

Pediatric inflammatory bowel disease in Greece: 30-years experience of a single center

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Abstract

Background Significant advances have been made in the care of children with inflammatory bowel disease (IBD). We aimed to describe the trends during the last 3 decades in the clinical presentation, management, and outcome of pediatric IBD at a single center.

Methods Medical records of children with IBD referred to a pediatric gastroenterology unit from January 1981 to December 2011 were reviewed retrospectively.

Results A total of 483 children were diagnosed with IBD, with mean age at diagnosis of 9.6 years (range 6 months – 18 years). Ulcerative colitis (UC) was diagnosed in 267 (55.2%), Crohn's disease (CD) in 167 (34.5%), and IBD unclassified (IBDU) in 49 (10.1%). Children with UC and IBDU were younger than those with CD [mean age at diagnosis 9.2, 8.9, and 10.5 years respectively; P (UC vs. CD)<0.01 and P (IBDU vs. CD)=0.028]. Patients received 5-ASA (96.6%), steroids (77.0%), thiopurines (50.2%), biological agents (14%), and 10% underwent surgical intervention. The cohort was divided into three subgroups according to the date of diagnosis; Group A: 1981-1989, Group B: 1990-1999, and Group C: 2000-2011. During the last two decades a significant increase in CD (Group A 18.5%, Group B 23.8%, Group C 48.8%; P<0.01) compared with the first decade with parallel decrease in UC (Group A 79.6%, Group B 71.9%, Group C 33.2%; P<0.001) was observed.

Conclusions Most children received 5-ASA, steroids, and immunomodulators. Patients with UC and IBDU were younger than those with CD. A significant increase in CD with parallel decrease in UC during the last decade was found.

Keywords Inflammatory bowel disease, children, Crohn's disease, ulcerative colitis, unclassified IBD, treatment

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Introduction

Inflammatory bowel disease (IBD) comprises Crohn's disease (CD) and ulcerative colitis (UC). A separate category, IBD unclassified (IBDU), is reserved for those who have clinical, endoscopic and histopathologic features of IBD but

no definite distinction can be made between CD and UC [1,2]. The peak age of onset is between 15 and 35 years [3], although IBD can occur as early as the first year of life [4]. Data suggest that 10-25% of patients with IBD are diagnosed before their 18th birthday [5,6]. Certain features of IBD presenting in childhood are unique compared with adults [7,8].

During the last decades, significant advances have been made in diagnosis and management of pediatric IBD, such as the introduction of magnetic resonance imaging (MRI) enteroclysis, videocapsule endoscopy for the assessment and the use of biological agents for therapy. These advances have had a beneficial impact on the care of these patients [9-13].

Recent epidemiological studies suggest an increase in the incidence of pediatric-onset IBD, particularly for CD over the past 10 years [14-17]. These studies showed incidence rates of CD ranging between 2-5 per 100,000 children per year [14] compared to 1.1 per 100,000 per year [14,18].

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Conflict of Interest: None

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Gastroenterology, Hepatology and Nutrition and our referral population for IBD approximates almost two thirds of the National Greek cohort. The aim of this study was to determine disease characteristics and to identify any particular trend regarding the clinical and therapeutic patterns of IBD in our center during the last 3 decades.

Patients and methods

A retrospective analysis of the database of all IBD patients referred to our pediatric gastroenterology unit between January 1981 and December 2011 was performed following approval by the local Ethics Committee. The medical records of children with IBD including endoscopic, histological and radiological reports were reviewed by two investigators (KD and IP).

The diagnosis was confirmed by standard endoscopic, histological, and contemporary recommended radiographic criteria [1,2]. The diagnosis of IBDU was assigned to patients for whom the diagnostic criteria did not distinguish between CD and UC. Therefore, patients were divided into 3 categories according to disease phenotype: those with CD, those with UC, and those with IBDU. The cohort was also divided into 3 groups according to the date of diagnosis: Group A 1981-1989, Group B 1990-1999, and Group C 2000-2011.

All patients underwent colonoscopy at diagnosis, while upper GI endoscopy was performed initially when upper GI symptoms were present or CD was suspected and later in accordance to Porto criteria [14]. The contemporary recommended radiographic studies were performed (upper GI series with small bowel follow-through, barium enema, or MRI enteroclysis) according to suspected diagnosis.

The following characteristics were investigated: sex, age at symptoms onset, age at diagnosis, diagnostic time lag, presenting symptoms, medications, and surgical procedures.

