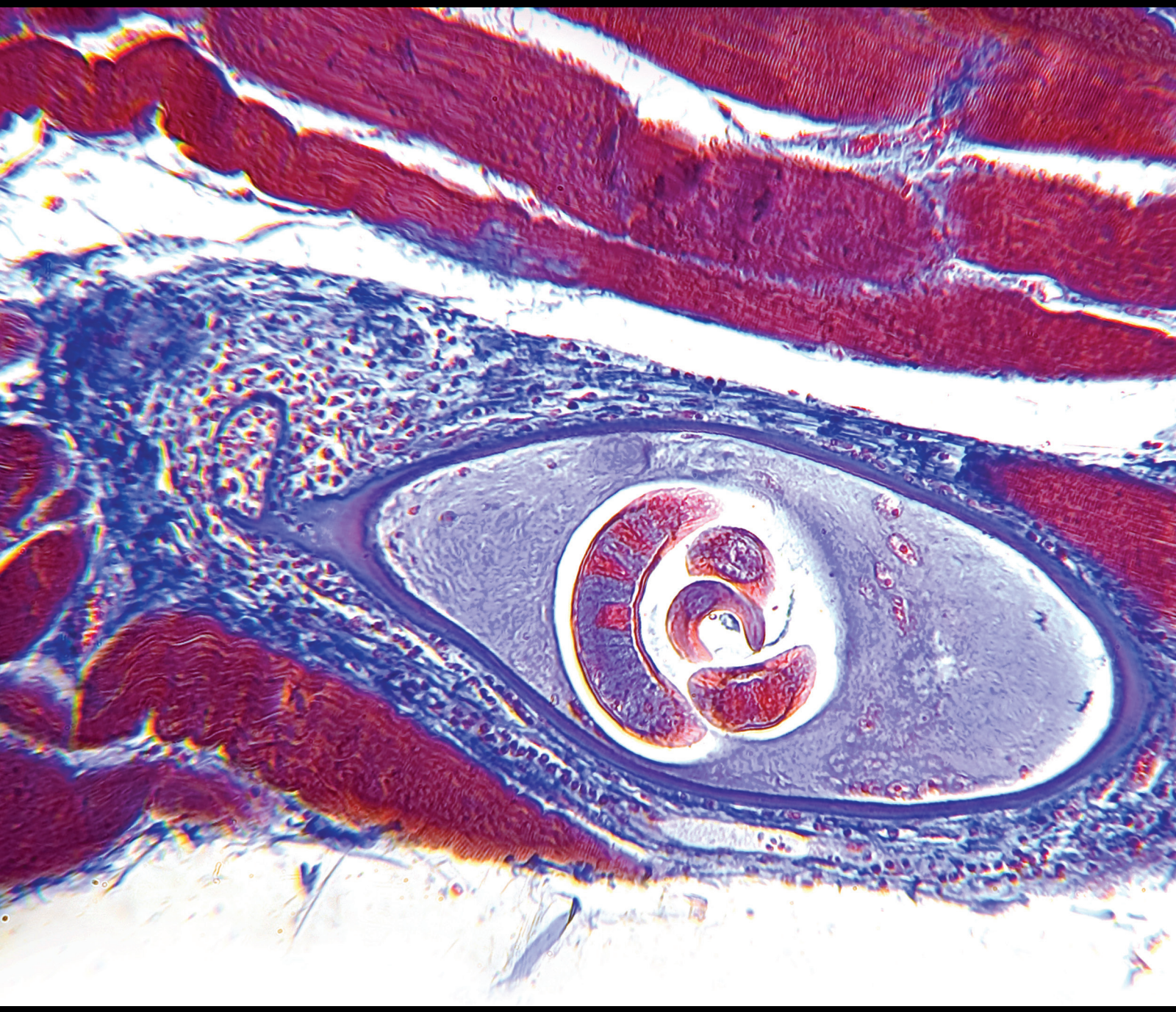
Gastroenterology Research and Practice

Epidemiology and Natural History of IBD in the Paediatric Age

Guest Editors: Graziella Guariso, Marco Gasparetto, Andrew S. Day, and Paul Henderson



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Editorial Board

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Editorial

Epidemiology and Natural History of IBD in the Paediatric Age

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The inflammatory bowel diseases (IBD) are chronic inflammatory conditions of the gastrointestinal tract characterised by episodes of relapse and remission. Although the aetiology of IBD is not fully elucidated, it is thought to be driven by a combination of genetic susceptibility, environmental triggers, and alterations in the gut microbiome that stimulate a dysregulated inflammatory response.

The two main forms of IBD, Crohn's disease (CD) and ulcerative colitis (UC), are diagnosed on the basis of clinical suspicion and laboratory, radiological, endoscopic, and histological findings. It is not always possible to classify patients as having one of these two forms using the diagnostic tools available, with the term inflammatory bowel disease-unclassified (IBD-U) currently used to categorize this subgroup presenting with chronic intestinal inflammation with features of both diseases; many children persist with this diagnosis into adult life. In contrast, the term indeterminate colitis is given to the histopathological description of intestinal inflammation involving bowel resection material.

Both CD and UC can present throughout the age range, including infancy, childhood, and adolescence. The number patients diagnosed with IBD, including childhood, has dramatically increased worldwide over the past 20 years. The reasons behind the rising incidence worldwide are not entirely clear. The current mean prevalence of IBD in the general population of Western countries is estimated at 1/1,000 inhabitants. At present, Scandinavia, Canada, and Scotland have the highest incidences of paediatric IBD worldwide; however, the reason for these high rates remains elusive. Although there are only few epidemiological data available regarding developing countries, the incidence and prevalence of IBD seem to be increasing over the past few decades practically in all regions of the world, indicating its emergence as a global disease.

The changing epidemiology of IBD across time and between geographic areas suggests that environmental factors are likely playing a major role in modifying disease expression. The rising incidence of IBD in developing nations may be linked to industrialization and a Western lifestyle, especially diet.

Insight into the worldwide epidemiology of this disease is, thus, important to identify geographic patterns and time trends. Recent findings will also make it possible to estimate the global public health burden so that health care resources can be allocated and research can be targeted in specific geographic regions. Information about environmental factors hypothetically affecting the incidence and prevalence of this disease may, finally, lead to preventative interventions where possible.

Although less prevalent in infants and in very young children, a number of case reports and small population studies have documented disease onset at very early ages. Underlying immune deficiency and monogenic disorders have been identified in a small subgroup of those diagnosed under the age of 2. An intestinal IBD-like pattern has been found to be associated in these cases with systemic immunodeficiency, within a complex scenario which can even lead to severe life-threatening events. Consequently those under the age of 6 should always have thorough investigation of other aetiologies before a diagnosis of IBD is given.

Assessing the incidence of IBD is complicated, as epidemiological investigations have often ignored cases of IBD-U although they are considered as a distinct disease subtype of IBD. IBD can also be difficult to recognize, particularly in children when extraintestinal symptoms and signs (such as iron deficiency, skin lesions, and liver pathology) are predominant and in third world countries where medical services are lacking.

The aim of this special issue is to review the current levels of knowledge with regard to IBD epidemiology worldwide and to examine its natural history in paediatric patients. The main topics of the issue include the most up-to-date definitions and classifications of paediatric IBD, the epidemiology of IBD worldwide, the epidemiology and natural history of paediatric IBD, and the disease burden within the general and paediatric populations.

We hope that readers of this special issue on paediatric IBD will not only find accurate data and updated reviews, but also consider the questions yet to be resolved such as disease distribution worldwide, its classification, and its impact on the healthcare system.

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Clinical Study

Geographic Mapping of Crohn's Disease and Its Relation to Affluence in Jiangsu Province, an Eastern Coastal Province of China

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Background. Geographical variation in the incidence of Crohn's disease (CD) has been reported in Europe and North American. However, there are no comparable data in mainland China. *Methods*. We retrospectively identified incident cases of CD patients registered in Jinling hospital during 2003 to 2012. The standardized incidence ratio (SIR) was calculated for each area of Jiangsu province and a thematic map of CD was made according to the local SIR. The association between incidence and local economic status was revealed by correlation between SIR of CD and different local economic indicators. *Results*. A total of 653 CD patients (male-to-female ratio, 1.8 : 1) from Jiangsu province were included. A steady increase was observed in the number of CD patients over the period of observation. Disease map of SIR showed a pronounced geographic concentration of CD in the south part of Jiangsu province. Spearman correlation analysis showed a positive correlation between local SIR of CD and local economic indicators. *Conclusions*. There is a marked geographic variability in CD incidence across Jiangsu province. CD incidence in affluent areas seems to be higher than that in less affluent areas. Further multicenter population-based studies are needed to assess the real disease map of CD.

1. Introduction

The incidence rates of Crohn's disease (CD) markedly differ geographically and among different ethnic groups presumably due to genetic and environmental factors [1–3]. Epidemiological studies show that the global map of CD can be broken down into several geographic zones according to the variation of incidence [3, 4]. It seems that CD is a disease of the western world [4]. However, a rising incidence and prevalence of CD has been recently observed in countries with traditionally low rates of CD, especially in Asian countries including China [5, 6].

China is a developing country which holds the largest population in the world [7]. The economic growth in China was visible since the Reform and Open Policy in 1978, followed by the increasing gap between the poor and the rich [8, 9]. On the other hand, compared to 1990, the nationwide ratio of patients with CD to total hospitalized patients has increased by 2.78 times in 2003 [10]. Also a study from Scotland showed that children from more affluent areas had a higher relative risk of developing CD [11]. As a result, the correlation between surging economy and the increasing incidence of CD in China has attracted a great deal of attention.

However, to our best knowledge, no study has been carried out to investigate the CD incidence and its relation to affluence in mainland China. Thus, we carried out a retrospective study based on the database of a large tertiary hospital, to investigate the geographic variation of CD in Jiangsu province, an eastern coastal province of China, and its relation to local economic status.

2. Materials and Methods

2.1. Study Setting and Patients. Jiangsu province is situated at the center of the eastern coast of China, with a population of

approximately 79.2 million. It covers a total area of 102,600 sq. km, making up 1.06% of China's total territory.

Jinling Hospital is a large tertiary hospital in Jiangsu province. Each year patients with CD from all over mainland China come to Jinling Hospital for further treatment. We selected patients through searching for "Crohn's disease," "CD," "inflammatory bowel disease," "colitis," "IBD," or "enteritis" among discharge diagnosis of patient's medical report. Medical records of CD patients who registered in Jinling Hospital during the period of 2003 to 2012 were reviewed retrospectively. We also checked with endoscopy lists, pathology reports, and IBD team records, which linked with medical records system in our hospital. Two senior physicians (GW and GS) confirmed the diagnosis of CD by review of the case records and reference to the diagnostic criteria [12].

In our hospital, the diagnosis of adult CD should be based on the combination of physical examination, colonoscopy (with multiple biopsies), laboratory investigations (erythrocyte sedimentation rate, C reactive protein, and calprotectin), and small bowel imaging (computed tomography enterography (CTE) or magnetic resonance enterography (MRE)). For pediatric CD patients, initial investigation should also include double-balloon enteroscopy and assessment of nutritional condition and growth level. All patients involved in current study are hospitalized patients who have received or confirmed their CD's diagnosis in Jinling Hospital.

2.2. Data Sources. The main data collected include demographics, city of residence at diagnosis, and clinical parameters (including the disease classification [13, 14], radiological, endoscopic, and histological findings at the time of diagnosis). Here we choose several economic indicators to measure the local economic status, including saving deposits per capita, annual income per capita, disposable expenditure per capita, living expenditure per capita, gross domestic product (GDP) per capita, and Engel coefficient. The Engel coefficient is the proportion of family income that is spent on food. It is well accepted that the percentage of income families spent on food declined as their income level rose [15]. All the economic data mentioned in current study came from the annual reports published on the website of China's National Bureau of Statistics (CNBS, http://www.stats.gov.cn/english/).

2.3. Disease Map. The incidence rates of CD were calculated by the number of registered CD cases during the period of 2003 to 2013 divided by the population at risk (population of different areas of Jiangsu province). Standardized incidence ratios (SIRs) were estimated for each of the 13 areas of Jiangsu province, using regional gender- and age-specific rates as a reference. SIR is the ratio of the number of cases actually observed to the number expected. The latter was calculated by applying the age-specific incidence rate of the whole population to the number of population in each province. Gradient colors were applied into different areas in the map of Jiangsu province according to its SIR to show the distribution of patients intuitively.

2.4. Statistical Analysis. Statistical analysis was performed using GraphPad Prism Software (version 5.01; GraphPad, San Diego, CA). Data visualization was performed using PowerPoint software (version 2010, Microsoft). All analyses were two-tailed and differences were considered statistically significant when P value < 0.05. For continuous variables, mean and standard error of mean (SEM) were calculated. Student's t-test was used to compare variance between groups. For categorical variables, percentages were provided and chi-squared test was used. Spearman analysis was used to calculate the correlation between number of CD patients and local economic indicators.

3. Results

3.1. General Results. A total of 1446 cases were identified with CD when searching for "Crohn's disease," "CD," "inflammatory bowel disease," "colitis," "IBD," or "enteritis" among discharge diagnosis of medical reports. Fifty-four cases were excluded (33 patients were excluded due to lack of data and 21 patients were identified to be misdiagnosed with CD after surgery or during their second/third time of hospitalization).

Among the rest 1392 CD patients, 653 (420 male and 233 female; male-to-female ratio is 1.8 : 1) came from Jiangsu province. There are 26 pediatric patients (below 17 years old) and 627 adult patients (above 17 years old). All patients were ethnically Chinese. A steady increase was observed in the number of CD cases over the period of 2003–2012 (Figure 1). The median age at diagnosis was 33.6 (interquartile range, IQR: 40.0–27.9) years. As shown in Figure 2, the age-specific frequency analysis showed that the peak incidence of CD was in the 21–30 years age group.

3.2. Disease Classification. For adult patients, the most common disease location was the ileo-colon (39.2%), followed by colonic (34.0%) and isolated ileal (26.8%) disease. As for disease behavior, 59.5% patients were identified to be inflammatory, followed by stricturing (32.5%) and penetrating (8.0%), as shown in Table 1.

For pediatric patients, the most common disease location was ileo-colon (50.0%), followed by distal 1/3 ileum (26.9%) and colonic (23.1%). As for disease behavior, 42.3% were identified to be inflammatory disease, followed by stricturing (34.6%), penetrating (19.2%), and both penetrating and stricturing (3.8%), as shown in Table 2.

3.3. Incidence, Disease Map, and Correlation with Affluence. The incidence rates of CD ranges from 1.3 cases/10^6 population in the north area to 21.4 cases/10^6 population in the south area. Age-sex specific incidence was provided in Table 3. According to the SIR of different provinces, the disease map of CD showed a marked geographic variability across the Jiangsu province (Figure 3). We found that the south region of Jiangsu province showed higher incidence of CD compared with that of north. The location of Jinling Hospital was also marked out in Figure 3. Regionally, the SIR of CD ranges from 0.15 in the north area (Xuzhou) to 2.42 in the south area (Nanjing).

Table 1: Classification of adult Crohn's disease from Jiangsu province.

Variables	$n = 627$	Percentage (%)
Age at diagnosis		
A2 (17–40 y)	412	65.7
A3 (above 40 y)	215	34.3
Disease locations at diagnosis		
L1 (terminal ileal)	168	26.8
L2 (colonic)	213	34.0
L3 (ileocolonic)	246	39.2
L4 (Isolated upper disease)	22	3.5
Disease behavior at diagnosis		
B1 (inflammation)	373	59.5
B2 (stricturing)	204	32.5
B3 (penetrating)	50	8.0
P (perianal disease)	74	11.8

Table 2: Classification of paediatric Crohn's disease from Jiangsu province.

Variables	$n = 26$	Percentage (%)
Age at diagnosis		
A1a (0–10 y)	2	7.7
A1b (10–17 y)	24	92.3
Disease locations at diagnosis (%)		
L1 (distal 1/3 ileum)	7	26.9
L2 (colonic)	6	23.1
L3 (ileocolonic)	13	50.0
L4 (upper disease)	5	19.2
Disease behavior at diagnosis (%)		
B1 (inflammation)	11	42.3
B2 (stricturing)	9	34.6
B3 (penetrating)	5	19.2
B2B3 (penetrating and stricturing)	1	3.8
P (perianal disease)	4	15.4
Growth		
G0 (No evidence of growth delay)	6	23.1
G1 (growth delay)	20	76.9

We further investigated the relationship between economy status and CD incidence. Spearman correlation analysis showed a positive correlation between local CD incidence and average disposable expenditure (rh = 0.637; $P = 0.019$), living expenditure (rh = 0.659; $P = 0.014$), and GDP per capita (rh = 0.648; $P = 0.016$). However, there is no significant correlation between CD incidence and average saving deposits, annual income, or household Engel coefficient (Table 4).

