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Original Article

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Pediatric Inflammatory Bowel Disease: A Multicenter Study of Changing Trends in Argentina Over the Past 30 Years

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ABSTRACT

Purpose: To analyze the characteristics of pediatric inflammatory bowel disease (IBD) over the past three decades in Argentina and determine if there are differences between the first two decades and the past decade.
Methods: We conducted a retrospective multicenter analytical study in children with IBD between 0 and 18 years of age diagnosed between 1987 and 2017 in three tertiary health centers in Argentina. The evaluation included clinical characterization, endoscopy, histology, and imaging data together with therapeutic strategies. The patients were divided into two groups: Group 1, diagnosed between 1987 and 2007, and Group 2, diagnosed between 2008 and 2017.
Results: Of the 756 patients included, 409 (54%) had ulcerative colitis (UC), 250 (33%) had Crohn's disease (CD), and 97 (13%) had IBD-unclassified (IBD-U). The positive family history was 3.8%, which was more frequent among children under two years of age (6.7%). There were no significant differences in clinical presentation and extraintestinal manifestations between periods, with hepatic manifestations being the most frequent. In the last decade, we found an upward trend in CD, a downward trend in UC/IBD-U, even after adjustment for socioeconomic status, and a decrease of 50% in surgical treatments coinciding with the advent of biological therapy.
Conclusion: This is the first multicenter cohort study in a Latin American country to describe clinical, endoscopic, and therapeutic data across the past 30-year period. Although CD was responsible for the overall increase in incidence, UC was still prevalent in this region.

Keywords: Crohn disease; Ulcerative colitis; Inflammatory bowel disease

INTRODUCTION

The global incidence of inflammatory bowel disease (IBD) varies greatly among different geographical areas, with the highest rates in Europe and North America [1,2]. However, the overall trend over time shows a worldwide increase in prevalence and incidence in the general

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Conflict of Interest
The authors have no financial conflicts of interest.

population [1,2], as well as in the pediatric population [3-8]. More specifically, the incidence of Crohn's disease (CD) has increased significantly in several countries, with most studies reporting a stable incidence of pediatric-onset ulcerative colitis (UC) between 1950 and 2009 [2]. In Latin America, particularly Argentina, the incidence of IBD is less than 0.4/100,000 people in children under 18 years of age [9]. A recent publication by the Latin American Society of Pediatric Gastroenterology, Hepatology, and Nutrition [10] showed the results of a survey by Latin American pediatric gastroenterologists who followed patients with IBD between 2005–2016 and found that pediatric IBD in this region appears to have increased with a predominance of moderate or severe UC. Their perception is that the incidence of IBD follows a course similar to that of Western countries in the Northern Hemisphere, although with a delay by a few decades. However, there are no recent publications on the topic of Latin American populations; therefore, it would be desirable to have a greater number of epidemiological studies to document the trend of pediatric IBD in our environment [11].

This study aimed to evaluate the demographic and phenotypic characteristics of pediatric IBD over the last 30 years (1987–2017) in three reference centers in Argentina, and the overall trends of UC, CD, and total IBD.

MATERIALS AND METHODS

A multicenter, observational, descriptive study of a retrospective cohort of pediatric patients with IBD was performed. The intervening centers were Hospital Juan P. Garrahan, Hospital de Niños Ricardo Gutiérrez, and Hospital Italiano de Buenos Aires. These are tertiary health centers; the first two centers are pediatric hospitals in the public health system, while the third center is a private university general hospital. The first national pediatric IBD registry was conducted in Argentina in 2017 [9]; 70% of the patients recruited were followed up with in one of these three centers. In addition, although these three hospitals were located in Buenos Aires City, only 13 (37%) lived in the city, while the rest lived in other regions across the country. Therefore, it can be inferred that most patients in our country are followed up with at these three referral centers.

Population

Patients between 0 and 18 years of age diagnosed with IBD between January 1, 1987 and December 31, 2017 were included. Our population was mainly Caucasian (European immigration), with a small proportion of the indigenous population. It is noteworthy that, unlike other Latin American countries, there is no strong representation of the Afro-American population, and very little representation of Asian origin. The diagnosis was made according to the Porto criteria [12] and the revised Porto Criteria [13], comprising clinical, laboratory, endoscopic (ileocolonoscopy and esophagogastroduodenoscopy), histological, and imaging study data (with radiologic contrast imaging of the small bowel, enterotomography, magnetic resonance enterography, or wireless capsule endoscopy in the earlier years of the study) of patients with symptoms compatible with IBD for more than four weeks. Patients with infections, malformations, tumors, and other causes of acute or chronic enteritis and colitis were excluded.