Statistical analysis

Continuous data are presented as mean \pm standard deviation (SD) and compared by Student's *t*-test, or Mann-Whitney test, whenever the number of observations was <30 . Correlations between continuous data were estimated by Pearson's correlation coefficient (*r*), or Spearman's ρ . Categorical variables are presented as absolute (*n*) and relative (%) frequencies and comparisons between groups were performed by Fisher's exact test. A level of 0.05 or less was considered statistically significant. Analyses were performed using Stata 11.0 MP (StataCorp, College Station, TX).

Results

A total of 483 children (50.2% males) with IBD were identified. UC was diagnosed in 267 (55.2%, 51.8% males),

CD in 167 (34.5%, 50.9% males), and IBDU in 49 (10.1%, 38.6% males).

According to the period of diagnosis, between 1981 and 1989 (Group A) 54 children with IBD were found (UC: *n*=43, 79.6%; CD: *n*=10, 18.5%; IBDU: *n*=1, 1.8%), between 1991-1999 (Group B) 211 children (UC: *n*=152, 72.0%; CD: *n*=50, 23.7%; IBDU: *n*=9, 4.3%), and between 2000-2011 (Group C) 218 children (UC: *n*=72, 33.0%; CD: *n*=107, 49.1%; IBDU: *n*=39, 17.9%). During the last two decades a significant relative increase in CD ($P<0.01$) compared to first decade with parallel relative decrease in UC was seen.

In our cohort 8.9% of the IBD children had a family history of IBD and among them 6% had a 1st-degree relative, while 2.9% had a 2nd-degree relative with IBD. There was no statistical difference of family history of IBD between UC (*n*=20, 7.7%), CD (*n*=17, 10.3%), and IBDU (*n*=6 12.8%) patients ($P=0.186$).

Mean age at diagnosis was 9.6 ± 3.9 (range: 5.7-13.5) years for all pediatric patients with IBD. More specifically, mean age of children with UC was 9.2 ± 3.9 (range 5.3-13.1) years; of children with CD 10.5 ± 3.7 (range: 6.9-14.2) years; and of those with IBDU 8.9 ± 4.0 (range 4.8-13.7) years. Children diagnosed with UC and IBDU were younger than those with CD ($P<0.01$ and $P=0.028$ respectively).

Diagnosis mean age time trends were also investigated. The mean age at diagnosis for the total IBD cohort was similar over the study period. For Group A it was 9.3 (range 0.7-15.5) years; for Group B 9.8 (range 0.7-18.5) years; and for Group C 9.5 (range 0.6-16.7) years. The same was true for UC and IBDU. However, children with CD were diagnosed at earlier younger age during the last decade compared to the previous decade (Group B 11.5 years vs. Group C 9.8 years) (Table 1).

Mean age at presentation of symptoms was 8.9 ± 4.1 (range: 4.8-12.9) years for the whole pediatric IBD population. Age at presentation for UC was 8.5 ± 4.1 (range: 4.5-12.7) years; for CD 9.6 ± 3.9 (range: 5.7-13.5) years; and for IBDU 8.3 ± 4.2 (range: 4.1-12.5) years. Symptoms in children with UC started significantly earlier than in those with CD ($P=0.048$).

Mean disease duration prior to diagnosis was 0.8 ± 1.6 (range: 0-2.3) years for the total study IBD cohort. Mean disease duration for patients with UC was 0.6 ± 1.5 (range: 0-2.1) years and was relatively stable over the study period [Group A 0.5 years (0-1); Group B 0.6 years (0-2.3); Group C 0.61 years (0-2.3)]. Total mean disease duration for IBDU was 0.5 ± 0.8 (0-1.3) years [Group A (only one patient) 1.2 years; Group B 0.3 (0-0.7) year; and Group C 0.6 (0-1.5) years]. Total mean disease duration for CD was 0.9 ± 1.9 (0-1.9) years [Group A 1.9 (0-5.3) years; Group B 1.5 (0-4.2) years; and Group C 0.5 (0-1.4) years]. A significant decrease in mean disease duration prior to diagnosis in CD patients between the last two decades (Group C vs. Group B $P=0.012$) but no any other significant difference was noticed among the other two disease phenotypes over the study period (Fig. 1).

For the majority of IBD patients, blood in stools was the commonest presenting symptom, followed by diarrhea and abdominal pain, while hepatic involvement was found in a small proportion of patients. Extraintestinal symptoms were more common in children with CD compared to those with UC (Table 2).