4. Discussion

In the present study, we found that the number of CD cases increased steadily in Jiangsu province during 2003 to 2012. We also observed striking spatial variations in the distribution of CD in Jiangsu province. Map of SIR showed a pronounced geographic concentration of CD in the south area. Moreover, a positive correlation was observed between CD incidence and local economic status.

We do not know the exact reason of the increasing CD incidence in China. The speed of city industrialization in China is increasing in recent years, accompanied with surging economy and rising living standard. Although the economic growth was visible since the Reform and Open Policy, the gap between the poor and the rich is also increasing. We assumed that the increasing incidence of disease consistently observed as a society that becomes modernized or developed may be attributed to westernization of diet, changing lifestyle and antibiotic use, or improved hygiene status [16].

In the present study, the peak age for CD occurrence is 20–30 years and the age distribution of CD in current study is similar to reports from Western countries [17, 18]. Studies from Western countries showed that CD occurs 20%–30% more frequently in women [18, 19], while a male

Table 3: Age-sex specific incidence of Crohn's disease.

Gender by age group	Population (10^6)	Number of cases	Incidence rate/10^6
Males			
0–14	7.12	9	1.3
15–34	12.85	241	18.8
35–54	12.96	138	10.6
>55	8.01	33	4.1
Females			
0–14	6.04	3	0.5
15–34	12.43	97	7.8
35–54	12.58	96	7.6
>55	7.23	38	5.3
Total			
0–14	**13.16**	**12**	**1.8**
15–34	**25.28**	**338**	**26.6**
35–54	**25.54**	**234**	**18.2**
>55	**15.24**	**71**	**9.4**

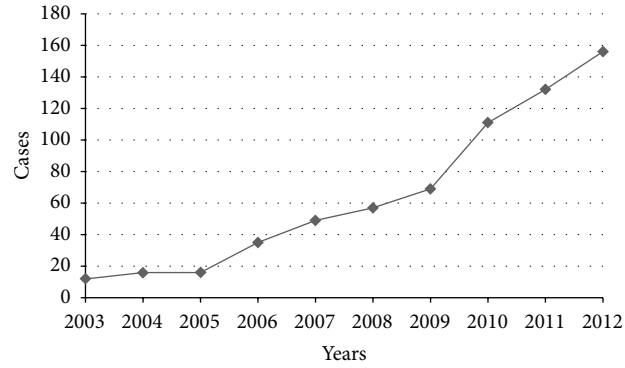

Figure 1: Annual newly registered CD patients from Jiangsu province between 2003 and 2012.

Table 4: Correlation between CD incidence and local economic status in different areas of Jiangsu province.

Economic indicators	rh	*P*
Annual average saving deposits	0.341	0.255
Annual average income	0.445	0.128
Annual average disposable expenditure	0.637	**0.019**
Annual average living expenditure	0.659	**0.014**
GDP per capita	0.648	**0.016**
Household Engel coefficient	−0.146	0.635

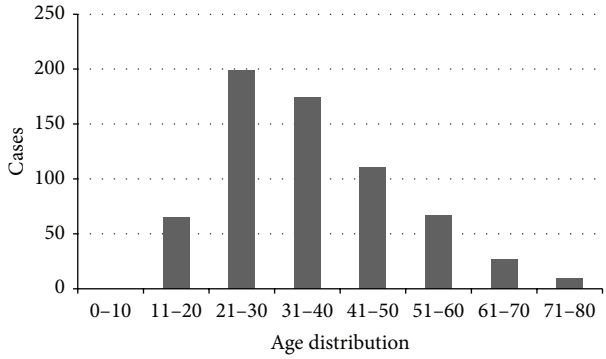

Figure 2: Age distribution of CD patients when registration.

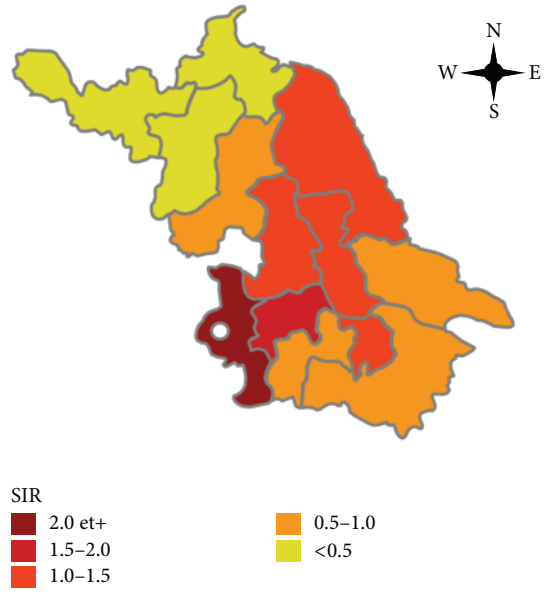

Figure 3: Geographic variations of SIRs of CD in Jiangsu province. Jinling Hospital has been marked out as a white dot.

preponderance was observed in CD patients in the current study. We also realized that the proportion of isolated ileal disease in pediatric CD patients in our study is much higher than that of previous study [20]. We assume that this may be explained by the high frequency using of sigmoscope but not colonoscopy for the initial investigation at the department of pediatrics at our hospital, since parents believe that the examinations of sigmoscope and capsule endoscopy may be less harmful to their children than colonoscopy is.

The wide geographic variation of CD that we observed in the current study is consistent with other studies showing geographic variability in the incidence of CD [11, 21–25]. There are many possible reasons for the high degree of geographic variation. One of them is the increasing gap of economy status and living standards between different regions. In our study we observed a positive correlation between local CD incidence and average disposable expenditure (rh = 0.637; $P = 0.019$), living expenditure (rh = 0.659; $P = 0.014$), and GDP per capita (rh = 0.648; $P = 0.016$).

We do not know the exact mechanism of the association between the increasing CD incidence and rising economy status, but it may be explained by that people living in affluent areas spend more time in the office, in meetings, and at dinner, and they do less physical labor. Higher tension, more fast and fatty foods, and less physical exercise may be risk factors for CD, but these explanations need to be confirmed by further case-control studies in China.

Another possible explanation for the greater variability seen in current study is the study design, which is also a limitation of the current study. It is a single center study and our hospital is located in Jiangsu province. Hence, the geographic distribution of CD patients was influenced and limited by the location of our hospital and the distance between our hospital and different areas in Jiangsu province.

Finally, immigration of populations should also be considered as one of the aspects that may affect the geographic distribution of CD. Since the Reform and Open Policy in 1978, a large number of people have migrated to several affluent cities from rural or suburban areas to search for opportunities and a better quality of life. It is possible that such moves to urban zones have created new environmental pressures against which this population was not protected.

Previous studies have also shown an increased incidence of CD in affluent areas, classified using a social/material deprivation index [11, 24, 26, 27]. It has been suggested that higher incidence rates among those of higher socioeconomic status may be due to a delayed and/or low level of exposure to common infectious agents during childhood. This could be due to improved domestic hygiene, resulting in altered immune responses in genetically susceptible hosts, the so-called "hygiene hypothesis" [28].

The present study has several limitations. First, although the national medical insurance policy makes it easier to receive patients from all over mainland China and our hospital seems very attractive to CD patients from around China, especially Jiangsu province, it will still underestimate the true incidence and prevalence due to some underlying selection bias. A population-based multicenters study would be needed to explore the exact incidence and disease map of CD. Second, since the critical exposure factor in IBD is unknown, the lag time between exposure and disease onset is unknown, which raises a critical uncertainty in estimating incidence in relation to area of residence. It would be important to try to determine whether the critical area of residence is the one lived in at time of symptom onset

(or within 2 years from diagnosis) or the residence of early childhood.

In conclusion, CD is an emerging disease in Jiangsu province. It affects predominantly young and middle-aged male patients. There is a marked geographic variability in CD incidence across Jiangsu province. CD incidence in affluent areas seems to be higher than that in less affluent areas. Further multicenter population-based studies are needed to assess the real disease map of CD.

Conflict of Interests

There is no conflict of interests to declare.

Acknowledgment

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Review Article

Inflammatory Bowel Disease in Australasian Children and Adolescents

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Many reports indicate increasing rates of inflammatory bowel disease, with data also showing changing patterns of this chronic disease in children and adolescents. This review focuses upon the available data of the epidemiology of inflammatory bowel disease in children and adolescents in Australia and New Zealand (collectively termed Australasia). Recent data show high incidence of IBD (especially Crohn disease) in this area and indicate rising rates of IBD in children and adolescents.

1. Introduction

There are numerous reports documenting increasing rates of the inflammatory bowel diseases (IBD), Crohn disease (CD), and ulcerative colitis (UC), over recent years [1]. Whilst initial publications focused on the incidence and prevalence of CD and UC in western populations, a number of reports have also described increasing rates in other parts of the world, especially Asian countries [2].

Furthermore, paediatric reports have noted increasing rates of IBD in children and adolescents [3–5]. Reports from various countries especially show higher rates of CD, and some of these publications also show onset in younger children.

Recent data from New Zealand (NZ) and Australia (collectively known as Australasia) indicate high incidence of IBD, especially CD [6, 7]. Several reports also indicate increasing diagnoses in children and adolescents [8, 9]. This review focuses on the patterns of CD and UC in Australasian children and adolescents whilst illustrating some key aspects of IBD in this region of the world.

2. Patterns of IBD in New Zealand and Australia

Prior to 2006, the only reports of IBD in Australia [10, 11] or NZ [12–14] were small hospital-based or tertiary case series. Several of these reports focused on series of patients, especially describing surgical experiences [10, 11, 13]. Overall, these reports suggested low incidence and prevalence of IBD [12, 14]. More recently there have been comprehensive and prospective population-based studies that have more clearly illustrated key aspects of IBD in Australasia.

The first of these studies was a population-based study of IBD in the Canterbury province in the South Island of NZ [6]. Using overlapping methodologies, including capture/recapture, the investigators established a population of 1420 individuals, which was estimated to represent more than 91% of those diagnosed with IBD within this geographical region. This population included those with existing disease and an incidence cohort ($n = 116$) collected prospectively over the calendar year of 2004. This cohort established an incidence of 16.5 per 100,000 for CD and incidence of 7.6 per 100,000 for UC (Table 1). The point prevalence (as at

Table 1: Incidence of Crohn disease in Australia and New Zealand. Incidence data obtained from large population-based studies conducted in Australia and New Zealand (NZ). Incidence data represent diagnoses per 100,000 population for the relevant year.

	Canterbury, NZ	Geelong, Australia	Nelson, NZ
Year of observation	2004	2007-8	2012
Incidence	16.5	17.4	15.2

January 1st, 2005) was calculated for IBD, CD, and UC to be 308.3, 155.2, and 145/100,000, respectively. These incidence and prevalence data were amongst the highest rates for CD at that time.

These high rates of CD seen in Canterbury are supported in a further population-based study from the Nelson region in the north of the South Island of NZ (unpublished data, RB Gearry). The region of Nelson is a distinct geographical area that features a stable population served by one secondary level hospital. A population-based assessment of individuals diagnosed with IBD in the Nelson area delineated 224 individuals with CD and 160 with UC. The overall prevalence of IBD was calculated to be 389/100,000 population. The incidence of CD was noted to be rising over the last decade, with incidence for the 2012 year calculated as 15.2/100,000: one of the highest rates reported to date (Table 1). Ongoing prospective assessment of incidence rates in this well-defined area will provide valuable information on the epidemiology of IBD in NZ.

A further population-based study focused upon a well-defined population in the Geelong area in the Australian state of Victoria [7]. This study was conducted over a one-year period from April 2007 within a specific geographic region comprising a total population of 259,015 people. Seventy-six new diagnoses of IBD were made over this period: 45 CD, 29 UC, and two IBDU. The overall incidences of CD and UC were calculated to be 17.4 and 11.2 per 100,000, respectively (Table 1). The peak age at diagnosis was in the 20–24-year group: just fourteen (21%) of the total group were less than 22 years of age at diagnosis.

These prospective population-based studies have together demonstrated high rates of IBD in Australasia. They have particularly indicated a high incidence of CD in both countries. Although these data likely represent the broader populations in the two countries, comparative studies in other locations have not yet been reported.

In addition, a further study arising from the Canterbury cohort study examined environmental factors contributing to the development of IBD [15].

This study incorporated a case-control design, with the cases comprising 638 individuals with CD and 653 with UC from the wider cohort. Six-hundred age and sex-matched controls without IBD were included for comparison. All subjects were asked to complete a questionnaire informing their current or previous exposure to various environmental risk factors. Key factors associated with IBD were higher socioeconomic status, European ethnicity, family history of IBD, and smoking history at diagnosis. Family history was the strongest factor (odds ratio of 3.1 for CD and 2.5 for UC). Living in an urban location was linked with risk of CD, whilst those who had moved to the region from another country were more likely to have developed UC. In contrast, breast feeding in infancy and having a vegetable garden in childhood were both protective factors against the development of IBD. This population-based case-control study confirmed the findings of prior work in regard to the protective benefit of breast-feeding [16] and has emphasised the importance of early life events (e.g., rural living) that may modify or modulate the development of the intestinal microflora and thereby influence the risk of developing IBD.

A further recent study has also looked at environmental risk factors for IBD: this report focused upon immigrants moving to Australia from the Middle East [17]. The study included 84 adults of Middle Eastern ethnicity with IBD seen and assessed in Sydney, Australia, with comparison to European cases and controls, and with Middle Eastern controls in Australia and in Lebanon. Family history of IBD was a key risk factor. Breast-feeding, pet ownership, rural residence, and contact with farm animals were shown to be additional factors modifying the risk of IBD. Within families that had migrated to Australia from the Middle East, diagnosis of IBD was seen earlier in the second generation than in the first generation. A number of the risk factors for IBD (such as rural dwelling) were also more prominent in the second generation of migrants. As in the NZ cohort, many of the key factors reflected early life events (e.g., breast feeding) and factors influencing the development of the intestinal microflora.

3. IBD in the Indigenous Peoples of Australasia

Although Australasia is predominantly populated by individuals of European ethnicity, both Australia and NZ have indigenous populations: Aborigines and Maori, respectively.

The total group of patients assembled in the Canterbury population-based cohort were predominantly (97.5%) of European extraction, with only 14 (0.98%) being of Maori ethnicity [6]. Eight (1.1%) of the 715 patients with CD were Maori. At this time, Maori people represented 7.3% of the Canterbury population and approximately 15% of the total NZ population. Earlier hospital-based studies in NZ have also indicated that IBD is very uncommon in Maori people [12–14]. These studies have also indicated that IBD is uncommon in other Polynesian peoples resident in NZ, such as those from the islands of Samoa and Tonga.

As the data incorporated in the Geelong study did not include ethnicity data, rates of IBD in Aborigines were not available to be ascertained in that report [7]. However, data obtained from the Australian Paediatric and Adolescent IBD Database, a prospective registry commenced in 1996, suggests very low rates of IBD in children of Aboriginal extraction

compared to non-Aboriginal Australian children [18]. Only 13 (0.57%) of 2300 children included in the database came from families with one or two parents of Aboriginal descent. Based upon the 2006 Australian census, Aborigines comprise around 5% of the overall Australian population. This census data was also used to estimate 2006 point prevalence figures: these suggested rates of 5.2 (per 100,000) for Aboriginal children and 47.9 (per 100,000) for non-Aboriginal children. The census data also illustrated that the Aboriginal population has similar rates of urban and rural living compared to non-Aboriginal populations, suggesting that higher rural exposure does not explain the variation in IBD prevalence. Furthermore, Aboriginal populations appear to have adopted similar patterns of diet and lifestyle to Europeans, reflected in similar or higher rates of lifestyle-related disease, such as cardiovascular disease [19]. These observed differences could also be consequent to lower recognition (i.e., underreporting) of IBD in this population. This was not able to be explored further in this study, but given the significant and broad impacts of IBD upon patients, this would seem unlikely to explain the huge differences.

Interestingly, low rates of IBD are also observed in the indigenous peoples of Canada [20]. The reasons for lower rates in these three distinct indigenous populations (contrasting to higher rates in the predominantly European peoples in the three countries) are not fully characterised but could reflect a number of factors, including those relating to the pathogenesis of IBD, such as genetic differences or variations in enteric infections. Socioeconomic factors and access to healthcare could also be important variables.

