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### **Inflammatory bowel disease in children and adolescents in Italy: data from the pediatric national IBD register (1996-2003).**

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# Inflammatory Bowel Disease in Children and Adolescents in Italy: Data from the Pediatric National IBD Register (1996–2003).

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**Background:** The purpose was to assess in Italy the clinical features at diagnosis of inflammatory bowel disease (IBD) in children.

**Methods:** In 1996 an IBD register of disease onset was established on a national scale.

**Results:** Up to the end of 2003, 1576 cases of pediatric IBD were recorded: 810 (52%) ulcerative colitis (UC), 635 (40%) Crohn's

disease (CD), and 131 (8%) indeterminate colitis (IC). In the period 1996–2003 an increase of IBD incidence from 0.89 to 1.39/10<sup>5</sup> inhabitants aged <18 years was observed. IBD was more frequent among children aged between 6 and 12 years (57%) but 20% of patients had onset of the disease under 6 years of age; 28 patients were <1 year of age. Overall, 11% had 1 or more family members with IBD. The mean interval between onset of symptoms and diagnosis was higher in CD (10.1 months) and IC (9 months) versus UC (5.8 months). Extended colitis was the most frequent form in UC and ileocolic involvement the most frequent in CD. Upper intestinal tract involvement was present in 11% of CD patients. IC locations were similar to those of UC. Bloody diarrhea and abdominal pain were the most frequent symptoms in UC and IC, and abdominal pain and diarrhea in CD. Extraintestinal symptoms were more frequent in CD than in UC.

**Conclusions:** The IBD incidence in children and adolescents in Italy shows an increasing trend for all 3 pathologies. UC diagnoses exceeded CD.

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**Key Words:** inflammatory bowel diseases, incidence, clinical features, pediatric population

Inflammatory bowel diseases (IBD) include ulcerative colitis (UC), Crohn's disease (CD), and indeterminate colitis (IC). It is estimated that 20%–30% of patients experience onset of their symptoms under 20 years of age.<sup>1–4</sup> There are literature reports of cases where the diseases began before 1 year of age.<sup>5,6</sup> The pathogenesis of IBD is still unknown; environmental, genetic, and immunological factors seem to play an important role.<sup>7–11</sup>

Since the 1950s the available epidemiological data on the adult population showed an increased incidence of both

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UC and CD and, especially in North America and in Europe, a prevalence of CD. European data show that northern countries present higher rates of IBD than southern ones.<sup>12–15</sup>

The incidence of pediatric IBD varies in different countries, the highest being reported in Western countries, especially in the northern parts of America and Europe.<sup>16–20</sup> Most studies report a predominance of CD incidence over UC, although some articles indicate the contrary.<sup>7,16,21</sup> However, according to recent reports the incidence of CD is rapidly increasing, especially in young children, while the UC incidence remains stable.<sup>17,18</sup>

Due to the lack of studies on pediatric patients affected by IBD in Italy, the Italian Society of Pediatric Gastroenterology, Hepatology and Nutrition (SIGENP) established a National Register of Pediatric IBD in order to define demographics, disease distribution at diagnosis, clinical presentation, and family history in Italian children and adolescents.

## MATERIALS AND METHODS

### Study Setting

In 1996 the SIGENP IBD Study Group started an IBD register of pediatric and juvenile onset on a national scale. It was established to input data at the time of diagnosis of IBD patients whose symptoms began before 18 years of age. A summary file of data from every patient at the time of diagnosis was developed. Data collected included: gender, age at onset of symptoms, age at diagnosis, type of disease (CD, UC, IC), symptoms, locations, and family history for IBD. One center was chosen for collecting data and coordinating the study.

All 40 centers of pediatric gastroenterology present in Italy distributed all over the national territory participated. The first phase of the register was retrospective and the participating centers were invited to collect data of patients diagnosed before 1996 from their medical records. A second prospective phase consisted of the compilation of a file for each new diagnosis. All centers could fill out the forms online. Data were protected by a username and a password different for each participant so that each had the possibility to access, modify, and insert data concerning their own patients. Initials, date, and place of birth of each patient helped to avoid registration of the same patient by more centers.

### Criteria of IBD Diagnosis

The IBD diagnosis was based on clinical history, physical examination, radiological studies, endoscopy, and histology, as previously reported.<sup>22–25</sup> All patients underwent upper and lower (up to the terminal ileum) endoscopy with multiple pinch biopsies and histologic assessment of mucosal specimens.