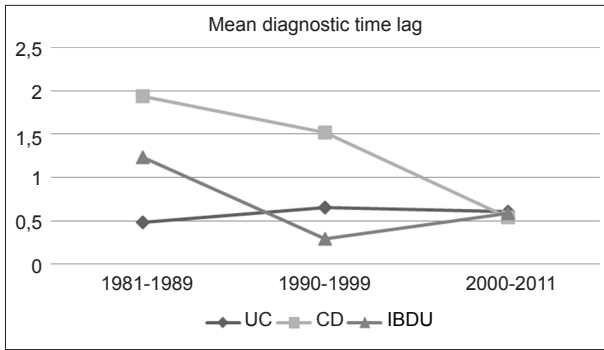


Figure 1 Mean diagnostic time lag over the study period
 Significant decrease in mean disease duration prior to diagnosis in CD patients during the last 2 decades (P=0.012)
 UC, ulcerative colitis; CD, Crohn's disease; IBDU, inflammatory bowel disease unclassified

The majority of children with IBD received 5-ASA and steroids, while about half of them received thiopurines. Other immunomodulators such as cyclosporine, methotrexate and anti-tumor necrosis factor (TNF) agents were used less often (Table 3, Fig. 2).

Ten percent (n=43) of the IBD pediatric patients underwent surgical intervention (total or partial colectomy). Of the children who underwent surgery 60% had UC, 30% CD, and 10% IBDU (Fig. 3). However, in each phenotype of the disease the need for colectomy was not significantly different (CD 10.84%, UC 10.51%, and IBDU 6.76%; P=0.8). There was also no significant difference in the need for surgical treatment between males (n=26) and females (n=17) (P=0.2). During the last decade a significant decrease in the need for surgical intervention was noticed (Group A n=21, Group B n=14, Group C n=8; P<0.001), despite that the

Table 1 Mean age at diagnosis (years)

	Total IBD	SD	UC	SD	CD	SD	IBDU	SD
Groups A+B+C mean age (years)	9.7	3.9	9.2	3.9	10.6	3.7	8.9	4
Group A (1981-1989)	9.3	3.9	8.6	4	12.4	1.6	10.5	0
Group B (1990-1999)	9.8	3.9	9.3	3.9	11.5	3	8.7	8.8
Group C (2000-2011)	9.5	3.8	9.5	3.7	9.9	3.9	8.8	4

Children diagnosed with UC and IBDU were younger than those with CD (P<0.01 and P=0.028 respectively), CD was diagnosed at a younger age during the last decade (Group C) compare to the previous one (Group B) P=0.024

IBD, inflammatory bowel disease; SD, standard deviation; UC, ulcerative colitis; CD, Crohn's disease; IBDU, inflammatory bowel disease unclassified

Table 2 Symptoms of the total cohort and according to disease phenotypes

Symptoms at diagnosis	Total		UC		CD		IBDU		P
	n	%	n	%	n	%	n	5	
Bloody stools	393	81.37	233	87.27	121	72.46	39	79.59	0.001
Abdominal pain	216	44.72	118	44.19	75	44.91	23	46.94	0.920
Diarrhea	298	61.70	158	59.18	107	65.27	31	63.27	0.430
Vomiting	20	4.14	6	2.25	11	6.59	3	6.12	0.050
Rash	16	3.31	5	1.87	9	5.38	2	4.08	0.080
Hepatic manifestations	16	3.31	7	2.62	7	4.19	2	4.08	0.316
PSC	6	37.50	2	28.57	3	42.86	1	50.00	
AIH	3	18.75	2	28.57	1	14.29	0		
Overlapping syndrome	3	18.75	2	28.57	1	14.29	0		
Hypertransaminasemia	4	25.00	1	14.29	2	28.57	1	50.00	
Anemia	95	19.67	38	14.23	50	29.94	7	14.28	0.001
Arthritis	24	4.97	5	1.50	16	9.50	4	8.16	0.001
Fever	78	16.15	20	7.49	51	30.53	7	14.28	0.001
Weight loss	105	21.74	44	16.48	54	32.33	7	14.28	0.001
Growth retardation	31	6.42	11	4.12	18	10.77	2	3.85	0.016
Mouth manifestations	12	2.48	2	0.75	10	5.98	0		0.007
Eye manifestations	3	0.62	1	0.37	1	0.61	1	1.92	0.329

US, ulcerative colitis; CD, Crohn's disease; IBDU, inflammatory bowel disease; PSC, primary sclerosing cholangitis; AIH, autoimmune hepatitis

Table 3 Medication of the total IBD cohort and according to disease phenotype

Disease	ASAs (%)	Steroids	AZA-6MP	Cyclo	MTX	anti-TNF
Total IBD	96.6	76.99	50.22	8.01	5.98	14.01
UC	99.24	68.85	35.5	7.98	3.45	3.03
CD	91.19	94.34	76.58	8.39	9.77	31.87
IBDU	100	63.04	43.18	6.82	6.25	14.89