In regard to important genes related to risk of IBD, one NZ study evaluated rates of CARD15 polymorphisms in 90 Maori and 201 European individuals [21]. Overall a low frequency of polymorphisms was observed in NZ Maori. A linear relationship was described between the presence of polymorphisms and increasing ancestry. This study indicated that Maori are much less likely to carry this risk gene and could contribute to lower rates of IBD. However, low rates of CARD15 polymorphism carriage are also seen in other ethnic groups, such as in Japanese individuals [21]. Furthermore, the rates of other risk genes have not been fully considered in the Maori population.

We have previously hypothesised that differences in gastric and enteric infections could also influence the development of IBD in Maori in NZ [22]. Maori have higher rates of *Helicobacter pylori* colonisation in childhood than Europeans in the same community [23]. Higher rates of this gastric infection have also been seen in Canadian First Nation peoples [24]. In contrast, rates of Campylobacter infection appear to be lower in NZ Maori populations than in respective Europeans [22]. Other studies have indicated low rates of *H. pylori* infection in individuals diagnosed with IBD, suggesting that this provides a protective environment against the development of this chronic inflammatory condition [25]. This could reflect that *H. pylori* colonisation provides a degree of protection against subsequent enteric infections that then trigger the onset of IBD. Further work is required to further understand these complex interactions.

4. Paediatric IBD in Australia

A series of reports from Australia have described patterns of IBD in Australian children. Increasing rates of CD and UC in recent years have clearly been demonstrated in several of these publications.

Schildkraut et al. [8] retrospectively evaluated the patterns of UC in children aged 16 years or less in the Australian state of Victoria over a 60-year period from January 1950. The authors determined that 342 children were diagnosed with UC over this time, with a sixty-fold increase in the incidence over the period, with this change being pronounced in the final ten years of observation. The incidence in 2009 was calculated to be 1.61 per 100,000 population.

The authors also delineated presenting features and disease phenotype in these children. Almost all of the children (93%) had been born in Australia and Indian or East Asian children comprised just 3% of the total group. Other details of ethnicity (such as Middle-Eastern background) were not provided. Diarrhoea and rectal bleeding were common symptoms at diagnosis, and children had a median of 16 weeks of symptoms before presentation. Of the 296 children where disease location was clearly defined at diagnosis, two thirds had pancolitis, with one quarter having left-sided disease and isolated proctitis seen in only 9%. Overall the children were lighter and shorter than the reference population (weight z score −0.21 and height z score −0.91).

Although not considered further in this publication, Schildkraut et al. [8] also identified 825 children diagnosed with CD and 143 with IBD unclassified (IBDU) in Victoria over this 60-year period. An earlier report had retrospectively reviewed children diagnosed with CD in the same area over a 31-year period (from 1971 to 2001) [9]. In this series of 351 children, the incidence of CD increased more than fifteen-fold to 2.0 per 100,000 population. The presenting features, duration of symptoms prior to diagnosis, or anthropometric data were not included in this report. Ethnicity data were also not available. In terms of disease phenotype at diagnosis in the last decade of the study, 102 children (45%) were found to have upper gastrointestinal involvement, with 93% having colonic involvement and 57% having ileal involvement. Overall, 18 children were also noted to have perianal disease at diagnosis, whilst 21 had perioral involvement.

Together, these two reports from the same area of Australia show large increases in the numbers of children and adolescents diagnosed with IBD, with most of the changes observed in recent years.

A further study evaluated the phenotype and patterns of disease in a group of 86 children diagnosed with IBD at one tertiary hospital over a four-year period [26]. Sixty-one (71%) of this group were diagnosed with CD, 13 (21%) with UC, whilst 12 (20%) were labelled as IBDU. The children ranged from 0.6 years to 16.6 years (mean 9.8 years) at diagnosis and 55% were male. Forty-two of children with CD had diarrhoea, thirty-six had abdominal pain, and thirty-one (51%) had poor weight gains or weight loss before diagnosis.

Overall, 38 (44%) of the full group were found to have endoscopic and histological evidence of pancolitis [26]. Twenty-five of these 38 children were diagnosed with CD: in

thirteen of this group the diagnosis of CD was based on upper gastrointestinal tract findings, including granulomatous gastritis or duodenitis. In contrast, nine children diagnosed with CD had no endoscopic or histological abnormalities on ileocolonoscopy—their diagnosis was based solely upon changes located in the upper gastrointestinal tract. This case series focused upon the presentation and location of disease, especially with regard to involvement in the upper gut: this study was not designed to delineate any changes over time.

One other Australian publication also focused on the patterns of upper gastrointestinal tract involvement in children diagnosed with CD [27]. This study showed upper gut involvement in 71% of 56 children diagnosed with CD. In 41% of these children, the findings detected in the upper gut were critical in making a diagnosis of CD.

A further Australian study has evaluated early life events in the risk of developing CD [28]. This study utilised a birth cohort born in Victoria between 1983 and 1998. Within this cohort, 278 children were diagnosed with CD by their 16th birthday. Perinatal factors linked with risk of CD included urban location, higher socioeconomic status, and delivery by caesarean section. In addition, the children born between 1992 and 1998 were 1.54 times more likely to have developed CD than the children born earlier. This difference was not related to changes in perinatal factors.

One study has focused on 42 Australian children diagnosed in the first six years of life (unpublished data, DA Lemberg). Twenty-four of this group were male and the median age at diagnosis was 3 years (range from 0.6 to 5.9 years). Two-thirds of the children ($n = 28$) were diagnosed with CD, whilst four were diagnosed with UC and ten labelled as IBDU at diagnosis. A first degree family history was seen in 8 children (19%) and most of the children (88%) had European background. Other ethnicities included Jewish, Indian, Australian Aboriginal, and Middle Eastern. These children predominantly presented with diarrhoea, rectal bleeding, and abdominal pain (present in 83%, 81%, and 52% of children, resp.) and symptoms were present for an average of 37.9 (±29.9) weeks.

Only one retrospective study to date has focused on rates of IBD in children within a specific population immigrating to Australia. The patterns of IBD in a group of 24 children of Middle-Eastern ethnicity were contrasted to age- and gender-matched children from non-Middle Eastern backgrounds within the IBD Clinic at a Sydney tertiary hospital [29]. Using 2006 population data, estimates of point incidence and point prevalence were 33.1 per 100,000 per year and 165.4 per 100,000, respectively, for the Middle-Eastern group. In contrast, the comparative rates in the control population were 4.3 per 100,000 and 28.7 per 100,000. Fourteen of the 24 Middle-East children had CD, seven had UC, and three had IBDU.

Some aspects of the phenotype and patterns of disease differed between the study and control groups [29]. At diagnosis the children of Middle-Eastern extraction had higher Pediatric Crohn Disease Activity Index (PCDAI) scores (37 ± 13 versus 27 ± 11, $P = 0.033$) and less colonic disease ($P = 0.01$) at diagnosis than the control group. The duration or patterns of symptoms before diagnosis did not differ. Growth data at diagnosis were similar in the two groups. The Middle-Eastern children had higher rates of thiopurine use after diagnosis ($P = 0.002$). Other outcomes (medical or surgical) did not differ between the two groups. Although this work included a relatively small group of patients, the patients were well characterised and were all seen and managed within one IBD Clinic. The role of early-life events and other environmental factors was not explored in this cohort.

5. Paediatric IBD in New Zealand

Within the NZ population-based cohort assembled by Gearry et al. [6] 126 patients were diagnosed prior to their 17th birthday. Eighty-five (67%) of this group were diagnosed with CD, whilst 40 (32%) had UC and one had IBDU. Half the patients were male. Other than two patients with Maori ancestry and one Asian child, all the other children were of European background.

Of the 83 children with CD who had adequate details of disease location, 27 had ileal disease, 32 colonic, and 24 ileocolonic location [30]. These children were more likely to have ileocolonic disease than adults diagnosed over the age of 40 years of age. Sixty-four children had inflammatory disease at diagnosis, with 9 having structuring disease and 11 having penetrating disease: penetrating disease at diagnosis was more common in children than in adults aged over 40 years. Over time, however, age at diagnosis was not associated with risk of progression from inflammatory to complicated disease.

Twenty-four of this cohort were diagnosed with UC in childhood. These children were more likely to have pancolonic involvement and less likely to have isolated proctitis than those diagnosed over 17 years of age. Given the small size of the paediatric group, it was unclear if age at diagnosis had any impact upon disease progression over time.

Just one report has focused expressly upon IBD in children across NZ. Yap et al. [31] undertook a prospective assessment of children and adolescents diagnosed with IBD in NZ over a two-year period using an existing paediatric surveillance system to delineate incidence and presentation patterns. Fifty-two children were diagnosed over this period: 34 (66%) with CD, 9 (17%) with UC, and 9 with IBDU. The authors estimated an incidence for IBD of 2.9 per 100,000; however, this may be an underestimate given the use of a surveillance program to identify the patients.

These 52 children were diagnosed at a median age of 11 years, with a median diagnostic delay of 8.4 months. The most common symptoms seen were pain and bloody diarrhoea (63% and 57% resp.). Less than a quarter of the children diagnosed with CD presented with the triad of pain, diarrhoea, and weight loss. Forty-four (85%) of the children were described to be of European extraction, with other patients being Indian ($n = 2$), Polynesian ($n = 3$), Middle-Eastern ($n = 2$), and African ($n = 1$).

Overall, 73% of the 33 children with CD had upper gastrointestinal involvement, with colonic disease the most common location (48%). Thirteen of these children had perianal disease at diagnosis. Of the nine children with UC,

eight had pan-colonic involvement, with the other child having left-sided disease.

This report was not able to provide any data on rates of paediatric IBD across NZ over a longer period of time. However, it does provide a "snap-shot" of the patterns and phenotype of disease in NZ within the two years of observation. Furthermore, this report was not designed to evaluate the wider impact of IBD in children and adolescents.

The impact of IBD upon quality of life and health care costs was evaluated in separate studies undertaken in NZ. Lowe et al. [32] evaluated quality of life (QOL) using the well-established IMPACT-III questionnaire in a small group of 16 children and adolescents with CD in the Wellington region of NZ. These children were aged between 9 and 18 years and had been diagnosed with CD for a mean of 2.7 years. Overall, the mean IMPACT-III score was 119.2 (±30.7), with maximum score of 175. Poor QOL was associated with current disease activity. Further evaluation of this group showed that many did not have peer support with other children with CD and care givers indicated a need for social supports.

The health care costs associated with CD in NZ children were evaluated in a recent study conducted in the Canterbury region of NZ [33]. Based upon a sample of 24 children diagnosed with CD, the direct and indirect health care costs were estimated to be NZ$14,375 per patient per year. Indirect costs included school absence and parental leave from work. Furthermore, an extrapolation of this data suggested an annual cost for paediatric CD of NZ$25.9 million across the country.

6. Discussion and Conclusions

Recent Australasian data indicate high incidence of IBD, especially CD, in both countries. Paediatric data, especially arising from Australian studies, indicates increasing rates of both CD and UC.

Prior to the large population-based studies summarised here, the patterns of IBD in Australasia were represented by a series of small reports predominantly arising from tertiary hospitals and reflecting a selection bias. Furthermore, the rates of IBD in this region were not appreciated at all, with prior studies indicating high rates of IBD in other developed countries. The recent Australasian data clearly delineate high rates of IBD, especially CD, in this region of the world.

The changing epidemiology of paediatric IBD has been described in recent reports [3, 4]. Overall, these data indicate that paediatric-onset IBD has been increasing in recent years. Reports from Ireland [34] and Scotland [35] illustrate very similar changes to those observed in Australia.

The recent Australian adult [7] and paediatric [8, 9] studies have been based in just one state of Australia (Victoria). Although it is likely that the conclusions drawn in these reports are representative of other locations in Australia, such data are not yet available. Given that Australia comprises a large land mass, with variations in climate and population distribution, it will be important to establish patterns in other locations.

The current impressions of IBD in NZ children are based upon a comprehensive population-based study in one area of NZ [6] and a national two-year prospective cohort [31]. As in Australia, it is likely that the patterns of IBD in Canterbury and Nelson reflect patterns elsewhere in NZ. However, climate and population variations along the length of NZ could influence rates in other areas. Both the Nelson and Canterbury regions of NZ have a predominantly European population. Higher numbers of Maori and Pacific Island people (for instance, in Auckland, the world's largest Polynesian city) could reflect differences in the prevalence of IBD in those areas. Though providing an impression across NZ, the paediatric surveillance study is limited by its relatively short duration and the collection method itself. Although the national paediatric surveillance program is well established, reporting relies upon the cooperation of the individual practitioners. Furthermore, some older children may have not been included if they were diagnosed by adult gastroenterologists unaware of the study.

Despite these short-comings, however, the Australasian data overall indicates high rates of IBD in children and adolescents, with increasing incidence in recent years. Furthermore, it appears that diagnosis of IBD is predominantly seen in children of European ancestry.

Generally, the available data suggest that the phenotype of IBD observed in Australasian children is similar to that observed elsewhere [36, 37]. These patterns include a predominance of CD over UC, frequent involvement of the upper gastrointestinal tract in CD, and extensive disease distribution in UC and CD.

Overall, the available data demonstrate low rates of IBD in the indigenous populations of Australia and NZ. It is not yet clear if this reflects differences in genetic risk factors or environmental factors. Variable rates of enteric infections, such as with *Helicobacter* or *Campylobacter* organisms, could be a further possible explanation [22]. Underreporting of symptoms and consequent underdiagnosis is a further possibility, but this appears less likely given the chronic and pervasive nature of IBD.

Currently there is little data on the patterns of IBD in immigrant populations in Australia and NZ. The recent studies have indicated that few individuals with IBD in NZ or Australia were first or second generation migrants [8, 9, 31]. Just one study has focused upon children from a specific ethnic group: these data demonstrated much higher rates of IBD in children whose family originated in the Middle East region [29].

Prior studies have shown that the children of individuals moving from the Indian subcontinent to countries such as Canada and the United Kingdom have higher rates of IBD upon settling in their new home compared to their region of origin or the baseline rates in their new location [38–40]. It is likely that the same patterns will be observed in Australia and NZ: specific studies focusing on these groups would be required to confirm this.

Further epidemiology studies are required in other locations throughout Australia and NZ to establish patterns of IBD across the two countries. Furthermore, natural history studies of disease cohorts in this region are required to

establish and follow changes in the incidence and phenotype of disease in this region. Such studies will also help to better illustrate changes in patterns of IBD in immigrant and indigenous groups in these two countries.

Conflict of Interests

The authors have no conflict of interests to declare.

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Review Article

Incidence and Paris Classification of Pediatric Inflammatory Bowel Disease

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New epidemiological data suggest that the incidence of inflammatory bowel disease (IBD) is increasing. As a result the burden of disease accounts for more strains to the health care system. The clinical variability queries whether disease characteristics are related to clinical outcome. Our aim was to delineate the latest results of incidence trends in pediatric IBD and to compare the first experiences with Paris Classification. Incidence of pediatric IBD has been increasing in Western Europe and in Eastern Europe. To better characterize IBD, Paris Classification was introduced and validated recently. Ileocolonic involvement is the most characteristic disease location in Crohn's disease (CD) based on applying Paris Classification. The rate of perianal disease and complicated behaviour in CD was similar. It is of interest that CD patients with colonic involvement were less likely to have stricturing disease compared with patients with ileal involvement. In addition, pancolitis dominated in ulcerative colitis (UC). However, most countries lack prospective, nationwide epidemiological studies to estimate incidence trends. This review emphasizes the importance of nationwide registries that enroll all pediatric IBD cases serving reliable data for "everyday practice." These first reports have shown that Paris Classification is a useful tool to determine the pediatric IBD phenotype.

1. Introduction

The inflammatory bowel diseases (IBD), Crohn's disease (CD), and ulcerative colitis (UC) are chronic inflammatory disorders of the gastrointestinal tract of unknown etiology. It is hypothesized that IBD is due to a dysregulated mucosal immune response to commensal gut flora in genetically susceptible individuals. However, causes of the dysregulated immune response are not delineated. The fluctuating disease course affects quality of life in IBD patients significantly. Furthermore, CD and UC account for substantial costs to the health care system and society [1]. New epidemiological data suggest that the incidence and prevalence of IBD are increasing. In addition, medical therapy and disease management have changed significantly in the last decade. IBD develops during childhood or adolescence in up to 25% of IBD patients. According to a recent report from the USA the total hospital charges for pediatric CD increased significantly from $81 million in 1997 to $194 million in 2009. Similarly, total hospital charges for UC rose from $53 million in 1997 to $143 million in 2009 [2].