CD was defined by evidence of a discontinuous chronic inflammation of the gastrointestinal tract with or without

granulomas and supported by clinical, biochemical, and radiological evidence.

UC was defined by the presence of continuous inflammation limited to the colon with histologically typical chronic inflammation limited to the mucosa.

IC was defined as inflammatory colitis with endoscopic and histologic findings that were consistent with both CD and UC. In addition, such patients did not present any evidence of small bowel disease at the time of diagnosis.

Our study analyzed data from files entered up to December 31, 2003.

### Statistical Analysis

A chi-square test was applied for category data; 1-way analysis of variance (ANOVA) was performed to compare multiple comparisons of continuous variables with Bonferroni post-hoc test. Significance was set at  $P < 0.05$ . SPSS v. 11.0 (Chicago, IL) was used for statistical analysis.

## RESULTS

### Population Characteristics

Up to the end of 2003 data from 1576 patients were entered into the register. The majority (99%) were Caucasian, only 15 were immigrant children born abroad. Out of them, 810 patients (52%) had UC (365 males and 445 females, M:F ratio 0.82), 635 (40%) had CD (344 males and 291 females, M:F ratio 1.18), and 131 (8%) were registered as affected by IC (77 males and 54 females, M:F ratio 1.42). The M:F ratio of all patients with IBD was 0.99. The M:F ratio was lower in UC patients, higher in those with IC, while its value was intermediate in CD patients. This distribution was significantly different from a random one.

Furthermore, we divided the patients into 3 groups based on age of onset of symptoms: group 1 from 0–5 years, group 2 from 6–12, and group 3 from 13–18. Sixty-four percent of patients in the first group were diagnosed as affected by UC, while patients diagnosed with IBD belonging to the second and third groups were equally affected by UC and CD, with a slight predominance of UC diagnoses in the second group and a slight predominance of CD in the third group (Table 1). IC was most prevalent in patients of the first age group (14.5%) and declined with increasing age. The highest number of cases of IBD was observed in the second age group ( $n = 905$ , 57%).

The mean interval from onset of symptoms to diagnosis was higher in patients affected by CD and IC compared to that observed in patients with UC, although this difference was not statistically significant. We observed that the mean interval from onset of symptoms to diagnosis decreased with an increase of the patients' age (Table 1).

Figure 1 reports the number of new diagnoses of UC, CD, and IC/year. The total number of new diagnoses/year is

**TABLE 1.** Mean Age at Onset of Symptoms at Diagnosis and Diagnostic Delay for the 3 Diseases

	UC (810 Patients)	CD (635 Patients)	IC (131 Patients)	UC vs CD	UC vs IC	CD vs IC
Mean age at onset (years)	9.2 (± 4.2)	10.6 (± 3.6)	8.2 (±4.6)	<i>P</i> < 0.001	<i>P</i> = 0.07	<i>P</i> < 0.001
median	9.4	11.1	8.6			
Mean age at diagnosis (years)	9.6 (± 4.1)	11.5 (± 3.5)	8.9 (± 4.6)	<i>P</i> < 0.001	<i>P</i> = 0.3	<i>P</i> < 0.001
median	9.9	11.7	9.2			
Latency period between onset of symptoms and diagnosis (months)	5.8 (± 10.5)	10.1(± 17)	9 (±17.5)	<i>P</i> = 0.2	Ns	Ns
Median	2	4	4			

in continuous increase. The total number of UC diagnoses is greater than CD, even if in 2000 and 2003 the number of CD were slightly higher than UC. There was an increase of the overall incidence in the 3 diseases that rose from 0.89/10<sup>5</sup> inhabitants under 18 years of age in 1996 to 1.39/10<sup>5</sup> in 2003. This increase was evident in each disease. From 1996 to 2003 the Italian population aged <18 years was about 10.5 million and remained stable for the entire period.

**Familial Incidence**

Family history was reported in 1470 forms. Overall, a positive family history of IBD was found in 162 patients (11%) (Table 4). Family history of UC was reported in 88% of patients affected by UC, while 59% of relatives of patients with CD were affected by the same disease; therefore, a high concordance between the type of disease of the patients and the type of disease of their relatives was observed.