UC, ulcerative colitis; CD, Crohn's disease; IBDU, inflammatory bowel disease unclassified, ASAs, aminosalicilic acids; AZA, azathioprine; 6MP, 6 Mercaptopurine; Cyclo, cyclosporine; MTX, methotrexate; TNF, tumor necrosis factor

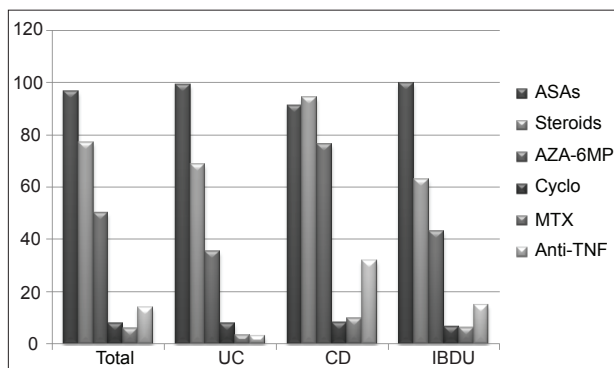


Figure 2 Medication of the total IBD cohort and according to disease phenotype

ASAs, aminosalicilic acids; AZA, azathioprine; 6MP, 6 Mercaptopurine; Cyclo, cyclosporine; MTX, methotrexate; TNF, tumor necrosis factor

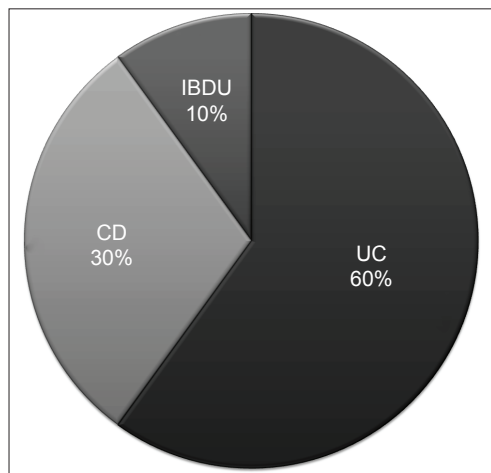


Figure 3 Percentage of surgical intervention according to disease phenotype

UC, ulcerative colitis; CD, Crohn's disease; IBDU, inflammatory bowel disease unclassified

fact that the number of children diagnosed with IBD was increased.

From the whole IBD cohort 5 children died: an 8-year-old girl with CD and B cell lymphoma who underwent bone marrow transplantation; a 9-year-old girl with UC under

immunosuppression died after varicella infection; a 3-year-old girl with UC died of shock after upper mesentery artery thrombosis and bowel ischemia; a 14-year old boy with UC since the age of 3, who developed colon cancer; and finally an 18 year-old boy with CD and primary sclerosing cholangitis who died after liver transplantation.

Discussion

In the present study a relative increase in CD with parallel relative decrease in UC during the last 2 decades was documented. Our findings are consistent with the well-established observation from other studies that the relative incidence of CD has markedly increased over the last few decades [19-21]. The reasons are unclear. It is possible that changes in the epidemiology of the disease and environmental changes contributed to the difference. Also changes in technical aspects of pediatric colonoscopy during the last decades allowed better visualization and tissue sampling of the terminal ileum together with the ability to detect small bowel involvement with MRI and videocapsule endoscopy.

The improvement in technical aspects, the increased awareness of general pediatricians and the improvement in the healthcare in our country most possibly also account for the decreased disease duration prior to diagnosis observed for CD during the last 2 decades.

Positive family history was found in 8.9% of the IBD cohort with no difference among the disease phenotypes. This finding is in accordance with that of 8.5% found in our previous study [22] where 6.1% of IBD children had a 1st degree relative with IBD and very close to that of 7% found in another Mediterranean study [23].

IBD can develop at any age. Epidemiological studies show that the peak of incidence for CD is during late adolescence or early adulthood, whereas for UC it is between 10 and 18 years of age [24,25]. Diagnosis in infancy or childhood occurs in 15-20% of cases, and there has been a significant increase in the incidence of the three forms of IBD in young people over the last 2 decades [26,27]. In our study population, children diagnosed with UC and IBDU were younger than those with CD while a significant decrease of the mean age at diagnosis of CD was observed during the last 2 decades. The aforementioned decreased time lag to diagnosis together with the decreased age at symptoms presentation probably account for the decrease of age at diagnosis observed in our cohort for CD.