The clinical presentation of CD and UC is highly variable, with significant diversity in phenotypes of the diseases [11]. This diversity in adults is specified by differences in the location, the natural history, and the outcomes. The clinical heterogeneity raised the question whether disease characteristics (age, location, and behaviour) had been related to clinical outcome. As a result Vienna and Montreal Classifications have been processed to classify IBD using clinical and epidemiological features. Patients are classified based on phenotypic characteristics (age, location, and behaviour). Oostenbrug et al. analyzed disease characteristics of 292 adult CD patients according to Vienna classification. The operation rate was higher in patients with ileocolonic localization ($P <$

Table 1: Incidence rates of pediatric- and adult-onset Crohn's disease and ulcerative colitis in different countries (/100,000).

	Pediatric Crohn's disease	Adult Crohn's disease	Pediatric ulcerative colitis	Adult ulcerative colitis
Hungary (2007–2009/2002–2006) [3, 4]	4.8	8.9	2.1	11.9
Northern France (1988–1998/2006-2007) [5, 6]	2.3	6.7	0.8	3.4
Nationwide/Madrid, Spain (2003–2007/2003–2005) [7, 8]	1.7	7.3	0.88	7.1
Copenhagen County, Denmark (2002–2004/2003–2005) [9, 10]	3.1	8.6	2.7	13.4

0.05) and stricturing and penetrating disease behaviour ($P < 0.001$) [12], confirming that disease and epidemiological characteristics are associated with outcome in CD.

Previous epidemiological studies reported marked differences in pediatric- and adult-onset IBD. Nevertheless, previous classification systems (e.g., Montreal Classification) were not designed or validated for pediatric patients. The Paris Classification is a new evidence-based consensus recommendation for pediatric modification of the Montreal criteria [13]. So far, this new classification system has only been applied in a few population-based studies.

In this report we summarize the latest incidence trends of pediatric IBD and the first experiences with Paris Classification.

2. Incidence of Adult-Onset Inflammatory Bowel Disease and Geographic Distribution

Crohn et al. published a case series with ileitis terminalis in 1932 where the "terminal" word, contrary to the popular belief, indicated not the location (terminal ileum) but the "deadly, terminal disease" [14]. The increasing incidence of IBD was observed from the middle of the 20th century. According to the first epidemiological studies the incidence of IBD differed greatly in geographical areas. The frequency of IBD was higher in developed countries than in developing countries and higher in northern areas than in southern regions (Table 1) [15, 16].

Of note, according to the recent studies the traditional geographical distribution of IBD has changed in the last 20 years. In most Western countries the incidence of adult UC and CD has stabilized, while incidence has been rising in regions with previously low incidence (Southern and Eastern Europe and Asia). In the latest systemic review about the changes in the worldwide incidence of IBD the highest incidence of adult UC was $24.3/10^5$ person-years in Europe, $19.2/10^5$ in North America, and $6.3/10^5$ in Asia and the Middle East. The highest incidence of adult CD was $20.2/10^5$ in North America, $12.7/10^5$ in Europe, and $5.0/10^5$ in Asia and the Middle East. Furthermore, a statistically significant increase in incidence of IBD was observed in 75% of CD studies and 60% of UC studies [17]. Extrapolation of the incidence figures on the total European population indicates around 78.000 new cases of CD and 178.000 of UC yearly [1]. The prevalence of CD may be up to 1.6 million people with CD and 2.1 million people with UC in Europe if reported prevalence rates are extrapolated for the total European population.

Some studies suggested that the incidence of IBD decreases from the north to the south comparing incidence within some countries and between countries. The incidence of UC in Copenhagen, Denmark ($8.1/10^5$), was four times higher than in Bologna, Italy ($1.9/10^5$) [18]. For CD, the rate of $4.1/10^5$ in Copenhagen was five times higher than in Galicia, North-West Spain ($0–8/10^5$). To establish the north-south gradient in Europe a prospective study (EC-IBD) was conducted in 20 centers that focused on frequency of IBD across the continent. According to the EC-IBD study rates of UC in northern centers were 40% higher than those in the south ($11.4/10^5$ versus $8.9/10^5$) [18]. It was concluded that the excess is less than expected on the basis of previous studies that may suggest an increase in the incidence of IBD in Southern Europe whereas those in the north may have reached a plateau. However, some recent studies still show significant difference in frequency of IBD within countries in children and in adults [6, 7, 19, 20]. The etiology of the north-south gradient is not delineated. The latest hypothesis suggests that level of vitamin D is lower in populations living in Northern Europe. Vitamin D is known to be an inducer of NOD2 function and the lack of vitamin D may result in the lower activity of NOD2 and this factor may contribute to the higher incidence of CD in regions with low sunrise exposure [21, 22].

A few population-based cohort data have been reported from Eastern Europe showing an increase in previously less industrialized countries recently [23]. The elevating rates of IBD in these countries could be due to methodological bias rising awareness of the disease and improved availability of diagnostic tools. Consequently, a prospective, population-based cohort study (EpiCom study) was established to investigate whether there is an east-west gradient in the incidence of IBD in Europe. Thirty-one centers participated across Europe and this cohort of IBD patients covers a background population of 10.1 million people. The overall annual incidence rates in all Western European centers were roughly twice as high as rates in all Eastern European centers for CD (incidence rate ratio (IRR = 1.9)) and UC (IRR = 2.1). The diagnostic approach for CD and UC seemed similar in Eastern and Western Europe. It is of interest that the incidences correlated with the GDP of each country [24].

The difference in incidence between Eastern and Western Europe and the rapid increase in incidence rates in Eastern Europe support the role for environmental factors. In the past two decades there has been a change in the lifestyle in Eastern Europe, including the diet (western lifestyle). Due to westernized diet ("junk food," food additives) luminal antigen exposure has been changed in this region. This alteration may be an important trigger in the pathogenesis of IBD [23].

Briefly, the incidence of IBD is rising with time around the world, indicating its emergence as a global disease [17]. The heterogeneity of IBD frequency in different regions highlights the role of environmental factors.

3. Incidence of Pediatric-Onset IBD

The majority of pediatric population-based reports before 1990s showed that the incidence of pediatric IBD is rising and the frequency of CD is higher than that of UC (Figure 1) [25–27]. Some studies mainly from Northern Europe described the dominance of UC [28, 29]. Incidence of pediatric IBD has been also rising according to the registry of Veszprem Province (Hungary). In CD, incidence increased from 0 in 1977–1981 to 7.2/10^5 in 2007–2011. The incidence of pediatric UC increased from 0.7/10^5 in 1977–1981 to 5.2/10^5 in 2007–2011 [30].

Temporal trends in the incidence of pediatric-onset IBD were controversial until recently (Figures 1 and 2). A systematic review describing the epidemiology of childhood-onset IBD was conducted to evaluate the alteration in incidence over the last decades. Articles published during 1950–2009 were searched and analyzed. Statistical trends in incidence of pediatric IBD were tested in nine publications; seven (77.8%) reported increased incidence over time. Twenty-five studies calculated temporal trends in CD incidence, and 15 (60.0%) described a significant increase. Twenty studies analyzed temporal trends of incidence in UC. Four (20.0%) of them reported significant increase; however, 13 reports (65.0%) showed no significant change. Rising rates of pediatric IBD were observed in both developed and developing nations [31].

Recently a few new epidemiological pediatric cohort studies revealed an increasing trend in incidence of pediatric IBD. Hope et al. investigated the incidence rate of pediatric IBD between 2000 and 2010 in Ireland. Incidence of IBD was 2.5/10^5 in 2000 that elevated to 5.6/10^5 by 2010. The mean annual increase in CD incidence was 0.153 ($P = 0.04$), and for UC it was 0.175 ($P < 0.01$) between 2000 and 2010 [32]. Geographically close to Ireland a Scottish report found a similar rising trend. A national cohort of prospectively and retrospectively acquired incident cases of pediatric IBD diagnosed less than 16 years old in pediatric services in Scotland was captured for the period 2003–2008. The incidence of CD was 4.75/10^5, and incidence rate of UC was 2.06/10^5. Significant increase in the incidence of IBD (from 4.45/10^5, $P < 0.0001$), CD (from 2.86/10^5, $P < 0.0001$), and UC (from 1.59/10^5, $P = 0.023$) was found compared with data from 1990 to 1995 [33].

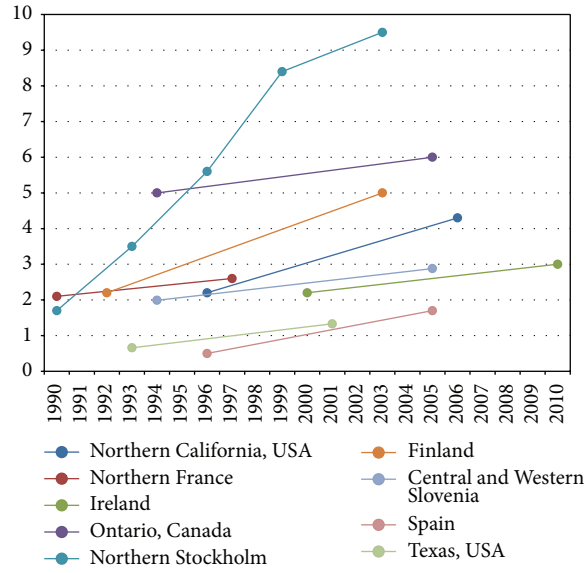

Figure 1: Incidence trends in pediatric Crohn's disease from 1990 to 2010 [5, 7, 32, 34–39].

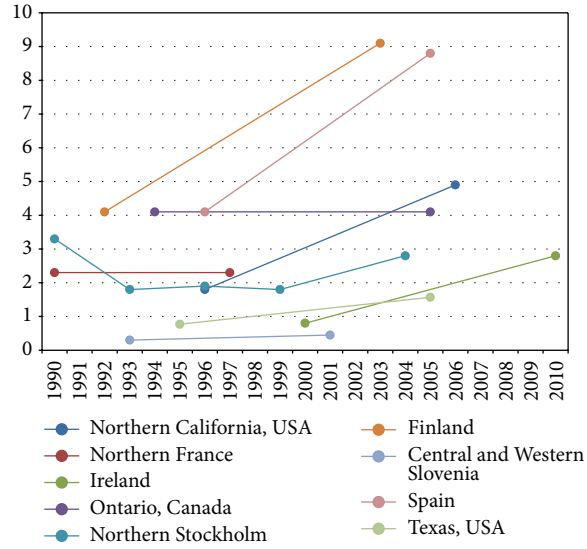

Figure 2: Incidence trends in pediatric Crohn's disease from 1990 to 2010 [5, 7, 32, 34–39].

The sex- and age-standardized incidence of pediatric IBD in Northern Stockholm during 2002–2007 was 12.8/10^5 for IBD, 9.2/10^5 for CD, and 2.8/10^5 for UC. An increasing incidence rate of UC (58.4%, $P < 0.01$) was observed during the study period. However, temporal trend for the incidence of IBD (3.2%, $P = 0.54$) was not remarkable. Meanwhile, the incidence rate of pediatric IBD in Northern Stockholm was significantly higher in 2002–2007 than that published in earlier study covering 1990–2001. The former sharp increase in incidence of pediatric CD seems to reach a plateau, although at a higher rate than reported from most other regions in the world [34]. Another Scandinavian report found similar trends. In Eastern Denmark the frequencies of

UC and CD have traditionally been similar [40]. The mean annual incidence rates in a prospective cohort during 2007–2009 were $6.4/10^5$ for IBD, $3.2/10^5$ for CD, and $3.1/10^5$ for UC. The mean incidence rates of IBD over the past 12 years (1998–2009) in Eastern Denmark increased significantly (trend test, $P = 0.02$).

The latest report from Southern Europe was conducted in Spain. A retrospective survey of patients diagnosed below 18 years of age in the period 1996–2009 was performed. Patients' data were obtained from the hospitals' databases. Martin-de-Carpi et al. described also a rise in IBD from $0.97/10^5$ to $2.8/10^5$ during 1996–2009. Although this increase is more evident for CD (from $0.53/10^5$ to $1.7/10^5$), UC has also risen (from $0.39/10^5$ to $0.88/10^5$) [7].

An east-west gradient has been reported in adults, as previously mentioned. A recent study from Eastern Europe has been published from the north-eastern part of Slovenia. The mean annual incidence was $7.6/10^5$ for IBD, $4.6/10^5$ for CD, and $2.8/10^5$ for UC. The incidence of total IBD, CD, and UC increased from $5.7/10^5$, $3.9/10^5$, and $1.8/10^5$ in the period 2002–2004, respectively, to $8.9/10^5$, $5.0/10^5$, and $3.4/10^5$ in the period 2008–2010. Data of our prospective Hungarian Pediatric IBD Registry (HUPIR) are comparable to the rate of Slovenia. The mean annual incidence rate of pediatric IBD was $7.48/10^5$, for CD it was $4.72/10^5$, and for UC it was $2.32/10^5$ during 2007–2009 in Hungary [3]. The incidence of childhood IBD in Eastern Europe seems to be high and comparable to that in western countries of Europe.

In conclusion, incidence rate of pediatric IBD has been increasing in Northern and in Southern Europe as well as in Eastern Europe.

4. Methodological Problems in Assessing Incidence of IBD in Different Regions

Incidence rates reported in different studies are not always directly comparable due to heterogeneity in study design and diagnostic criteria, and these factors can dramatically affect the incidence rates. A key issue is that some studies use hospital records while others use surveys and administrative data. The age limit is an important inclusion criterion with great impact on incidence rate. Most data are retrospective, only a few prospective population-based studies were conducted, especially reports from Asia or Eastern Europe [4, 41]. Furthermore, the incidence rates are often an extrapolation from one or more regions of a country; however, some studies reported regional variation in frequency of IBD using consistent methodologies, implying that different regions within a country may have different incidence rates [31]. In summary, most countries lack accurate estimates of incidence of pediatric IBD.

5. Reasons for Rising Incidence

The cause of increasing incidence is not established. Rising incidence seems to be true both in children and adults, suggesting that the apparent increases in IBD incidence are genuine [42]. Twin studies have shown 16%–36% concordance rates in monozygotic twins and 4% concordance rates in dizygotic twins suggesting that genetic risk factors have some role in the pathogenesis of IBD [31]. As a result, in the absence of large genetic background shifts, changing rates of IBD incidence highlight the importance of environmental factors.

The socioeconomic alteration in previously low-incident areas "from developing to developed" may be related to this rising occurrence. The spread of western lifestyle seems to be related to the elevation in incidence of Eastern European countries and in Asian countries. In concordance, emigrants of South Asian origin emigrating to Canada and UK have been observed to have an increased risk for IBD, confirming that environmental factors contribute to this higher risk [43].

The "cold chain hypothesis" suggested that refrigeration may have altered the bacterial content of our diet, resulting in the increased growth of disease-triggering organisms [44]. The well-known "hygiene hypothesis" suggests that a cleaner environment, smaller families, and lower exposure to farm animals have resulted in increased risk of IBD in westernized nations [45]. Furthermore, perinatal and early life events may also play a significant role in developing IBD [46].

6. Incidence Rates in Childhood in Different Age Groups

The rising incidence could be the consequence of the shift towards onset at a younger age; however this increase is evident in adult [17] and in pediatric-onset IBD [31] as well [47]. Incidence rate by age groups in childhood could also bring up further questions. Only a few studies reported trends of incidence after stratifying the children. Two studies divided patients into three age groups (0–5 years, 6–10 years, and 11–15 years). Henderson et al. compared incidence rates of two periods (1990–1995 and 2003–2008) and found that there was a significant increase in incidence of patients between 11 and 15 years (from $7.8/10^5$ to $11.8/10^5$, $P = 0.052$) and patients between 6 and 10 years (from $4.3/10^5$ to $7.4/10^5$, $P = 0.039$). Frequency of IBD also increased in children younger than 5 years, but this trend was not significant (from $0.9/10^5$ to $1.5/10^5$, $P = 0.292$) [33]. This result is similar to the report from Texas [35]. Incidence of IBD (compared in periods of 1990–1996 and 1997–2002) increased significantly in age groups 10–14 years and 15–17 years. However, in children between 5 and 9 years the rise was not significant and incidence was stable in children under five. Findings of a report from California are comparable; the rising trend of UC over time was significant for the age group 10 to 14 years (comparing periods of 1996–1999, 2000–2002, and 2003–2006), but the trend in children aged 15 to 17 years was not significant [36]. Chouraki et al. stratified patients into two age groups (0–9 years and 10–19 years) and also reported an obvious increase of IBD in older children and a slight increase in younger children comparing incidence rate of IBD in 1988–1990 and in 2006-2007 [6]. In contrast with these findings, Jakobsen et al. did not observe difference in incidence rates over a 12-year period (1998–2009) after

stratifying the patients into three 5-year age groups (0–4 years, 5–9 years, and 10–14 years) [48]. The only report describing a significantly rising incidence of IBD patients younger than 5 years came from Ontario, Canada [37].