**Clinical Presentation**

Tables 2–4 report the locations of the lesions at diagnosis in the 3 types of disease. Almost half of the patients affected by

UC had a diffused form (pancolitis plus colitis extended to the transverse colon), while only 7% of the patients had a colitis limited to the rectum. The most frequent location in patients affected by CD was the ileocolic one. Upper intestinal tract involvement was present in 11% of CD patients. The IC extensions were similar to those of UC.

No differences on the diseases extensions and locations were observed in the 3 age groups (Tables 2–4). The most frequent intestinal and extraintestinal manifestations at time of diagnosis are reported in Table 5. The presence of blood in the feces and abdominal pain were the most common features in UC and IC patients, whereas abdominal pain and diarrhea, not always with blood, were the most frequent symptoms in CD patients. Perianal disease and fistulas were more common in CD patients compared to UC and IC ones. Extraintestinal manifestations at the time of diagnosis were more frequently present in CD patients. In particular, loss of weight was present in 50%, fever in 40%, anemia in 24%, asthenia in 18%, and joint involvement in 22% of CD patients.

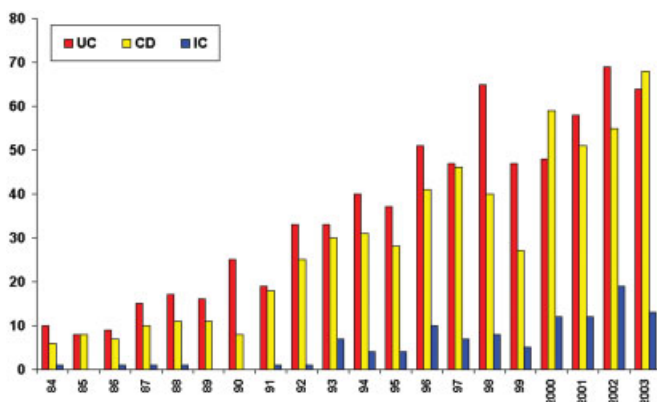
Table 6 reports the associated diseases: hepatic involvement was present in 5.2% of the patients and it was more frequently observed in those affected by UC. Sclerosing cholangitis was more frequent in UC patients (6%), whereas in CD it was present in only 2 patients.

**DISCUSSION**

This study reports the clinical features of a large cohort of pediatric Italian patients with IBD. As all Italian pediatric gastroenterology centers participated in the study, we can consider these data representative of the whole country.

In our study the number of UC diagnoses is higher than CD (52% versus 40%) and these data are in contrast with the ones reported in the Anglo-Saxon literature, but it agrees with previous studies in the adult Italian population.<sup>26,27</sup>

We noticed a prevalence of females in UC, whereas more males had CD. Our data agree with other studies that also reported a significantly higher percentage of males compared with females with CD.<sup>17</sup> Conversely, this finding con-



**FIGURE 1.** New diagnoses/year for the entire group of patients, divided for type of disease. [Color figure can be viewed in the online issue, which is available at [www.interscience.wiley.com](http://www.interscience.wiley.com).]

**TABLE 2.** UC: Locations at Diagnosis in the 3 Age Groups

Locations	0–5 Years	6–12 Years	13–18 Years	Total
Pancolitis	85 (42%)	165 (37%)	65 (40%)	315 (39%)
Up to transverse colon	16 (25%)	49 (11%)	16 (10%)	81 (10%)
Up to left colon	39 (19%)	109 (24%)	39 (24%)	187 (23%)
Up to sigmoid colon	51 (25%)	88 (20%)	31 (19%)	170 (21%)
Rectum	12 (6%)	34 (8%)	11 (7%)	57 (7%)
Total	203 (100%)	445 (100%)	162 (100%)	810 (100%)

trasts with previous studies, which have reported a slight female preponderance in CD.<sup>12</sup>

We also observed that IBD was more frequent in patients aged 6–12 years (57%) and this is in accordance with that reported by Turunen et al.<sup>21</sup> It should be underlined that 20% of our population had onset of their symptoms under 6 years of age. Moreover, 28 patients (1.8% of total) had a diagnosis of IBD before 1 year of age (11 affected by UC, 10 by CD, and 7 by IC).