In some cases, the original diagnosis was modified during the course of the illness, due to either disease progression or changes in diagnostic criteria [12,13]. If the patient was reclassified over time, the final diagnosis was used for statistical calculations.

Specialists in each unit analyzed the medical records and translated to a spreadsheet in compliance with the protection of personal data. The information recorded included sex, type of disease, age at symptom onset, age at diagnosis, diagnostic delay, family incidence, clinical presentation, extradigestive manifestations, extension and clinical characteristics, medical treatments received, need for surgery, and diagnostic reclassification during follow-up. Patients from the study period between 1987 and 2017 were divided into two groups: Group 1 with patients diagnosed between 1987–2007 (G1) and Group 2 with patients diagnosed between 2008-2017 (G2). The period was arbitrarily divided according to two points in time when data collection was carried out (after 20 and 30 years of registration).

Statistical analysis

For the description of the quantitative data, median and a 25–75 interquartile range were used, while for qualitative data, absolute and relative frequencies in percentages were used. For comparisons between groups for the type of IBD, decade, and age group, the Wilcoxon test was used, while the Chi2 or Fisher test was used for quantitative data, according to assumptions. A statistical significance level of less than <0.05 was considered. R Software Version 4.0.2 was used.

The crude and adjusted prevalence of UC and CD was estimated annually between 1996 and 2017, and this period was selected because of the presence of a sufficient number of cases to perform standardization; the denominator was the total number of patients with IBD. Standardization by age was direct, using the sum of the population over all years as the standard population. Prevalence was expressed per 100 patients with IBD, with a 95% confidence interval (95% CI).

Trends in UC and CD were assessed using the Joinpoint Regression Program 4.5.0.1 (National Cancer Institute, Bethesda, MD, USA). This analysis fits joined straight lines on a logarithmic scale to the observed annual rates and estimates the annual percentage change (APC) for each line segment. For this analysis, the default settings of the joinpoint software were applied: a maximum of one joinpoint was allowed for 11 years of data. APC was reported with a 95% CI to capture changes in the trends. Trends were described as “increasing” or “decreasing” when the APC was statistically different from zero at an alpha value of 0.05. Trends that did not meet this value were considered “stable”.

The study was approved by the Ethics Committees of each participating hospital (Hospital Italiano de Buenos Aires, Hospital de Niños Ricardo Gutierrez, Hospital de Pediatría S.A.M.I.C. “Prof. Dr. Juan P. Garrahan”; approval no. 3952).

RESULTS

A total of 756 patients were included: 409 (54%) with UC, 250 (33%) with CD, and 97 (13%) with IBD-unclassified (IBD-U). The overall UC:CD ratio was 2:1, and the male-to-female ratio was 1.21:1.

First-degree affected family history accounted for 3.8% of the entire population. The proportion of patients with affected family members was significantly greater in the infantile-onset age group (under two years of age, 6.7%) than in the rest of the patients.

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During the course of the disease, 28% of patients presented with at least one extra-intestinal manifestation. The three most common diagnoses were peripheral arthritis (7%), sclerosing cholangitis (7%), and autoimmune hepatitis (8.6%). Hepatobiliary complications occurred in 143/756 (18.9%) patients, while 13/143 (1.7%) required transplantation, and no cholangiocarcinomas were reported.

The clinical presentation, extraintestinal manifestations, and treatment by disease group are shown in **Table 1**. Colon cancer was a complication in three patients with CD and in one patient with UC.

Analysis by groups

Descriptions by decade (G1 and G2) are presented in **Table 2**. The Paris and Montreal classifications according to disease group and period are presented in **Table 3** [14,15].

There were no significant differences between the groups in terms of symptomatology and associated extraintestinal manifestations. Only three patients in G1 and one patient in G2 developed colon adenocarcinoma.

Trend analysis

The trend of the adjusted prevalence of UC/IBD-U showed a reduction in annual prevalence, with an APC of −2.5% (95% CI −3.9, −1.1; p<0.001), and an adjusted trend of CD with an increase in annual prevalence in APC of 7.1% (95% CI 4.6, 9.8; p<0.001) (**Fig. 1**). No joint points were observed.