Summarizing these data, only a few studies investigated long term changes of incidence in children stratified by age. According to these data, incidence is clearly increasing in children older than 10 years. In contrast, this trend is not obvious in children younger than 5 years, suggesting that this subgroup of patients is unique. One explanation could be that IBD in younger children is more likely to be genetically determined, and environmental factors may contribute to lesser extent to the pathogenesis of intestinal inflammation. However, in older children increasing incidence by age highlights the dominant role of environmental triggers. In conclusion, these results suggest that the rising incidence occurs mainly in children older than 10 years which could indicate the importance of environmental factors.

7. First Experiences with Paris Classification of Patients with Pediatric-Onset IBD

IBD develops during childhood or adolescence in up to 25% of patients. Pediatric IBD differs in some clinical characteristics from adult IBD. As previously mentioned, CD is more frequent in children than UC in contrast to adults. A male genome-wide association dominance has been observed in children with CD, while females are more frequently affected in adulthood. Despite higher familial occurrence of IBD in children genomewide association studies showed that multiple genes conferring susceptibility are comparable [49, 50]. A key feature of pediatric-onset IBD is the potential impaired growth retardation and delayed puberty. According to previous studies comparing IBD in children and adults [48, 51, 52], ileocecal location is more common in adults than in children, while panenteric disease is characteristic phenomenon in pediatric-onset CD. It is of interest that there is an association between pediatric CD patients carrying one of the three NOD2 mutations and ileocolonic involvement [53]. However, younger children with CD, similar to older adults and the elderly, are more likely to have colonic disease [54, 55]. Furthermore, upper gastrointestinal involvement is more common in pediatric IBD (16–51%). This wide range is due to two methodical approaches. On one hand, there is a difference in routine diagnostic procedure in adults and children, since workup of pediatric IBD includes gastroscopy, ileocolonoscopy, and small bowel imaging [56]; meanwhile adult gastroenterologists perform usually ileocolonoscopy and radiology. This routine may lead to underestimation of upper gastrointestinal involvement in adult CD patients. On the other hand, disease involvement was defined as ulceration or aphthous ulcers in Vienna Classification. However, in several pediatric reports, microscopic involvement has been applied as a diagnostic criterion. There is no consensus at present about what abnormalities should be regarded as proof of involvement in upper gastrointestinal biopsies. Thus, many nonspecific findings on gastroduodenal biopsies may be interpreted as evidence of disease involvement in this region [11]. In UC there is also clear difference in disease location between children and adults. Pediatric-onset UC patients are more likely to have pancolitis (60–70%); however, 20–30% of adults present with proctitis.

Table 2: Comparison of Montreal and Paris Classifications for Crohn's disease based on Levine et al. [13].

	Montreal Classification	Paris Classification
Age at diagnosis	A1: below 17 years A2: 17–40 years A3: above 40 years	A1a: 0–<10years A1b: 10–<17 years A2: 17–40 years A3: >40 years
Location	L1: terminal ileal/ limited cecal disease L2: colonic L3: ileocolonic L4*: isolated upper disease	L1: distal 1/3 ileum / limited cecal disease L2: colonic L3: ileocolonic L4a: upper disease proximal to ligament of Treitz* L4b: upper disease distal to ligament of Treitz and proximal to distal 1/3 ileum*
Behaviour	B1: nonstricturing nonpenetrating B2: stricturing B3: penetrating p: perianal disease modifier	B1: nonstricturing nonpenetrating B2: stricturing B3: penetrating B2B3: both penetrating and stricturing disease, either at the same or different times p: perianal disease modifier
Growth	—	G0: no evidence of growth delay G1: growth delay

*In both the Montreal and Paris Classification systems L4 and L4a/L4b may coexist with L1, L2, and L3, respectively.

Due to weaknesses of Montreal Classification with regard to pediatric IBD, a modified classification (Paris) has been devised [13]. The new Paris Classification included classifying age at diagnosis as A1a (0 to <10 years), A1b (10 to <17 years), A2 (17 to 40 years), and A3 (>40 years), distinguishing disease above the distal ileum as L4a (proximal to ligament of Treitz) and L4b (ligament of Treitz to above distal ileum), allowing both stenosing and penetrating disease to be classified in the same patient (B2B3), denoting the presence of growth failure in the patient at any time as G1 versus G0 (never growth failure), adding E4 to denote extent of ulcerative colitis that is proximal to the hepatic flexure, and denoting ever severe ulcerative colitis during disease course by S1 (Tables 2 and 3).

7.1. Newly Diagnosed Pediatric IBD Patients According to Paris Classification. Recently a few center- and population-based studies analyzed newly diagnosed pediatric IBD patients according to Paris Classification: (1) a study of prospectively collected IBD patients younger than 15 years diagnosed in Northern Stockholm (2002–2007) [34]; (2) a retrospective study of IBD patients younger than 16 years from

Table 3: Comparison of Montreal and Paris Classifications for ulcerative colitis based on Levine et al. [13].

	Montreal Classification	Paris Classification
Extent	E1: ulcerative proctitis E2: left-sided UC (distal to splenic flexure) E3: extensive (proximal to splenic flexure)	E1: ulcerative proctitis E2: left-sided UC (distal to splenic flexure) E3: extensive (hepatic flexure distally) E4: pancolitis (proximal to hepatic flexure)
Severity	S0: clinical remission S1: mild UC S2: moderate UC S3: severe UC	S0: never severe* S1: ever severe*

*Severe defined by Pediatric Ulcerative Colitis Activity Index (PUCAI).

Table 4: Paris Classification of patients with Crohn's disease in population-based studies in Europe [3, 32, 34, 57, 58].

	North-Eastern Slovenia	Northern Stockholm	Eurokids	Hungary (HUPIR)	Ireland
Crohn's disease (*n*)	43	96	582	247	31
Age, % (*n*/*n*)					
A1a	15	—	20% (244/1221)	11% (27/247)	26% (8/31)
A1b	—	—	80%	78% (197/247)	74% (23/31)
A2	—	—		9% (23/247)	
Location, % (*n*/*n*)					
L1*	20.9% (9/43)	8% (8/96)	16%	13.4% (33/247)	19% (6/31)
L1 + L4a	2.3%	—	3.6% (21)		
L1 + L4b	0	—	3.4% (20)	3% (7/247)	13% (4/31)
L1 + L4ab	7%	—	1.4% (8)		
*L2	4.6% (2/43)	71% (68/96)	28% (159/582)	27.5% (68/247)	45% (14/31)
L2 + L4a	0	—	4.1% (24/582)		
L2 + L4b	0	—	3.8% (22/582)	6.8% (17/247)	3% (1/31)
L2 + L4ab	0	—	1.2% (7/582)		
*L3	74.5% (32/43)	20% (19/96)	53%	58.7% (145/247)	32% (10/31)
L3 + L4a	23.3%	—	14.3%		
L3 + L4b	11.6%	—	6.5%	49	16% (5/31)
L3L4ab	16.3%	—	4.3%		
L4 (Isolated)	0	0	4% (18/582)	0.4% (1/247)	3% (1/31)
All upper gastrointestinal involvement				0.4% (1/247)	
L4a	48.9% (21/43)	17% (16/96)			
L4b	34.9% (15/43)	1% (1/96)			
Behaviour					
B1	86% (56/65)	95% (91/96)	82% (959/1177)	12.1% (216/256)	90% (28/31)
B2	6% (4/65)	5% (5)	12% (144/1177)	2.3% (31/256)	6% (2/31)
B3	8% (5/65)	0	5% (55/1177)	1.2% (6/256)	3% (1/31)
B2B3	—	0	2% (19/1177)	0.6% (3/256)	—
Perianal disease	—	8% (8/96)	9% (114/1207)	14.5% (37/247)	10% (3/31)
Growth (G1) G1				6.6% (16/244)	23% (4/31)

*L1 + L4a, L1 + L4b, and L1 + L4ab patients are included in patients with L1 location.
A1a: 0–<10 years, A1b: 10–<17 years, and A2: 17–<40 years. B1: nonstricturing-nonpenetrating; B2: stricturing; B3: penetrating; B2B3: both penetrating and stricturing; G1: evidence of growth delay; L1: distal 1/3 ileal disease (limited cecal disease); L2: colonic disease; L3: ileocolonic disease; L4: upper gastrointestinal tract disease; L4a: esophagogastroduodenal disease proximal to ligament of Treitz; L4b: distal to ligament of Treitz.

Table 5: Paris Classification of ulcerative colitis patients in population-based studies in Europe [3, 32, 34, 57, 58].

	North-Eastern Slovenia	Northern Stockholm	Eurokids	Hungary (HUPIR)	Ireland
Ulcerative colitis (*n*)	39	29	578	121	14
E1	5.2% (2/39)	11% (3/29)	5% (27/578)	5% (6/121)	14% (2/14)
E2	25.6% (10/39)	14% (4/29)	18% (104/578)	24.8% (30/121)	14% (2/14)
E3	7.7% (3/39)	4% (1/29)	9% (50/578)	13.2% (16/121)	7% (1/14)
E4	61.4% (24/39)	75% (21/29)	69% (397/578)	57% (69/121)	65% (9/14)
Severity (S1)	—	—	—	18.6% (13/121)	43% (6/31)

E1: ulcerative proctitis; E2: left-sided ulcerative colitis (distal to splenic flexure); E3: extensive colitis (hepatic flexure distally); E4: pancolitis (proximal to hepatic flexure); S1: severe at some stage.

Ireland; (3) the Eurokids registry, a prospective, center-based registry of newly diagnosed pediatric IBD patients in 44 IBD centers in 18 countries [57]; (4) a retrospective study on a cohort of newly diagnosed children aged 0–18 years from North-Eastern Slovenia (2002–2010) [58]; (5) our prospective, nationwide, incident cohort of pediatric IBD patients younger than 18 years from Hungary [3] (Tables 4 and 5). The main findings were similar to earlier reports and were comparable to each other: (1) ileocolonic involvement was the characteristic disease location in CD; (2) pancolitis dominated in UC; (3) rate of perianal disease and complicated behaviour was similar.

However, the reports from Northern Stockholm and Ireland showed a higher rate of pure colonic CD than the others (71% and 45% versus 27–28%), which is in contrast with most population-based studies from both Europe and North America [40, 59, 60]. Among earlier studies two reports described similar figures of isolated colonic CD (Scotland 66% [51]) and Sweden 43% [61]). Further studies are needed to determine if these contrasts point to possible disease-modifying environmental or other factors. However, all of these studies applied an age limit of 16 years, whereas the age limit of studies with lower rate of isolated colonic involvement included patients younger than 18 years. This difference in inclusion criteria may contribute to a shift of proportion of patients with purely colonic CD.

7.2. Follow-Up and Paris Classification. Hope et al. followed up Irish IBD patients for 2 years and found that the progression of disease extension in CD during the first 2 years of disease course was not frequent [32]. This result is in contrast with the disease extension presented by van Limbergen et al. (39% at 2 years) [51] and by Vernier-Massouille et al. (31% at median follow-up of 84 months) [60]. Analysis of the 196 childhood-onset CD patients demonstrated that 53 of 196 (27.0%) had panenteric involvement (L3 + L4) at diagnosis [51]. During 2 years follow-up, 56 (39.1%) children had progression in disease extension: changes were mostly due to extension from localized disease to more extensive disease involving the lower gastrointestinal tract (41/56, 73.2%). Meanwhile, the proportions of disease location in UC had not changed significantly [51] at last follow-up. The conflicting results may be due to methodological differences (longer recruitment and follow-up period in earlier studies). However, the location of disease changed over time in other publications conducted in adults as well [62]. This may query the relationship of disease course and initial disease characteristics.

In the report from North-Eastern Slovenia progression of disease extension was also investigated. At diagnosis, 16.3% had panenteric disease (L3L4ab), while extensive involvement was observed in 21.6% of patients during the follow-up period [58]. In UC, proportion of patients with pancolitis (E4) increased from 61.5% to 76.5%, respectively. At presentation, only 6% of CD patients had stricturing and 8% had penetrating phenotype, and these complicated phenotypes doubled during the follow-up. In agreement with these figures other studies also observed a similar 2-fold rise in complicated CD behaviour during the follow-up [32, 51, 60]. In UC, rate of patients with pancolitis (E4) increased from 61.4% to 76.5%.

7.3. Paris Classification and Clinical Characteristics. Association of epidemiological and disease characteristics, like family history and extraintestinal manifestations (EIM), with phenotype according to Paris Classification has been analyzed in two recent studies. In our study we did not find any significant relationship between age and gender distribution or family history, EIM, and disease location in CD or in UC [3]. In contrast, de Bie et al. described that isolated colonic disease was recorded in 41% (47/114) of children diagnosed before 10 years of age compared with 24% (111/467) of older children ($P < 0.001$) [57]. A similar trend was found in the Hungarian cohort, though the difference was not significant. The two studies concurred that upper gastrointestinal involvement was not related to age, gender, family history of IBD, or presence of EIM. However, Lazarev et al. described a significantly greater risk for multiple abdominal surgeries in patients with jejunal involvement than in patients with upper gastrointestinal involvement proximal to the ligament of Treitz [63].

According to Eurokids, rate of perianal disease occurred more often in patients with B3 than in patients with B1 (38% versus 8%, $P < 0.001$) and B2 (38% versus 7%, $P < 0.001$). In addition, patients with L2 disease were less likely to have stricturing disease complications compared with patients with L1 or L3 disease (6% versus 21% versus 15%, $P = 0.005$). These latter results were not observed in our study, which is may be due to the lower number of included patients (582 versus 247). This discrepancy is probably due to

the different population of the two studies. Eurokids registry is not a population-based cohort, but a selection of centers with special interest in IBD; meanwhile the HUPIR is a population-based incident cohort involving less severe cases. This phenomenon emphasizes the importance of nationwide registries that enroll all pediatric patients with IBD including less severe cases also.

In conclusion, the first reports have shown that Paris Classification is a useful tool to determine the characteristic pediatric CD phenotype. Location of disease is comparable in studies with Paris Classification to studies classifying patients according to earlier classification systems.

8. Conclusions

The worldwide increasing trends of IBD incidence seem to be evident in adults [17] as well as in children [31]. Exploring increase in incidence of IBD may provide useful insights into the pathogenesis, especially with regard to environmental factors related to industrialization, such as changes in hygiene, a more westernized diet, economic growth, and the shift from rural to urban environments [42]. Furthermore, clinical classification, like Paris Classification, may contribute to define distinct subgroup of patients with different prognosis with different therapeutical approach.

However, there are several methodological clues that complicate comparing studies from different regions. Consequently, more prospective, population-based studies (data should not only come from center specialized for IBD) are needed to delineate the frequency of IBD and disease phenotype.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Clinical Study

Functional Outcomes and Quality of Life after Restorative Proctocolectomy in Paediatric Patients: A Case-Control Study

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Background. Restorative proctocolectomy with ileal-pouch anal anastomosis (IPAA) has some peculiarities in paediatric ulcerative colitis (UC). *Aims*. The primary aim was to compare the bowel function of patients undergoing IPAA between those operated on in childhood and adulthood. The secondary aim was to compare the quality of life (QoL) and outcomes for children between medical and surgical therapies. *Method*. Children undergoing IPAA were compared with adult patients undergoing IPAA between 2007 and 2012. Function was assessed 1 year after ileostomy closure. Function and QoL of medically managed paediatric patients were compared with their surgical counterparts. *Results*. Twelve paediatric IPAA patients were compared with 24 adult ones. Acute presentation was common in the former, usually after failed biological treatment. Recurrent pouchitis was more frequent in children. Younger patients exhibited a trend toward better discrimination and continence. QoL was excellent in both groups. Twelve medically treated children were enrolled for secondary aim. Functioning was similar in IPAA- and medically managed children, but the former had a better QoL, confirmed by parents' perception. *Conclusions*. Similar function is achieved by IPAA in childhood or adulthood. IPAA may offer a better QoL compared to prolonged medical management. The beneficial effects of IPAA experienced by children were similarly observed by their parents.