IC diagnoses were more frequent in children aged 0–5 years (more than double that observed in older children). Other authors report a higher incidence of IC diagnoses in younger patients,<sup>21,22,28</sup> and these data reflect the difficulties in the primary diagnosis of IBD in very young children. However, the IC incidence we observed is similar to that indicated in other pediatric studies that report that IC accounts for 10%–15% of newly diagnosed patients with IBD.<sup>29,30</sup>

Our study shows a rising incidence of pediatric IBD in Italy (1.39/10<sup>5</sup> inhabitants aged < 18 years in 2003 versus 0.89 in 1996). The incidence increase was observed in all 3 diseases. The pediatric IBD incidence in Italy is remarkably lower than the previous ones reported in other European countries,<sup>16,18–21</sup> as well as North America.<sup>17</sup> In this study all 40 centers of pediatric gastroenterology in Italy, spread all over the nation, participated and this guarantees that the data

collected are representative of the whole country and included all pediatric patients with IBD. This is because IBD in Italy is recognized as a social disease and pediatric patients affected by IBD (the pediatric age in Italy is up to 18 years) need to have their diagnosis certified by official pediatric gastroenterology centers.

As reported in other surveys, the mean interval from onset of symptoms and diagnosis is higher in patients affected by CD and IC compared to that observed in patients with UC, although this difference is not statistically significant. In particular, it should be underlined that in children under 6 years of age the diagnosis of CD was made with an average delay of 22 months, more than double compared to the other 2 age groups. Such delay can be explained by the objective difficulties to diagnose CD and by the necessity of an accurate differential diagnosis with other more frequent pathologies in younger children.

Eleven percent of total patients had a positive family history for IBD among first-degree relatives. Such data tally with those reported by other authors,<sup>18</sup> while it is much lower than that reported by Heyman et al,<sup>22</sup> who report a significantly higher incidence in the group of patients under 2 years of age affected by UC. Conversely, in our study we have not noticed any significant difference regarding the IBD family history in the 3 age groups among patients affected by UC, while in CD its frequency results was much lower in younger

**TABLE 3.** CD: Locations at Diagnosis in the 3 Age Groups

	0–5 Years	6–12 Years	13–18 Years	Total
Ileocolon	28 (40%)	193 (48%)	90 (55%)	311 (49%)
Colon	24 (34%)	91 (23%)	37 (22%)	152 (24%)
Terminal ileum	9 (13%)	46 (12%)	9 (5%)	64 (10%)
Ileum	3 (4%)	29 (7%)	8 (5%)	40 (6%)
Ileum-colon-upper intestinal tract	4 (6%)	25 (6%)	10 (6%)	39 (6%)
Ileum-upper intestinal tract	1 (1.5%)	7 (1.75%)	6 (4%)	14 (2%)
Colon-upper intestinal tract	0	8 (2%)	4 (2.4%)	12 (2%)
Upper intestinal tract	1 (1.5%)	1 (0.25%)	1 (0.6%)	3 (1%)
Total	70 (100%)	400 (100%)	165 (100%)	635 (100%)

**TABLE 4.** IC: Location of Disease at Diagnosis

	0–5 Years	6–12 Years	13–18 Years	Total
Pancolitis	14 (31%)	23 (36%)	8 (37%)	45 (34%)
Up to transverse colon	3 (7%)	4 (6%)	4 (18%)	11 (9%)
Up to left colon	13 (29%)	18 (28%)	4 (18%)	35 (27%)
Up to sigmoid colon	15 (33%)	12 (19%)	2 (9%)	29 (22%)
Rectum	0	7 (11%)	4 (18%)	11 (9%)
Total	45 (100%)	64 (100%)	22 (100%)	131 (100%)

patients. IC younger patients presented a higher frequency of positive family history of IBD. Furthermore, as far as family history is concerned, we observed a concordance of pathology, higher for UC (88%) than for CD (59%).

Extended colitis (pancolitis and colitis extended up to transverse colon) was the most frequent in both UC and IC, as well as the ileocolic form of CD, thus confirming the higher severity of such diseases in children.