Table 1. Clinical presentation, extraintestinal manifestations, and treatment by diagnosis

Variable	UC/IBD-U (n=506, 67%)	CD (n=250, 33%)	p-value
Sex, male	261 (51.6)	153 (61.2)	0.015
Median age at diagnosis (y)	10.00 (5.68, 13.00)	10.03 (5.52, 13.07)	0.926
First degree family history	15 (3.0)	14 (5.6)	0.116
VEO-IBD	128 (25.3)	64 (25.6)	0.999
Clinical presentation			
Abdominal pain	308 (60.9)	175 (70.0)	0.017
Bloody diarrhea	370 (73.1)	136 (54.4)	0.001
Chronic diarrhea	175 (34.6)	132 (52.8)	0.001
Weight loss	138 (27.3)	114 (45.6)	0.001
Pubertal delay	16 (3.2)	17 (6.8)	0.035
Fever	51 (10.1)	52 (20.8)	0.001
Perianal disease	13 (2.6)	34 (13.6)	0.001
Oral aphthae	20 (4.0)	31 (12.4)	0.001
Classic triad (chronic diarrhea, abdominal pain and weight impairment)	91 (18.0)	96 (38.4)	0.009
Extraintestinal manifestations	135 (26.7)	78 (31.2)	0.160
Peripheral arthritis	25 (4.9)	28 (11.2)	0.003
Autoimmune hepatitis	49 (9.7)	16 (6.4)	0.407
Treatment			
Salicylates	479 (94.7)	214 (85.6)	<0.001
Corticotherapy	362 (71.5)	192 (76.8)	0.147
Thiopurines	164 (32.4)	162 (64.8)	<0.001
Biological treatment (Anti-TNF)	60 (11.9)	72 (28.8)	<0.001
EEN	4 (0.8)	30 (12.0)	<0.001
Colectomy - ileoanal pouch anastomosis	31 (6.1)	0 (0)	<0.001
Colectomy - ileostomy	5 (1.0)	8 (3.2)	0.003
Stricture resection	0 (0)	5 (2.0)	<0.001
Perianal surgery	0 (0)	2 (0.8)	<0.001

Values are presented as number (%) or median (25–75 interquartile range).
IBD: inflammatory bowel disease, UC: ulcerative colitis, IBD-U: IBD-unclassified, CD: Crohn's disease, VEO-IBD: very early onset inflammatory bowel disease (<6 years), Anti-TNF: anti tumor necrosis factor, EEN: exclusive enteral nutrition.

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Table 2. Clinical presentation, extraintestinal manifestations, and treatment by period

Variable	G1 (n=445, 58.9%)	G2 (n=311, 41.1%)	*p*-value
UC and IBD-U	335 (75.3)	171 (55.0)	<0.001
CD	110 (24.7)	140 (45.0)	<0.001
Sex, male	248 (55.7)	166 (53.4)	0.572
Median age at diagnosis (y)	10 (6, 13)	10 (5, 13.27)	0.925
VEO-IBD	106 (23.8)	86 (27.7)	0.269
Median delay at diagnosis (mo)	18 (5–43)	10 (5–22)	<0.001
First degree family history	21 (4.7)	8 (2.6)	0.187
Public health system	319 (71.7)	212 (68.2)	0.570
Clinical presentation			
Abdominal pain	282 (63.4)	201 (64.6)	0.781
Bloody diarrhea	292 (65.6)	214 (68.8)	0.401
Chronic diarrhea	203 (45.6)	104 (33.4)	0.001
Weight loss	163 (36.6)	79 (25.4)	0.001
Perianal disease	27 (6.1)	20 (6.4)	0.960
Extraintestinal manifestations	125 (28.1)	87 (28.0)	0.486
Peripheral arthritis	36 (8.1)	17 (5.5)	0.213
Central arthritis	12 (2.7)	3 (1.0)	0.157
Sclerosing cholangitis	32 (7.2)	21 (6.8)	0.029
Autoimmune hepatitis	31 (7.0)	34 (10.9)	0.093
Treatment			
Salicylates	420 (94.4)	272 (87.5)	0.001
Corticotherapy	308 (69.2)	246 (79.1)	0.001
Thiopurines	119 (26.7)	207 (66.6)	<0.001
Biological treatment (Anti-TNF)	18 (4.0)	114 (36.7)	<0.001
EEN	10 (2.2)	24 (7.7)	0.001
Bowel resection	45 (10.1)	16 (5.1)	<0.001
Liver transplantation	9 (2.0)	4 (1.3)	0.200

Values are presented as number (%) or median (25–75 interquartile range).
G1: Group 1 - patients diagnosed with inflammatory bowel disease (IBD) between 1987–2007, G2: Group 2 - patients diagnosed with IBD between 2008–2017, UC: ulcerative colitis, IBD-U: IBD-unclassified, CD: Crohn's disease, VEO-IBD: very early onset inflammatory bowel disease (<6 years), Anti-TNF: anti tumor necrosis factor, EEN: exclusive enteral nutrition.