1. Introduction

Restorative proctocolectomy involving the formation of an ileal pouch and ileal-pouch anal anastomosis (IPAA) is the treatment of choice for refractory or complicated ulcerative colitis (UC) [1]. IPAA is regarded as the mainstay treatment for UC in both the elderly [2] and the paediatric population [3]. However, this is a very complex procedure, and inadequate data exist comparing the functional outcomes of patients undergoing IPAA for UC between those operated on in childhood and adulthood. The available reports are difficult to interpret because of disparities in patient assessments and the wide range of observations [4]. The primary aim of this study was to compare the functional outcomes of IPAA between a paediatric cohort and adult patients. The secondary aim was to compare the bowel function and quality of life (QoL) of children diagnosed with UC between those undergoing IPAA and those treated medically.

2. Materials and Methods

The data of patients diagnosed with UC and treated or referred to our institutions between 2007 and 2012 were collected prospectively.

2.1. Primary Aim. The data of 12 patients aged between 5 and 16 years undergoing IPAA for UC during the study period were collected and compared with those of patients aged between 30 and 45 years of age (ratio 1 : 2). The patients in

each group were matched according to sex, disease duration, and surgical details.

The surgical treatment was performed as a two- or three-stage procedure in an elective or emergency setting, respectively, and, in the case of paediatric patients, always required fashioning of a stoma at the time of IPAA [5–7]. Adult patients undergoing one- or two-stage modified IPAA surgery were not included. The operative variables and complications were evaluated in the perioperative phase, within 30 days of the IPAA. Functional outcomes were assessed at the 1-year follow-up after ileostomy closure, which was carried out after clinical and endoscopic evaluations. A pouchography was performed in selected cases [7]. Patients were asked to complete a 7-day diary of bowel movements. QoL was assessed 1 year after ileostomy takedown using the age-adjusted Pediatric Quality of Life Inventory (PedsQL) Short Form-15 (SF-15) [8] and the inflammatory bowel disease questionnaire (IBDQ) [9] for the children and adults, respectively.

2.2. Secondary Aim. The data of patients aged between 5 and 16 years undergoing IPAA for UC ($n = 12$) were compared with those of consecutive age-matched patients with UC who were managed medically ($n = 12$). Patients serving as controls were included, if they had been diagnosed with UC at least 1 year previously.

Bowel control and symptoms were graded according to the PedsQL Gastrointestinal Symptom Scale (PedsQL-GSS) [10], which was administered to the patients and parents of both groups. QoL was evaluated using the PedsQL-SF-15 in both groups 1 year after ileostomy closure and after the first medical treatment.

2.3. Statistical Analysis. The results are expressed as median (range) or n (%) values, as appropriate. Differences in medians between subgroups were compared using the Mann-Whitney U test. Comparisons between categorical variables were analysed using Fisher's exact test. The cutoff for statistical significance was set at $P < 0.05$. Data were analysed using the SPSS statistical package (version 17.0, SPSS for MS Windows, Chicago, IL, USA).

3. Ethical Considerations

This study was conducted following the Guidelines for Good Clinical Practice and was approved by the internal Institutional Review Board. Written informed consent to participate was provided by all of the paediatric patients' parents and by all of the adult patients serving as controls.

4. Results

Twelve patients who underwent IPAA for UC during the study period were included in the study. Twenty-four adult UC patients with IPAA and 12 age-matched, paediatric UC patients who were managed with medical treatment during the study period served as controls for the primary and secondary aims, respectively.

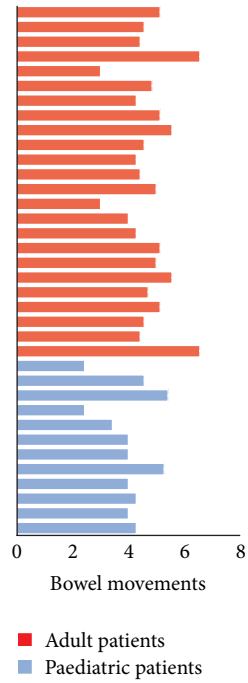

Figure 1: Stool frequency in adult and paediatric patients with IPAA. Bars represent the mean scores of a 7-day diary. Most patients reported four to six bowel movements daily. No significant differences were observed relative to age at surgery [paediatric versus adult IPAA, median (range): 5 (1–9) versus 5 (2–9), $P = 0.54$].

4.1. Primary Aim. The demographic, clinical, and surgical data of the IPAA patients are reported in Table 1, sorted according to the age at surgery. Although the adult patients appeared more likely to be receiving immunosuppressant drugs at the time of first surgery and on treatment with drugs for conditions other than UC when compared with the younger patients, the difference was not statistically significant. Conversely, a three-stage approach was carried out significantly less frequently among the adult patients.

Patients undergoing IPAA in childhood were more often found with extra-intestinal manifestations (EIMs; $P = 0.02$). More than half of the adult patients but less than one-quarter of the children underwent surgery without receiving treatment with biological drugs ($P = 0.4$).

No significant differences were observed in terms of major perioperative complications (one child suffered a haemorrhage and one adult had an anastomotic leak; $P > 0.99$).

Three patients in each group experienced at least one episode of pouchitis at the 12-month follow-up (25% versus 12.5%, $P = 0.38$); all three of the paediatric patients with pouchitis experienced recurrent pouchitis, compared with one of the adult cases ($P = 0.09$). All cases of pouchitis were managed with antibiotic administration.

The functional results are given in Table 2. The median stool frequency was similar in the two groups, although the younger patients reported fewer bowel movements per day in their 7-day diaries (Figure 1). No significant differences were observed in patients with night-time incontinence and

Table 1: Characteristics of IPAA patients by age. Except where indicated otherwise, data are median (range) or n (%) values.

	IPAA childhood ($n = 12$)	IPAA adulthood ($n = 24$)	P
Age, years	12 (5–16)	33.5 (29–48)	**<0.0001**
BMI, kg/m^2	18 (15–23)	21.5 (17–28)	0.09
Sex (male/female), n	5/7	11/13	>0.99
Steroids at time of first surgery*	4 (33.3)	9 (37.5)	>0.99
Azathioprine at time of first surgery	0 (0)	2 (8.3)	0.54
Naïve to biologic drugs	2 (16.6)	13 (54.2)	**0.04**
Drugs other than anti-UC drugs	1 (8.3)	7 (29.2)	0.2
EIMs	7 (58.3)	4 (16.7)	**0.02**
Three-stage procedure	5 (41.7)	4 (16.7)	0.12
Hand-sewn anastomosis	4 (33.3)	9 (37.5)	>0.99
Major perioperative complications	1 (8.3)	1 (4.2)	>0.99
Pouchitis			
At least one episode	3 (25)	3 (12.5)	0.38
Relapsing at least once	3/3 (100)	1/3 (33.3)	0.09

IPAA: ileal-pouch anal anastomosis; BMI: body mass index; UC: ulcerative colitis; EIMs: extraintestinal manifestations.
*>20 mg of corticosteroids.

Table 2: Bowel function of IPAA patients by age. Except where indicated otherwise, data are n (%) values.

Function	IPAA in childhood ($n = 12$)	IPAA in adulthood ($n = 24$)	P
Stool frequency per day, median (range)	5 (1–9)	5 (2–9)	0.54
Night evacuation	3 (25)	5 (20.8)	>0.99
Urgency	1 (8.3)	1 (4.2)	>0.99
Frequent incontinence during day	0 (0)	1 (4.2)	>0.99
Frequent incontinence during night	1 (8.3)	1 (4.2)	>0.99
Impaired discrimination	1 (8.3)	5 (20.8)	0.64

IPAA: ileal-pouch anal anastomosis.

urgency, and although the younger patients exhibited a trend toward better discrimination (good discrimination in 92% of younger patients versus 80% of controls) and daytime continence (100% versus 96%), the difference did not reach statistical significance. Irrespective of the age at surgery, less than 35% of the patients in each group had a suboptimal QoL.

4.2. Secondary Aim. Table 3 lists the characteristics of the patients according to the treatment delivered. Twelve medically treated UC children served as controls. Although the IPAA patients appeared to have a lower body mass index (BMI) and higher rates of EIMs and treatment with biological drugs, the groups were actually statistically homogeneous.

The PedsQL-GSS revealed no differences in function or bowel control (Figure 2). The IPAA and medical patients achieved scores of 0.83 (0.71–0.91) and 0.87 (0.73–0.92), respectively ($P = 0.42$). Furthermore, the parent-reported that scores did not differ significantly between the two groups [0.82 (0.90–0.67) versus 0.86 (0.93–0.60), $P = 0.79$]. There was good agreement between the patients' and their parents' reports.

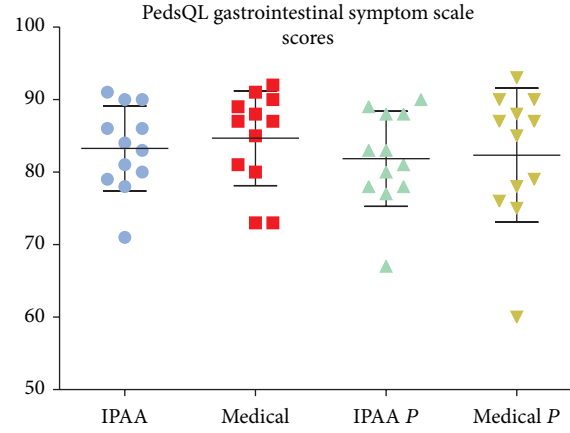

Figure 2: PedsQL-Gastrointestinal Symptom Scale scores in children receiving either surgical (IPAA, $n = 12$) or medical (medical, $n = 12$) therapy. The parents' scores for the two groups are reported as IPAAp and medicalp, respectively. No differences were observed: IPAA versus medical, 0.83 versus 0.87 ($P = 0.42$); IPAAp versus medicalp, 0.82 versus 0.86 ($P = 0.79$); IPAA versus IPAAp, 0.83 versus 0.82 ($P = 0.5$); medical versus medicalp, 0.85 versus 0.82 ($P = 0.62$). IPAA: ileal pouch-anal anastomosis; p: parent.

Table 3: Characteristics of patients in the childhood by treatment. Except where indicated otherwise, data are median (range) or n (%) values.

	IPAA ($n = 12$)	Medical ($n = 12$)	P
Age, years	12 (5–16)	11 (6–16)	0.67
BMI, kg/m^2	18 (15–23)	18 (15–21)	0.12
Sex (male/female), n	5/7	6/6	>0.99
Steroids at least once	5 (41.7)	4 (33.3)	>0.99
Azathioprine	1 (8.3)	2 (16.7)	>0.99
Naïve to biologic drugs	2 (16.6)	5 (41.7)	0.37
Drugs other than anti-UC drugs	1 (8.3)	2 (16.7)	>0.99
EIMs	7 (58.3)	2 (16.7)	0.08

IPAA: ileal-pouch anal anastomosis; BMI: body mass index; UC: ulcerative colitis; EIMs: extraintestinal manifestations.

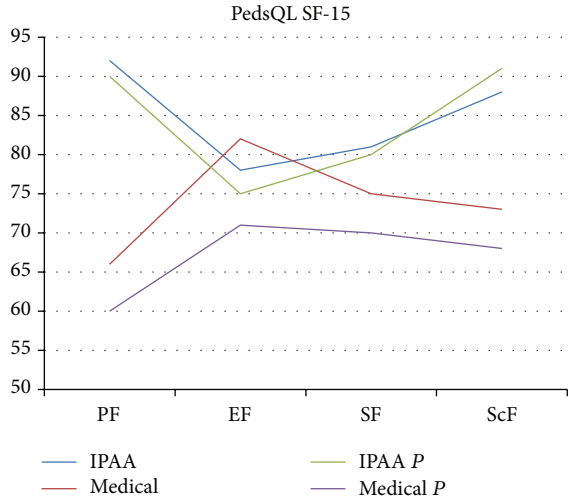

Figure 3: PedsQL-SF-15 scores of IPAA and medical patients. Each dimension of the questionnaire is reported separately. Several significant differences were observed. Overall QoL-IPAA versus medical, 0.84 versus 0.74 ($P = 0.04$); SF-IPAA versus medical, 0.92 versus 0.68 ($P = 0.02$); ScF-IPAA versus medical, 0.88 versus 0.72 ($P = 0.04$); overall QoL-medical versus medicalp, 0.72 versus 0.67 ($P = 0.04$). PF: physical function; EF: emotional function; SF: social function; ScF: school function; IPAA: ileal pouch-anal anastomosis.

The overall median QoL was higher for the IPAA patients than for the medically treated patients (0.84 versus 0.74, $P = 0.04$; Figure 3). Comparison of each dimension of the PedsQL-SF-15 revealed that the IPAA patients scored significantly higher than their medically managed counterparts in physical functioning (0.92 versus 0.68, $P = 0.02$) and school functioning (0.88 versus 0.72, $P = 0.04$). The parents of both groups reported lower scores compared with the patients; a statistically significant discrepancy was observed in medically treated patients, with their parents reporting worse QoL scores overall (0.72 versus 0.67, $P = 0.04$).

5. Discussion

The present data suggest that there are some age-related differences in the presentation and preoperative management of patients suffering from UC. IPAA can be safely performed in childhood by experienced surgeons to produce functional results that are comparable to those of patients undergoing the pelvic pouch procedure in adulthood. Irrespective of age, an excellent QoL can be expected in more than half of the patients undergoing IPAA; the results on continence and discrimination of the procedures performed at an earlier age are promising. However, refractory/recurrent pouchitis may be an issue.

Children diagnosed with UC who underwent IPAA had more similar bowel control than age-matched, medically managed controls in this study. IPAA patients may achieve higher QoL scores by 1 year after ileostomy closure and once they have adapted to the new function, a finding that was reflected by the parents' perception of their children's QoL.

The aims of the treatment of paediatric patients affected with active UC are to induce and maintain remission, improve QoL, ensure normal growth, and prevent colonic neoplastic degeneration [5]. Failure to gain weight, the significant side effects of corticosteroids and long-standing disease are peculiar indications to paediatric IPAA surgery [11]. Children more frequently present with pancolitis and a more aggressive disease course [3]. In the present series, the incidence of EIMs at disease onset was higher among the young patients than among their adult counterparts. Children more often required subtotal colectomy because of aggressive disease (Table 1) associated with intense activity of the immune system, with early medical refractoriness or rapid worsening of health status [4]. Biological drugs are useful for postponing surgery, thus allowing elective colectomy, and may be used to avoid immunosuppressive therapy [3, 12]. When compared with the adult IPAA patients, those undergoing IPAA in childhood were more likely to be receiving a rescue therapy with biological drugs, failing to avoid surgery. In addition to reflecting a greater confidence in biological drugs of paediatric gastroenterologists, this reveals a reluctance to refer young patients to surgery earlier in the course of their disease. Nonetheless, almost 50% of UC children who were managed medically were naïveto biological drugs (Table 3).

IPAA is the procedure of choice for the radical treatment of UC; it reduces the stool frequency when compared with straight ileoanal anastomosis [13] and dramatically diminishes the risk of cancer when compared with ileorectal anastomosis [14]. IPAA controls intestine-related EIMs and

avoids prolonged drug administration. Moreover, since UC in children is—by definition—fated to be long-standing, eliminating the risk of neoplastic degeneration is crucial. Strict, invasive, and sometimes painful follow-ups are the price to pay for the retention of a diseased colon. However, the morbidity associated with the surgery is high, and complications occurring in the perioperative period may affect function in the long term [15, 16]. We included only patients operated on by a team led by a senior surgeon with a large pouch-procedure caseload and extensive experience with pelvic pouch surgery. When these conditions are met, no significant differences are to be expected (Table 1).

The incidence of pouchitis in adult UC patients reportedly ranges between 15% and 18% during the first year after ileostomy closure, reaching 48% by the tenth postoperative year [17, 18]. The first episode is observed within 1 year after ileostomy closure in 70% of patients with pouchitis [19]. The incidence may be even higher in children [20], with more than half developing recurrent episodes, and chronic pouchitis developing in up to 10% [21]. Failure occurs in almost 10% of these patients within 10 years [18, 22]. By using very stringent criteria, we were able to identify pouchitis in 25% and 12.5% of the children and adults, respectively; these proportions are lower than those reported in the literature. Pouchitis was managed by probiotics and antibiotic administration. The recurrence rates, rather than the incidence itself, appeared to differ between the groups, with all children experiencing a recurrence within 6 months. This discrepancy may be attributable to differences between children and adults in disease severity at presentation, as well as in their preoperative medical management.