Our data of extended colitis (49%) in our patients with UC are more consistent with the data reported by Hyams et al,<sup>3</sup> who report pancolitis in 43% of a series of 171 patients affected by UC. These data are much lower than that reported

by Kugathasan et al,<sup>17</sup> who report an incidence of pancolitis equal to 90% of their cases affected by UC at the time of diagnosis. Ileocolic location was the most frequent one in our CD patients, contrary to that reported by other authors who indicated Crohn-colitis as the most frequent location in pediatric patients.<sup>18</sup>

No differences were observed with what is reported in the literature on intestinal and extraintestinal symptoms. Half of our CD patients at the time of diagnosis presented with weight loss, thus confirming that reported in other studies.<sup>31,32</sup> Joint involvement was present with a frequency twice that reported in the adult population affected by IBD.<sup>33,34</sup>

**TABLE 5.** IBD: Intestinal Symptoms

	UC: 810 Patients	CD: 635 Patients	IC: 131 Patients
<u>Intestinal</u>			
Bloody diarrhea	481 (59.5%)	170 (26.8%)	52 (39.4%)
Abdominal pain	403 (49.85%)	428 (67.4%)	61 (46.2%)
Rectal bleeding	378 (46.66%)	110 (17.32%)	65 (49.6%)
Chronic diarrhea	131 (16.2%)	238 (35.7%)	24 (18.2%)
Tenesmus	83 (10.3%)	18 (2.8%)	14 (10.6%)
Abdominal distention	22 (2.7%)	19 (3.0%)	6 (4.5%)
Vomiting	17 (2.1%)	56 (8.8%)	8 (6.1%)
Fecal occult blood	17 (2.1%)	29 (4.6%)	5 (3.8%)
Perianal disease	22 (2.7%)	94 (14.8%)	7 (5.3%)
Oral aphthous ulcers	17 (2.1%)	63 (9.9%)	3 (2.3%)
Constipation	10 (1.2%)	12 (1.9%)	1 (0.8)
Acute abdomen	2 (0.2%)	26 (4.1%)	21 (1.5%)
Fistulas	3 (0.4%)	41 (6.5%)	
Subocclusion	2 (0.2%)	13 (2.0%)	1 (0.8%)
<u>Extraintestinal</u>			
Weight loss	167 (20.6%)	318 (50.1%)	23 (17.4%)
Anemia	142 (17.6%)	151 (23.8%)	18 (13.6%)
Asthenia	51 (6.3%)	117 (18.4%)	14 (10.6%)
Joint pain	55 (6.8%)	143 (22.5%)	9 (6.9%)
Fever	102 (12.6%)	257 (40.5%)	17 (12.9%)
Anorexia	39 (4.8%)	125 (19.7%)	76 (5.3%)
Ocular disease	6 (0.7%)	11 (1.7%)	0

TABLE 6. IBD: Associated Diseases

	UC (810 Patients)	CD (635 Patients)	IC (131 Patients)	Total (1576 Patients)
Sclerosing cholangitis	49 (6%)	2 (0.3%)	5 (3.8%)	56 (3.5%)
Autoimmune hepatitis	11 (1.35%)	4 (0.6%)	0	15 (0.95%)
High levels of hepatic enzymes	10 (1.2%)	2 (0.3%)	1 (0.76%)	13 (0.82%)
Celiac disease	7 (0.86%)	1 (0.15)	0	8 (0.5%)
Cystic fibrosis	0	4 (0.62%)	0	4 (0.31%)
Pancreatitis	1 (0.12%)	4 (0.62%)	0	5 (0.31%)
Cerebral vascular disorders	4 (0.5%)	0	0	4 (0.25%)
Developmental delay	4 (0.5%)	4 (0.62%)	1 (0.76%)	9 (0.57%)
Kidney stones	3 (0.37%)	2 (0.3%)	1 (0.76%)	6 (0.38%)

Hepatic involvement was present in 5.25% of total IBD patients and it was more frequent in UC. Sclerosing cholangitis was more frequent in UC patients (6%). With regard to the 5 patients registered as affected by both IC and sclerosing cholangitis, most probably a further evaluation might reclassify them as affected by UC.

In conclusion, our study indicates that also in Italy there has been a progressive increase of IBD diagnoses in the pediatric population. Diagnoses of UC are prevalent when considering the series in toto, even if in the last years CD diagnoses were slightly higher than UC. The IC incidence we report (8%) is lower than that recently reported by other studies.<sup>17,20,22</sup> It should be pointed out that, compared to other series, the Italian experience reports a high frequency of IBD cases with an onset of symptoms in the first years of life (20% of total cases) without differences in the locations at the diagnosis in younger patients compared to older ones.

In summary, our study confirms the rising incidence of IBD in Italy. The number of total diagnoses of UC is higher than that of CD, in contrast with the data reported in the literature. However, our data agree with that of the adult IBD population reported by Italian gastroenterologists.

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