immunol* 2008;**8**(6):458–66.
23. Joossens S, Reinisch W, Vermeire S, et al. The value of serologic markers in indeterminate colitis: a prospective follow-up study. *Gastroenterology* 2002;**122**(5):1242–7.
24. Martinez-Salmeron JF, Rodrigo M, de Teresa J, et al. Epidemiology of inflammatory bowel disease in the Province of Granada, Spain: a retrospective study from 1979 to 1988. *Gut* 1993;**34**(9): 1207–9.
25. Ranzi T, Bodini P, Zambelli A, et al. Epidemiological aspects of inflammatory bowel disease in a north Italian population: a 4-year prospective study. *Eur J Gastroenterol Hepatol* 1996;**8**(7): 657–61.
26. 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**(5): 690–7.
27. Russel MG, Dorant E, Volovics A, et al. High incidence of inflammatory bowel disease in The Netherlands: results of a prospective study. The South Limburg IBD Study Group. *Dis Colon Rectum* 1998;**41**(1):33–40.
28. Arin Letamendia A, Burusco Paternain MJ, Borda Celaya F, Pueyo Royo A, Martinez Echeverria A, Jimenez Perez FJ. Epidemiological aspects of inflammatory bowel disease in the Pamplona area. *Rev Esp Enferm Dig* 1999;**91**(11):769–76.
29. Heikenen JB, Werlin SL, Brown CW, Balint JP. Presenting symptoms and diagnostic lag in children with inflammatory bowel disease. *Inflamm Bowel Dis* 1999;**5**(3):158–60.
30. Meucci G, Bortoli A, Riccioli FA, et al. Frequency and clinical evolution of indeterminate colitis: a retrospective multi-centre study in northern Italy. GSMII (Gruppo di Studio per le Malattie Infiammatorie Intestinali). *Eur J Gastroenterol Hepatol* 1999;**11** (8): 909–13.
31. Molinie F, Gower-Rousseau C, Yzet T, et al. Opposite evolution in incidence of Crohn's disease and ulcerative colitis in Northern France (1988–1999). *Gut* 2004;**53**(6):843–8.
32. Tsianos EV, Katsanos KH, Christodoulou D, Dimoliatis I, Kogevinas A, Logan RF. Continuing low incidence of Crohn's disease in Northwest Greece. *Dig Liver Dis* 2003;**35**(2):99–103.
33. Lakatos L, Mester G, Erdelyi Z, et al. Striking elevation in incidence and prevalence of inflammatory bowel disease in a province of western Hungary between 1977–2001. *World J Gastroenterol* 2004;**10**(3):404–9.
34. Rodrigo L, Riestra S, Nino P, et al. A population-based study on the incidence of inflammatory bowel disease in Oviedo (Northern Spain). *Rev Esp Enferm Dig* 2004;**96**(5):296–305.
35. Tragnone A, Corrao G, Miglio F, Caprilli R, Lanfranchi GA. Incidence of inflammatory bowel disease in Italy: a nationwide population-based study. Gruppo Italiano per lo Studio del Colon e del Retto (GISC). *Int J Epidemiol* 1996;**25**(5):1044–52.
36. Monferrer Guardiola R, Marin Jimenez JA, Pedraza Sanz RG, Moreno Sanchez I, Soler Bahilo E, Hinojosa del Val J. Incidence of inflammatory bowel disease in the 02 health area of Castellon (1992–1996). *Rev Esp Enferm Dig* 1999;**91**(1):40–6.
37. Garcia Rodriguez LA, Gonzalez-Perez A, Johansson S, Wallander MA. Risk factors for inflammatory bowel disease in the general population. *Aliment Pharmacol Ther* 2005;**22**(4):309–15.
38. Vind I, Riis L, Jess T, 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**(6): 1274–82.
39. Sincic BM, Vucelic B, Persic M, et al. Incidence of inflammatory bowel disease in Primorsko-Goranska County, Croatia, 2000–2004: a prospective population-based study. *Scand J Gastroenterol* 2006;**41**(4):437–44.
40. Moum B, Vatn MH, Ekbom A, et al. Incidence of ulcerative colitis and indeterminate colitis in four counties of southeastern Norway, 1990–93. A prospective population-based study. The Inflammatory Bowel South-Eastern Norway (IBSEN) Study Group of Gastroenterologists. *Scand J Gastroenterol* 1996;**31**(4):362–6.
41. Moum B, Vatn MH, Ekbom A, et al. Incidence of Crohn's disease in four counties in southeastern Norway, 1990–93. A prospective population-based study. The Inflammatory Bowel South-Eastern Norway (IBSEN) Study Group of Gastroenterologists. *Scand J Gastroenterol* 1996;**31**(4):355–61.
42. Hildebrand H, Fredrikzon B, Holmquist L, Kristiansson B, Lindquist B. Chronic inflammatory bowel disease in children and adolescents in Sweden. *J Pediatr Gastroenterol Nutr* 1991;**13**(3):293–7.
43. Spray C, Debelle GD, Murphy MS. Current diagnosis, management and morbidity in paediatric inflammatory bowel disease. *Acta Paediatr* 2001;**90**(4):400–5.
44. Castellaneta SP, Afzal NA, Greenberg M, et al. Diagnostic role of upper gastrointestinal endoscopy in pediatric inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2004;**39**(3): 257–61.
45. 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**(10):1432–4.
46. Kugathasan S, Judd RH, Hoffmann RG, et al. Epidemiologic and clinical characteristics of children with newly diagnosed inflammatory bowel disease in Wisconsin: a statewide population-based study. *J Pediatr* 2003;**143**(4):525–31.
47. Lindberg E, Lindquist B, Holmquist L, Hildebrand H. Inflammatory bowel disease in children and adolescents in Sweden, 1984–1995. *J Pediatr Gastroenterol Nutr* 2000;**30**(3):259–64.
48. Sawczenko A, Sandhu BK, Logan RF, et al. Prospective survey of childhood inflammatory bowel disease in the British Isles. *Lancet* 2001;**357**(9262):1093–4.
49. van der Zaag-Loonen HJ, Casparie M, Taminiau JA, Escher JC, Pereira RR, Derkx HH. The incidence of pediatric inflammatory bowel disease in the Netherlands: 1999–2001. *J Pediatr Gastroenterol Nutr* 2004;**38**(3):302–7.
50. Armitage E, Drummond HE, Wilson DC, Ghosh S. Increasing incidence of both juvenile-onset Crohn's disease and ulcerative colitis in Scotland. *Eur J Gastroenterol Hepatol* 2001;**13**(12): 1439–47.
51. Auvin S, Molinie F, Gower-Rousseau C, et al. Incidence, clinical presentation and location at diagnosis of pediatric inflammatory bowel disease: a prospective population-based study in northern France (1988–1999). *J Pediatr Gastroenterol Nutr* 2005;**41**(1): 49–55.
52. Turunen P, Kolho KL, Auvinen A, Iltanen S, Huhtala H, Ashorn M. Incidence of inflammatory bowel disease in Finnish children, 1987–2003. *Inflamm Bowel Dis* 2006;**12**(8):677–83.
53. Pozler O, Maly J, Bonova O, et al. Incidence of Crohn disease in the Czech Republic in the years 1990 to 2001 and assessment of pediatric population with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2006;**42**(2):186–9.
54. 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**(4):258–62.
55. Castro M, Papadatou B, Baldassare M, et al. Inflammatory bowel disease in children and adolescents in Italy: data from the pediatric national IBD register (1996–2003). *Inflamm Bowel Dis* 2008;**14**(9):1246–52.

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