Bowel function after IPAA is good in the large majority of patients and is stable with time over 20 years [23]. In the present series, despite the comparable overall number of evacuations per day between the adults and children, the latter had a lower mean number of evacuations per day per patient over a week. No differences were observed between patients according to age; however, there was a trend toward better discrimination and daytime continence among the younger patients.

Concerning health-related QoL, bowel control may be more important than stool frequency in children affected with UC. Uchida et al. [24] recently reported that children who experience good bowel function after IPAA may perceive their well-being to be identical to that of healthy individuals. A weak point of the QoL assessment in children with a pelvic pouch is the lack of standardized tools with which data is acquired. The wide time spans and data heterogeneity in most studies makes it difficult to interpret the data obtained in this population. In our practice, we routinely administer a QoL questionnaire to our patients. However, a statistical comparison between the QoL in adults and children was not performed in this series, since a child's perception of the world, life, death, and disease is quite different from that of adults.

IPAA resolves the interference between social functioning and the disruption of emotional status that is caused by refractory UC [25, 26]. We compared the bowel function of children who underwent IPAA and children whose UC was managed medically and found similar PedsQL-GSS scores in the two groups. This ruled out the risk of including control patients with unacceptably poor function (selection bias). We then evaluated QoL using the PedsQL SF-15. The results highlighted the superiority of IPAA over medical treatment in children suffering from UC. The difference was even more apparent on comparison of the QoL scores of the parents with those of their children, suggesting that parents of medically treated children are dealing with a feeling of uncertainty and fear due to potential relapse of the disease.

5.1. Study Limitations. The conclusions of this study should be considered in the light of several limitations. The follow-up period was short, although it was sufficient for our purposes and long-term results (i.e., pouch retention/failure) were not an aim of this research. The study may have lacked statistical power due to the smallness of the sample, which may have been responsible for the absence of significant differences. However, by considering bowel function after IPAA in paediatric versus adult UC patients as a primary aim, assuming success rates (i.e., good or optimal bowel function) of 90% and 80%, respectively, with a 20% noninferiority limit, 12 patients per group were required to be 70% sure that the upper limit of a two-sided 95% confidence interval would have excluded differences between groups ($\alpha = 0.05$). Furthermore, the data were collected prospectively, and there is a dearth of evidence on this topic in the literature.

6. Conclusions

The findings of this study suggest that the functional results of IPAA are similar irrespective of whether this procedure is performed in childhood or adulthood. The health-related QoL is likely to be better after IPAA than for prolonged medical management. Such a beneficial effect was similarly observed for the parents' perception of their children's disease.

Abbreviations

EIMs: Extra-intestinal manifestations
GSS: Gastrointestinal Symptom Scale
IBDQ: Inflammatory bowel disease questionnaire
IPAA: Restorative proctocolectomy with ileal-pouch anal anastomosis
PedsQL: Pediatric Quality of Life Inventory
QoL: Quality of life
SF-15: Short Form-15
UC: Ulcerative colitis.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Review Article

Highlights in IBD Epidemiology and Its Natural History in the Paediatric Age

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Background. The number of patients of all age brackets diagnosed with Inflammatory Bowel Disease (IBD) has risen dramatically worldwide over the past 50 years. IBD's changing epidemiology suggests that environmental factors play a major role in modifying disease expression. *Aim*. To review studies carried out worldwide analyzing IBD epidemiology. *Methods*. A Medline search indicating as keywords "Inflammatory Bowel Disease," "epidemiology," "natural history," "Crohn's Disease," "Ulcerative Colitis," and "IBD Unclassified" was performed. A selection of clinical cohort and systematic review studies that were carried out between 2002 and 2013 was reviewed. Studies referring to an earlier date were also considered whenever the data were relevant to our review. *Results*. The current mean prevalence of IBD in the total population of Western countries is estimated at 1/1,000. The highest prevalence and incidence rates of IBD worldwide are reported from Canada. Just as urbanization and socioeconomic development, the incidence of IBD is rising in China. *Conclusions*. Multicenter national registers and international networks can provide information on IBD epidemiology and lead to hypotheses about its causes and possible management strategies. The rising trend in the disease's incidence in developing nations suggests that its epidemiological evolution is linked to industrialization and modern Westernized lifestyles.

1. Introduction

The number of patients of all age brackets diagnosed with Inflammatory Bowel Disease (IBD) has dramatically increased worldwide over the past 50 years. The changing epidemiology of IBD across time and geography suggests that environmental factors are involved in modifying disease expression [1]. Insight into the worldwide epidemiology of this disease is, thus, important to identify geographic patterns and time trends. Recent findings will also make it possible to estimate the global public health burden so that health care resources can be allocated and research can be targeted in specific geographic regions. Information about environmental factors hypothetically affecting the incidence and prevalence of this disease may, finally, lead to prevention interventions when possible.

The aim of this paper is to review the current levels of knowledge concerning IBD epidemiology worldwide and to examine its natural history in paediatric patients.

The first paragraphs of Section 3 of this report will provide an overview of statistics concerning the incidence and prevalence in the general and paediatric worldwide population, considering its two forms, Crohn's Disease (CD) and Ulcerative Colitis (UC) separately. The rest of the section will outline disease trends in specific geographic areas. In Section 4, we will go on to describe the disease's natural history in the paediatric population examining, as before, the two forms separately.

2. Methods

A Medline search using the following keywords "Inflammatory Bowel Disease," "epidemiology," "natural history," "Crohn's Disease," "Ulcerative Colitis," and "Unclassified IBD" was carried out.

Clinical cohort and systematic review studies performed during the 2002–2013 time frame were reviewed. Studies

conducted earlier were also taken into consideration whenever the data outline was considered relevant to this review.

In view of the fact that they are characteristically based on homogeneous diagnostic criteria, practical aspects of phenotypic data collection, and clinical expertise on IBD treatment, population-based studies were given priority in the selection process. Studies based on health administrative databases were also included whenever they clarified epidemiology statistics in particular with reference to paediatric patients [2].

3. IBD Epidemiology Worldwide: Data Regarding the General and Paediatric Populations

The etiology of IBDs, which are disorders of chronic inflammation of the gastrointestinal tract marked by episodes of relapse and remission, is not yet fully elucidated. Its two main forms, CD and UC, are diagnosed on the basis of a clinical suspicion and laboratory, radiological, endoscopic, and histological findings [22]. It is not always possible to distinguish between these two forms using the diagnostic tools available, and the term Inflammatory Bowel Disease Unclassified (IBD-U) is currently used to categorise this subgroup of patients with chronic intestinal inflammation. It is important to remember that the misclassification and/or reclassification of the disease can cause diagnostic delays as well as underestimation of IBD's global prevalence and incidence [23, 24].

The reasons behind the rising worldwide trend are not entirely clear [1]. The current mean prevalence of IBD in the general population of Western countries is estimated at 1/1,000 inhabitants [25, 26]. Although there are only few epidemiologic data available regarding developing countries, the disease's incidence and prevalence seem to be increasing over the past 50 years in practically all regions of the world, indicating its emergence as a global disease [27, 28]. The trend appears to have stabilised for the adult population but not for the paediatric one, especially in Central and Southern Europe where it appears to be rising [29, 30].

Both forms of the disease are thought to be linked to a combination of individual genetic susceptibility, environmental triggers, and alterations in the gut microbiome that stimulate an inflammatory response. The changing epidemiology of IBD across time and geographic areas suggests that environmental factors play a major role in modifying disease expression, and its rising incidence in developing nations seems to be linked to industrialization and the Western lifestyle. The most important environmental associations that have been identified until now are cigarette smoking and appendectomy, although neither alone can explain the variation in the incidence of IBD worldwide. Urbanization in some developing countries, diet changes, antibiotics, hygiene status, microbial exposure, and pollution have all been implicated as potential environmental risk factors for IBD, and individual, familial, and community-, regional-, and country-based environmental risk factors could, singularly or together, contribute to its pathogenesis [31].

Estimates of the incidence of paediatric-onset IBD reported around the world vary considerably [24] as do its patterns and distributions in the various age brackets of the paediatric population [32, 33]. Although less prevalent in infants and in very young children, a number of case reports and small population studies have documented disease onset at very early ages. Heyman et al. [34] analyzed the data from a large multicenter registry of children and adolescents affected by IBD in the attempt to answer specific epidemiologic questions. The cohort—58% diagnosed with CD, 29% with UC, and 13% with IBD-U—contained both incident and prevalent cases enrolled over a 2-year period. According to multivariate analysis, the children younger than 8 were 2.5 times more likely to have UC and 3.5 times more likely to have IBD-U than those older than 8. Colonic involvement with or without disease at other sites was more prevalent in the younger patients. Patients with early-onset IBD, in particular very young patients with UC, were more likely to report a family history of IBD. Patients with familial forms (i.e., children whose parents also suffer from IBD) generally develop the disease earlier due to the genetic anticipation phenomenon [35].

Very early IBD onset appears to distinguish a subgroup of patients with unique characteristics [36–38]. Underlying immune deficiencies including glycogenosis, IL-10R deficiency, and other mutations involving cytokines, receptors, or mediators must always be excluded when a child under 5 is being diagnosed. An intestinal IBD-like pattern has been found to be associated in these cases with systemic immunodeficiency within a complex scenario which can even lead to severe life-threatening events (i.e., systemic infections) [39, 40].

Glocker et al. [41] identified mutations in genes encoding the IL10R subunit proteins in patients with early-onset enterocolitis, involving hyperinflammatory immune responses in the intestine. Genetic-linkage analysis and candidate-gene sequencing on samples from two unrelated consanguineous families with children affected by early-onset IBD and functional assays of patients' peripheral blood mononuclear cells were carried out. The investigators identified three distinct homozygous mutations in genes IL10RA and IL10RB, encoding the IL10R1 and IL10R2 proteins in four out of nine patients with early-onset colitis. The mutations abrogate interleukin-10-induced signalling. According to some case studies examining IL-10R deficient patients, hematopoietic stem cell transplantation (HSCT) is generally successful [40–42].

Assessing the incidence of IBD is complicated, especially in the developmental age, as epidemiological investigations tend to ignore cases of IBD-U although they are generally considered an early stage of the disease (in up to 13% of cases and in as much as up to 20% in some Northern European populations) [29, 30, 43]. IBD can also be difficult to recognize, particularly in children when these present atypical symptoms and in third world countries where medical services are lacking.

3.1. The Worldwide Incidence of UC and CD in the General and Paediatric Populations. The incidence of UC has been rising

in Western countries over the past 50 years, incrementing from 8–14/100,000 to 120–200/100,000 persons over that period [44]. Moreover, research on migrant populations and persons living in developing countries has reported a recent, gradual increase in the incidence of UC. The disease seems to peak between 10 and 18 years and to affect both genders equally [29, 43, 45].

The incidence of CD has also risen significantly over that time period, incrementing from 6–15/100,000 to 50–200/100,000 persons [44]. While initially relatively low, CD incidence has gradually risen to levels that are similar to those of UC [44]. While CD incidence rates seem to have stabilized in most industrialized countries since the 1980s, an increase in the childhood-onset form continues to be noted [3, 4] (Table 1).

CD incidence seems to peak late in adolescence and in young adulthood (up to 25 years of age). A second incidence peak has been noted for both CD and UC at the sixth or seventh decade [29, 43]. Moreover, a secondary peak is reported in several paediatric cohorts in the preschool age group (4-5 yrs of age) [29, 43, 46].

While CD appears to have a predilection for the female sex in the population at large, male predominance has been observed in the paediatric age bracket [29, 43, 45].

3.2. The Incidence and Prevalence of UC and CD in the General and Paediatric Populations Specific to Geographic Areas. A recent systematic review by Molodecky et al. [27] examined data from 167 studies concerning Europe (1930–2008), 52 concerning Asia and the Middle East (1950–2008), and 27 concerning North America (1920–2004). The highest annual incidence rate of UC—24.3 per 100,000 person-years—was registered in Europe, followed at 19.2 per 100,000 person-years registered in North America and then at 6.3 per 100,000 person-years noted in Asia and the Middle East. The highest annual incidence of CD was, instead, registered in North America at 20.2 per 100,000 person-years; it was followed at 12.7 per 100,000 person-years by Europe and then at 5 per 100,000 person-years by Asia and the Middle East. The highest reported prevalence values for IBD were found in Europe (for UC, 505 per 100,000 persons; for CD, 322 per 100,000 persons) and North America (for UC, 249 per 100,000 persons; for CD, 319 per 100,000 persons) [27].

3.3. Europe. The incidence of IBD appears to be twice as high in Western with respect to Eastern Europe [1], although an increasing incidence has also been noted in the latter area. A prospective, uniformly diagnosed population study by the EpiCom group [5] which analyzed the ECCO-EpiCom inception cohort of IBD patients was interested in investigating a possible East-West gradient in the incidence of IBD in Europe. A cohort of IBD patients attending 31 centers in 14 Western and 8 Eastern European countries providing medical services to a total population of approximately 10.1 million people was studied. Approximately 1500 patients aged 15 years or older were included in the study population. The overall incidence rate ratios in all the Western European centers were 1.9 (95% CI 1.5 to 2.4) for CD and 2.1 (95% CI 1.8 to 2.6) for UC compared with Eastern European centers. The median crude annual incidence rates per 100,000 in 2010 for CD were 6.5 (range 0–10.7) in Western European centers and 3.1 (range 0.4–11.5) in Eastern ones; for UC it was 10.8 (range 2.9–31.5) and 4.1 (range 2.4–10.3), respectively, and for IBD-U it was 1.9 (range 0–39.4) and 0 (range 0–1.2), respectively. The authors concluded that there is indeed an East-West gradient in IBD incidence in Europe [5] (Table 1).

According to the data from the EPIMAD Registry, collected between 1988 and 2007 and referring to a large area of Northern France populated by almost 6 million inhabitants representing 9.3% of the entire French population [47], there was an increase in CD incidence rates which rose from 5.2 cases/100,000 persons in 1988–1990 to 6.7 in 2006-2007 (+29%). The trend seemed to stabilize after a peak of 7.1 was reached in 1997–1999. CD incidence rates in the 10–19-year-old persons increased by 71% rising from 6.5 (1988–1990) to 11.1 (2006-2007). UC incidence rates, instead, decreased during that same period [47].

A sharp increase in paediatric (<16 years) IBD incidence was reported by a Swedish study carried out in a northern Stockholm County between 2002 and 2007 [6]. The increasing incidence in IBD was primarily explained by the rising incidence—registered at 9.2 (95% CI 7.5–11.2)—in CD patients. UC incidence was found to be 2.8 (95% CI 1.9–4.0). A significant increase in the incidence of UC ($P < 0.05$) but not of CD was observed over the study period. The authors concluded that CD continued to be predominant and there was an increase in UC incidence during the study period [6] (Table 1).

A study by Turunen et al. aimed to analyze the incidence and the clinical picture of IBD from 1987 to 2003 in a large paediatric population in Finland [7]. Data were collected from patient discharge and medical records at the country's 2 largest university hospitals. A total of 604 cases of IBD were diagnosed during the 17-year study period: 203 (34%) of these were registered as CD, 317 (52%) as UC, and 83 (14%) as IBD-U. The mean annual incidence rate increased from 3.9/100,000 (95% confidence interval (CI) 2.5–5.8) in 1987 to 7.0/100,000 (CI 5.0–9.4) in 2003 ($P < 0.001$). The majority of cases were patients who are 12 to <15 years old ($n = 200$, 33%); 5.1% were <3 years old, and 14% were <6 years old. IBD-U was most common in young children (29% of all IBD-U patients). Surgical procedures were generally carried out early during disease course [7] (Table 1).

Another Finnish study carried out by Jussila et al. [4] aimed to assess the geographic distribution of IBD in that country and to estimate its nationwide incidence between 2000 and 2007. The register included all new cases of IBD between 2000 and 2007 which received special reimbursement for IBD medication. Overall, 14,214 IBD patients were identified: 10,352 had UC and 3,862 CD. During the study period the mean annual incidence of IBD per 100,000 was 34.0 : 9.2 in CD and 24.8 in UC. The incidence of UC was notably higher in the males (27.8) than in the females (21.9). In CD the incidence increased only slightly and rates did not differ significantly between genders. The incidence of UC increased from 22.1 in 2000-2001 to 27.4 in 2006-2007. The authors concluded that the incidence of IBD is high in

Table 1: Summary of the main studies on IBD epidemiology that were reviewed for the special issue.