Table 3. Paris and Montreal classification by pathology and period

IBD pathology	UC/IBD-U			CD		
Period	G1: 335	G2: 171	Total: 506	G1: 110	G2: 140	Total: 250
Anatomical location*	E1: 25 (7)	E1: 41 (24)	E1: 66 (13)	L1: 14 (13)	L1: 18 (13)	L1: 32 (13)
	E2: 56 (17)	E2: 30 (17)	E2: 86 (17)	L2: 30 (27)	L2: 58 (41)	L2: 88 (35)
	E3: 253 (76)	E3: 101 (59)	E3: 354 (70)	L3: 54 (49)	L3: 49 (35)	L3: 103 (41)
Disease phenotype*	N/A			L4: 12 (11)	L4: 15 (11)	L4: 27 (11)
				B1: 84 (76)	B1: 116 (83)	B1: 200 (80)
				B2: 5 (5)	B2: 15 (11)	B2: 20 (8)
				B3: 21 (19)	B3: 9 (6)	B3: 30 (12)
Severity at onset†	S1: 129 (39)	S1: 89 (52)	S1: 218 (43)	N/A		
	S2: 163 (48)	S2: 59 (35)	S2: 222 (44)			
	S3: 43 (13)	S3: 23 (13)	S3: 66 (13)			

Values are presented as number (%).
G1: group 1 - patients diagnosed with inflammatory bowel disease (IBD) between 1987–2007, G2: group 2 - patients diagnosed with IBD between 2008–2017, UC: ulcerative colitis, IBD-U: IBD-unclassified, CD: Crohn's disease, N/A: not applicable.
*According to the Paris classification for IBD [14]. †According to the Montreal classification for IBD [15].

DISCUSSION

In contrast to what has been reported for Europe [16] and North America, we found that the most common diagnosis of IBD continues to be UC, in agreement with the findings of previous Latin American and Italian publications [11,17]. This was also highlighted by previous studies, which indicated that UC was more common in Hispanics than CD [18].

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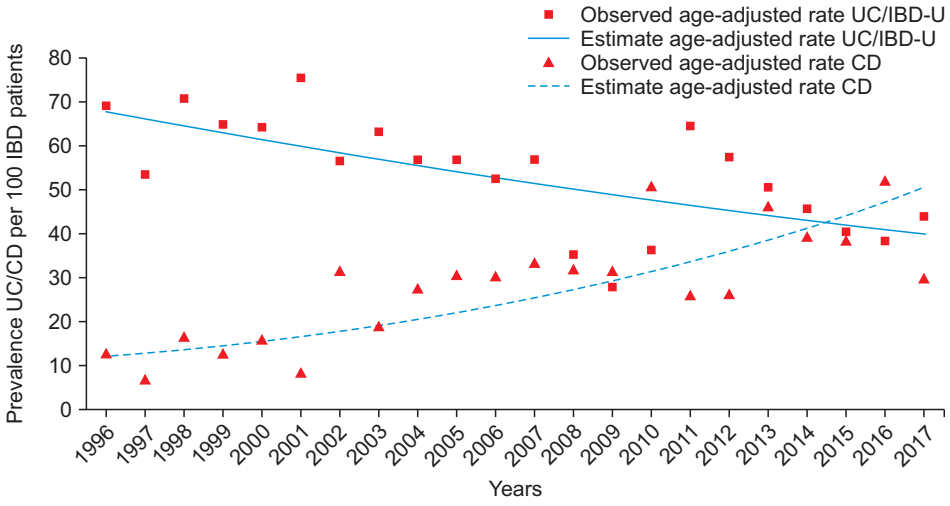

Fig. 1. Trend of the last 20 years of age-adjusted UC-IBD-U/CD.
IBD: inflammatory bowel disease, UC: ulcerative colitis, IBD-U: IBD-unclassified, CD: Crohn's disease.

The etiology underlying the phenotypic differences identified between the groups may be multifactorial. Changes in the environment are likely to underlie whether the primary phenotypic manifestations are CD or UC. In addition, Hispanics have a lower frequency of mutations in CARD15 in CD [19]. To identify these environmental factors, careful dietary and microbiome studies in combination with genetic studies are necessary.