Children with IBD may present with a range of symptoms, depending on the location, severity and chronicity of inflammation. Classically, CD most commonly presents with pain, diarrhea, and weight loss, whilst UC most commonly starts with bloody diarrhea [5,28]. Depending on disease location children may present with other defined gastrointestinal symptoms. Atypical or non-gastrointestinal symptoms may lead to delayed recognition and diagnosis. In contrast with other studies [7], in our cohort bloody stools was the commonest presenting symptom, followed by diarrhea

and abdominal pain for all three types of IBD, without any significant difference between them. In addition, most of the extraintestinal manifestations (arthritis, anemia, fever, weight loss, failure to thrive, mouth manifestations) were more common in children with CD than in those with UC.

The basic therapeutic goal in pediatric IBD is to induce and maintain clinical remission. The general practice for the treatment of UC prior to publication of the guidelines was for the mild UC 5-ASA, for moderate disease 5-ASA and steroids, for severe UC steroids and immunomodulators and for relapse 1st or 2nd course of steroids and immunomodulators. For newly diagnosed CD enteral feeding usually with steroids was the first line therapy together with 5-ASA when the colon was involved. A second course of steroids with immunomodulators was given in case of relapse. In severe CD enteral or parenteral feeding together with steroids and immunomodulators was used. Since 2000 the biologic agents were also introduced in the therapy in the step up manner. In few cases with fistulizing disease we used rapid step up therapy and in even fewer cases we used top down therapy.

Since 2006 the ECCO guidelines for the management of Crohn's disease were followed [29,30].

In 2012 the joint ECCO and ESPGHAN guidelines for the management of pediatric UC were published [31], which are since then followed in our department, while very recently the guidelines for management of pediatric CD have also been published [32].

In our center most of the children with IBD were treated with 5-ASA for induction and maintenance of remission. This seems to be a widespread practice reported in other studies [33,34] as well. The higher frequency of UC and the frequent use of ASAs in Crohn's colitis between 1981-2000 probably explain this observation. Corticosteroids were used to induce remission in active IBD in about three quarters of the study population. In half of our patients the disease severity and behavior indicated the use of thiopurines for maintenance of remission. Cyclosporine was used in severe UC as well as in severe CD, mainly prior to 2000, before the introduction of biologic agents, while methotrexate was mainly used in the setting of thiopurine failure or intolerance. During the last decade anti-TNF- α agents have been used for the induction and maintenance of remission in severe disease.

In addition to medical therapies, some children with IBD required surgical intervention. Indications for surgery in children with CD included disease unresponsive to medical therapy or fibrostenotic disease. In children with UC the indications for colectomy included fulminant UC unresponsive to medical therapy, severe colitis complicated by toxic megacolon or perforation and chronic colitis refractory to medical agents. Ten percent of the IBD patients underwent surgical intervention in our center, similar to previous studies [35-38].

This study shares the common disadvantages of a retrospective approach. However, it is a representative illustration of the history of pediatric IBD in Greece. As mentioned above our Pediatric Gastroenterology Unit is the largest Pediatric Gastroenterology, Hepatology and Nutrition Centre. All the pediatric IBD patients in our center, throughout

Summary Box

What is already known:

- The peak age of inflammatory bowel disease (IBD) onset is between 15 and 35 years and 10-25% of patients with IBD are diagnosed before their 18th birthday
- Certain features of IBD presenting in childhood are unique compared with adults
- Recent epidemiological studies suggest an increase in the incidence of pediatric-onset IBD, particularly for Crohn's disease (CD) over the past 10 years
- Very little data for pediatric IBD is available from Greece

What the new findings are:

- A relative increase in CD with parallel relative decrease in ulcerative colitis (UC) rates during the last two decades was documented in our Unit
- Children with UC and IBDU were younger at diagnosis than children with CD
- During the last decade a decrease of both age at diagnosis and diagnostic time lag in children with CD was found
- More than half of children with IBD required at some point treatment with steroids and immunomodulators

the last 3 decades, were managed by the same two pediatric gastroenterologists. The same two persons performed most endoscopies with the exception of the last 4 years when trainees were also implicated. The same uniformity stands also for histological assessments which were performed by only two histopathologists over the study period.

In summary, the present study describes the clinical behavior of pediatric IBD during the last 3 decades in Greece. More than half of children with IBD required at some point treatment with steroids and immunomodulators. Patients with UC and IBDU were younger at diagnosis than children with CD. During the last decade a decrease in both age at diagnosis and diagnostic time lag only in children with CD was found together with a significant increase in CD and parallel decrease in UC rates.

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