However, CD is beginning to show an upward trend in some regions [10]. This coincides with Italian, Chilean, and US Hispanic population data [20], with data from Spain showing 1996–2009 had tripled the incidence of IBD tripled with the greatest increase in CD [21]. This could be explained by the strong immigration wave that arrived in Argentina and Chile during the first half of the 20th century, especially from Italy and Spain. Genetic and food similarities would be greater than those of Scandinavian, English, or North American populations. Recent publications have shown that the Mediterranean diet in Southern Europe is associated with a lower risk of late-onset CD [22].

Regarding sex, we found a significant predominance of males in the CD group, whereas in the UC and IBD-U groups, there were no gender differences. These findings are in agreement with pediatric population-based studies from various countries, where the average male-to-female ratio was 1.5:1 for CD and close to 1 for UC. Sex differences remain a distinctive feature of this pathology in the adult population. Castro et al. [17] found similar data regarding age at diagnosis in the First National IBD Registry conducted in Italy between 1996 and 2003. Even if the proportion of patients with very early onset (VEO-IBD) did not change over time in the groups evaluated, the percentage of patients was higher than in that of other international publications (6–15%) [23], and was highest in the first decade. One possible explanation is that symptoms such as intestinal bleeding, chronic diarrhea, or growth impairment in young children have always been alarm signals leading to consultation with a pediatric gastroenterologist and early diagnosis. However, when these symptoms appear in older children in Argentina, infectious causes, such as intestinal parasitosis or celiac disease common to Argentina, should always be ruled out first. Another distinctive feature of our population was that we found a lower proportion of family relatives with IBD (3.8%), which is in contrast to other populations that reported a positive family history of 11–29% [22,24]. In CD, it is reported that first-degree relatives have 12–15 times higher risk of developing CD than in the general population [1]. In our

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population, we did not find this association, but it may occur in the future, as CD has an upward trend, and it is likely that the association may increase as the patients start to have offspring.

We found no differences in clinical presentation compared with those reported in the literature. As a distinctive feature, the higher number of cases with liver involvement in our cohort is noteworthy; while it usually occurs in fewer than 5% of cases, it was almost four times more frequent, ranking first among the extraintestinal manifestations. This could be related to the phenotype of the disease in our region, as liver disease is associated more with UC, specifically pancolitis, most patients with a mild-to-moderate onset. Arthritis is usually the most frequent extraintestinal manifestation in the literature [24]; in our case, it ranked second. Peripheral arthritis was significantly more common, confirming what has been described by other authors [22,25,26], and it was more frequent in CD. Upper gastrointestinal tract involvement, another peculiar aspect of pediatric IBD, remained low in our cohort at 10-11% of cases, which is similar to that reported by Kugathasan et al. [27] in the Wisconsin population-based study.

Some hypotheses have been proposed to justify this linear increase in IBD in recent decades. Although it is true that there is greater clinical suspicion among pediatricians and specialists, there is also better and more accessible technology and diagnostic methodology, which may facilitate diagnosis. Researchers tend to assume that environmental factors determine the epidemiological changes occur in pediatric IBD [28]. The hygiene theory postulates that due to "westernization," there is a lower microbial exposure in early childhood, and a consequent lack of tolerance of the immune system in the following years [29]. In turn, the concomitant emergence of chronic inflammatory pathologies involving other organs, such as asthma, reinforces the probable role of the environment in these disorders. Similar results have been reported in Spain, where pediatric IBD incidence is remarkably lower than those reported in other European countries as well as in North America, but the incidence trends observed seem equivalent to those observed in those countries [30]. Likewise, there has been a change in disease patterns; when evaluating the last two decades, it is clear that there is an upward trend in CD and a downward trend in UC/IBD-U. The socioeconomic status of the patients did not play a role in the observed trend. Our results show that over the past three decades, the proportion of patients with lower economic resources treated in public hospitals and patients with socioeconomic levels affording paid health insurance in private hospitals remained the same.

Finally, encouraging data from our database reinforces the revolution of treatment with biologics, and their impact on the quality of life and morbidity of our patients. In the last decade, when this treatment has been commonly used, a significant drop in surgical procedures has been observed.

Our study provides epidemiological data from Argentina, a mid-income country in a city with predominantly Spanish and Italian descendants, where there is practically no data available until now [31]. These findings may not be applicable to other Latin American countries where the majority of the population may have different ethnicities. Although our study has the limitation of being retrospective, and we do not have the population data that would allow us to determine the incidence of pediatric IBD, this was a multicenter study including three national reference centers in the management of pediatric IBD, where we were able to perform trend analysis on the total number of patients diagnosed with IBD during this period.

Future prospective population-based studies are needed to establish the incidence and prevalence of IBD in different Latin American countries.

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