Authors/paper/year [Reference]	Country	Number of IBD patients enrolled	Patients age	Time period of the study	IBD incidence
Benchimol et al., Gut 2009 [2]	Canada (Ontario)	Population-based clinical database	Paediatric (<15 yrs)	17 yrs (1991–2008)	Age- and sex-standardized prevalence 42.1/100,000 (in 1994) 56.3/100,000 (in 2005) incidence 9.5/100,000 (in 1994) 11.4/100,000 (in 2005).
Chouraki et al., Aliment. Pharmacol. Ther. 2011 [3]	Northern France (EPIMAD Registry)	12.084 CD 7428 UC 4656	Paediatric	20 yrs (1988–2007)	CD In 1988–1990: 5.2/100,000 In 2006-2007: 6.7/100,000
Jussila et al., J. Crohn's Colitis 2013 [4]	Finland	Patients with special reimbursement of medications for IBD in the years 1993 (n = 10,958) and 2008 (31,703)	Paediatric and adult	14 yrs (1998–2002)	Nationwide point prevalence of IBD 216/100,000 in 1993 and 595/100,000 in 2008.
Burisch et al., Gut 2013. [5]	Europe (31 centers from 14 Western and 8 Eastern European countries)	1515 patients 535 (35%) CD 813 (54%) UC 167 (11%) IBD-U	Adult (≥15 yrs)	—	Overall incidence rate ratios in all Western European centres were 1.9 (95% CI 1.5 to 2.4) for CD and 2.1 (95% CI 1.8 to 2.6) for UC compared with Eastern European centres Median crude annual incidence rates per 100,000 in 2010: CD 6.5 (range 0–10.7) in Western European centres 3.1 (range 0.4–11.5) in Eastern European centres UC 10.8 (range 2.9–31.5) in Western European centres and 4.1 (range 2.4–10.3) in Eastern European centres IBDU 1.9 (range 0–39.4) in Western European centres and 0 (range 0–1.2) in Eastern European centres
Malmborg et al., J. Pediatr. Gastroenterol. Nutr. 2013 [6]	Sweden (Stockholm county)	133	Paediatric (<16 yrs at onset)	6 yrs (2002–2007)	IBD 12.8/100,000 (95% CI 10.8–15.2) CD 9.2 (95% CI 7.5–11.2) UC 2.8 (95% CI 1.9–4.0)
Turunen et al., Inflamm. Bowel Dis. 2006 [7]	Finland	604 CD 203 (34%) UC 317 (52%) IBD-U 83 (14%)	Paediatric (<18 yrs at onset) 12 to <15 yrs: 200 (33%) <3 yrs: 5.1% <6 yrs: 14%	17 yrs (1987–2003)	IBD In 1987: 3.9/100,000 (95% CI 2.5–5.8) In 2003: 7.0/100,000 (CI 5.0–9.4) ($P < 0.001$)
Sawczenko and Sandhu, Arch. Dis Child 2003 [8]	Great Britain and Ireland	739 CD 431 UC 211 IBD-U 86	Paediatric (<16 yrs at onset)	13 mths (June 1998–June 1999)	—

Table 1: Continued.

Authors/paper/year [Reference]	Country	Number of IBD patients enrolled	Patients age	Time period of the study	IBD incidence
Armitage et al., Gastroenterology 2004. [9]	Scotland	580	Paediatric (<16 yrs at onset)	15 yrs (1981–1995)	CD 2.3 (95% CI: 2.0–2.5) (Northern Scotland 3.1, 95% CI: 2.6–3.8; Southern Scotland 2.1 95% CI: 1.9–2.4, $P < 0.001$)
Pozler et al., J. Pediatr. Gastroenterol. Nutr. 2006 [10]	Czech Republic	470 CD 223	Paediatric (<15 yrs at onset)	12 yrs (1990–2001)	CD In 1990: 0.25/100,000, in 2001: 1.25/100,000
Castro et al., Inflamm Bowel Dis 2008. [11]	Italy	1576 UC 810 CD 635 IBD-U 131	Paediatric (<18 yrs)	8 yrs (1996–2003)	IBD incidence: 0.39/100,000 (1996)–0.89/100,000 (2003)
Rocchi et al., Can. J. Gastroenterol. 2012 [12]	Canada	233,000 CD 129,000 UC 104,000 (5900 children with IBD)	Paediatric and adult (<18 yrs at onset)	12 yrs (1998–2009)	IBD Prevalence 0.67% Incidence: 10,200 cases/yr
Zeng et al., J. Gastroenterol. Hepatol. 2013 [13]	China (Guangdong province)	48 CD 17 UC 31	Paediatric and adult	1 yr (2011-2012)	IBD 3.14/100,000 CD 1.09/100,000 UC 2.05/100,000
Kugathasan et al., J. Paediatr. 2003 [14]	Winsconsin, US	—	Paediatric	2 yrs	IBD 7.05/100,000 CD 4.56/100,000, UC 2.14/100,000
Basu et al., Am J. Gastroenterol. 2005 [15]	Houston, Texas, US	148 Whites 40%, African Americans 37%, Mexican Americans 20%, Asians 3%	Paediatric and adult	4 yrs (June 1999–November 2003)	—
Tozun et al., J. Clin. Gastroenterol 2009. [16]	Turkey	877 CD 216 UC 661	Paediatric and adult	3 yrs (2001–2003)	CD 2.2/100,000 UC 4.4/100,000
Abdul-Baki et al. Inflamm Bowel Dis 2007 [17]	Lebanon	251 UC 142 CD 100 IBD-U 9	Paediatric and adult	5 yrs (2000–2004)	CD 1.4/100,000 UC 4.1/100,000 (range, 0–6.9/100,000 for both)
El Mouzan et al., J. Trop. Pediatr. 2006 [18]	Saudi Arabia (Riyadh region)	50 CD 38% UC 48% IBD-U 16%	Paediatric (<18 yrs at onset) <12 yrs: 16%	10 yrs (1993–2002)	0.5 cases/100,000
Tsai et al., J. Formos. Med. Assoc. 2004 [19]	Taiwan	17 CD 9 (53%) UC 6 (35%) IBD-U 2 (12%)	Paediatric (<18 yrs at onset)	22 yrs (1979–2000)	CD From 1979 to 1995: 0.85% From 1996 to 2000: 2.6% ($P < 0.001$), UC From 1979 to 1995: 0.85% From 1996 to 2000: 0.99% ($P = 0.16$)
Ng et al., Gastroenterology 2013 [20]	Asia-Pacific (8 countries between Asia and Australia)	419 CD 166 UC 232 IBD-U 21	Paediatric and adult	1 yr (2011-2012)	Asia IBD 1.37/100,000 (95% CI: 1.25–1.51) CD 0.54 UC 0.76

Table 1: Continued.

Authors/paper/year [Reference]	Country	Number of IBD patients enrolled	Patients age	Time period of the study	IBD incidence
					IBD-U 0.07 China 3.44 per 100,000 individuals Australia IBD 23.67/100,000 (95% CI: 18.46–29.85) CD 14 UC 7.33 IBD-U 2.33
Pinsk et al., Am. J. Gastroenterol. 2007. [21]	South Asian population in British Columbia, Canada	75 CD 48% UC 33.3% IBD-U 18.7%	Paediatric (<16 yrs)	21 yrs (1985–2005)	In 1996–2001: IBD 15.19/100,000 CD 6.41/100,000, UC 6.70/100,000 IBD-U 2.08/100,000

IBD: Inflammatory Bowel Disease, CD: Crohn's Disease, UC: Ulcerative Colitis, IBD-U: Unclassified IBD, yrs: years, CI: confidence interval.

Finland with UC being almost three times more frequent with respect to CD. The incidence rate of UC since the year 2000 has increased, while that of CD has remained fairly stable. A North-South gradient was clearly identified for IBD and UC but not for CD [4] (Table 1).

Sawczenko and Sandhu [8] prospectively described the presenting features, disease localisation, and disease growth in newly diagnosed cases of IBD in a multicenter study conducted between June 1998 and June 1999 in the UK and Ireland. A total of 739 new IBD cases of patients younger than 16 were identified. Only one-quarter of the CD cases presented with the "classic triad" of diarrhoea, weight loss, and abdominal pain; nearly half did not report diarrhoea. The median delay from onset of symptoms to diagnosis was 5 months (mean 11 months). Delays were more common in the CD patients and in the younger children. Short stature was noted only in the patients with CD and not in those with UC. One-fifth of the CD cases had small bowel involvement and also significantly reduced stature. Ileocolonic involvement was documented in most of the CD cases, with only a small minority having isolated ileal or isolated colonic disease. Pancolitis was reported in most of the UC cases, with only a very few affected with isolated proctitis [8] (Table 1).

A study by Armitage et al. [9] aimed to analyse the sociodemographic and geographic distribution of paediatric-onset CD in Scotland. Using a national database, 580 Scottish children (<16 years of age at symptom onset) who were diagnosed with IBD between 1981 and 1995 were identified. The incidence of paediatric-onset CD was 2.5 cases per 100,000 population per year (95% CI: 2.0–2.5) for the 1981–1995 time period and it was significantly higher in Northern (3.1, 95% CI: 2.6–3.8) with respect to Southern Scotland (2.1, 95% CI: 1.9–2.4, $P < 0.001$). The incidence of paediatric-onset UC did not, instead, show any north/south variations ($P = 0.677$). While children from more affluent areas had a higher relative risk of developing CD, paediatric-onset UC did not seem to be associated with affluence [9] (Table 1).

A study conducted in the Czech Republic [10] between 1990 and 2001 aimed to assess the paediatric population suffering from IBD and to determine the incidence of CD in children younger than 15 during the study period. The diagnostic criteria were met by 470 IBD patients; 201 of these turned 18 during the study period. CD was diagnosed in 223 patients. The incidence of CD in the patients younger than 15 rose from 0.25/100,000 in 1990 to 1.25/100,000 in 2001. Severe growth retardation was recorded in 6.4% of the adolescents with CD at the age of 18. UC was diagnosed in 202 patients. The criteria for IBD-U were met in 9.8% of all the IBD patients [10] (Table 1).

A study was carried out by Italian investigators utilizing the National Paediatric IBD Register which was instituted in 1996. The data analysed by the study were collected from the time the register was instituted until 2003 [11]. According to those data, IBD was more frequent in children between 6 and 12 years (57%), although 20% developed their first symptoms before the age of 6. In 1.8% of cases a diagnosis was made within the first year of life. Diagnosis of IBD-U was more frequent in children between 0 and 5 (more than twice as high with respect to older children) and accounted for 10–15% of all new diagnoses of IBD. Mean values of the time interval between onset of symptoms and IBD diagnosis were 10.1 months for CD, 9 months for IBD-U, and 5.8 months for UC. 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 (Table 1).

3.4. The Americas. Canada has one the highest prevalence and incidence rates of IBD in the world [48]. A comprehensive review analysing the burden of IBD, its direct and

indirect medical costs, and humanistic impact in Canada was recently conducted by Rocchi et al. [12]. Approximately 233,000 Canadians were diagnosed with IBD by 2012 (129,000 with CD and 104,000 with UC), corresponding to a prevalence of 0.67%. Approximately 10,200 new cases are diagnosed annually. IBD is diagnosed at all ages, with typical onset occurring in the second or third decades of life. Compared to the general population, the quality of life of IBD patients was low across all health dimensions and medical costs associated to its care were high [12]. The review by Rocchi et al. highlighted the elevated burden of the disease in that country due to its high prevalence and medical costs. The authors concluded that Canada is characterized by lack of awareness of IBD as a chronic disease, late or inappropriate diagnosis, inequitable access to health care services, costly medication, diminished employment prospects, and limited community-based support [12] (Table 1).

Benchimol et al. [2] used a population-based clinical health administrative database of IBD patients younger than 15 years living in Ontario, Canada, to define paediatric-onset IBD and to describe its epidemiology. The most accurate algorithm was validated with chart data regarding children from 12 medical practices. Identification of children with IBD required four physician contacts or two hospitalisations with International Classification of Disease (ICD) codes for IBD within 3 years' time if they underwent colonoscopy and seven contacts or three hospitalisations within 3 years' time in those without colonoscopy. Age- and sex-standardised prevalence per 100,000 population of paediatric IBD increased from 42.1 (in 1994) to 56.3 (in 2005). Incidence per 100,000 increased from 9.5 (in 1994) to 11.4 (in 2005). Statistically significant increases in incidence were noted in 0–4-year-old persons (5.0%/year, $P = 0.03$) and in 5–9-year-old persons (7.6%/year, $P < 0.0001$) but not in 10–14- or 15–17-year-old persons [2] (Table 1).

A recent study by Kappelman et al. was carried out in North Carolina to determine the prevalence of CD and UC in a commercially insured US population and to compare prevalences across sociodemographic and temporal conditions [49]. Data from three consecutive 2-year cross-sectional studies based on claims data collected from approximately 12 million Americans were analysed. In 2009, the prevalences of CD and UC in children were 58/100,000 (95% confidence interval (CI) 55–60) and 34/100,000 (95% CI 32–36), respectively. In adults, the respective prevalences were 241/100,000 (95% CI 238–245) and 263/100,000 (95% CI 260–266). According to data analysis, IBD prevalences had slightly increased over time. Based on census data, estimated 1,171,000 Americans have IBD (565,000 CD and 593,000 UC). The authors concluded that the burden of IBD has been increasing in the US over recent years [49] (Table 1).

A study by Kugathasan et al. [14] aimed to define epidemiologic and clinical characteristics of newly diagnosed paediatric IBD patients in a large population-based model in Winsconsin. All paediatric gastroenterologists providing care for Winsconsin children voluntarily identified all new cases of IBD during a 2-year period. The incidence of IBD in children living in that state was 7.05 per 100,000, and the incidence for CD was 4.56, more than twice that of UC (2.14). The IBD incidence rate was found to be similar in the different ethnic groups as well as in the sparsely as opposed to densely populated counties. The majority (89%) of new IBD diagnoses were nonfamilial [14] (Table 1).

Basu et al. [15] conducted a survey on 148 IBD patients attending a university gastroenterology clinic in Houston, Texas, between June 1999 and November 2003 to analyse and compare the impact of IBD on the quality of life in the various ethnic groups living in the United States. Whites made up 40%, African Americans 37%, Mexican Americans 20%, and Asians 3% of the total IBD population. African Americans and whites predominantly had CD, while Mexican Americans predominantly had UC. There was no difference between African Americans and Mexican Americans when separately compared to whites in terms of intestinal manifestations of CD and UC. African Americans with CD had a significantly higher incidence of IBD-associated arthritis ($P = 0.004$) and ophthalmological manifestations, notably uveitis ($P = 0.028$), compared to whites. White UC patients had significantly higher incidences of joint symptoms ($P < 0.0001$) and osteoporosis ($P = 0.001$) with respect to Mexican American UC patients. Whites had a stronger family history of IBD and colorectal carcinoma compared to the other ethnic groups. The authors concluded that there are significant differences in IBD subtypes and serologic markers in the different racial/ethnic groups living in the United States [15] (Table 1).

Hispanics are the fastest growing minority in the US. A recent retrospective study [50] aimed to compare IBD presentation in Hispanic and non-Hispanic whites (NHWs) and in US-born and foreign-born Hispanics. The fact that differences in IBD presentation were found in NHW, US-born Hispanic, and foreign-born Hispanic groups in this study underlines the importance of environmental factors in the disease's development. A total of 325 adult patients were included, 208 of whom were Hispanics. The foreign-born Hispanics, accounting for 68% of the total, were diagnosed at an older age than the US-born Hispanics and the NHWs (45 versus 25 and 27, resp., $P < 0.05$). The foreign-born Hispanics manifested more UC than the US-born Hispanics or NHWs (59.9% versus 41% and 28.2%, resp., $P < 0.05$). No difference was noted in the prevalence of extraintestinal manifestations between the Hispanics and NHWs. More cases of upper gastrointestinal tract CD were found in the NHWs (12.5% versus 3.9%, $P < 0.05$). The rate of IBD-related surgical procedures was higher in the NHWs than in the Hispanics (22.9 versus 7.3 surgeries/100 person-years, $P < 0.01$). The Hispanic patients had fewer prescriptions for biologics and immunomodulators with respect to the NHWs (22.2% versus 55.6%, $P < 0.01$, and 35.7% versus 53.8%, $P < 0.01$, resp.) [50].

In two recent retrospective multicenter studies conducted in Argentina and Brazil on cohorts of paediatric patients ($N = 424$) diagnosed with IBD between 1988 and 2007, the proportion of UC and CD was 62% and 24%, respectively, in Argentina, and 52% and 48%, respectively, in Brazil. Age at diagnosis ($P = 0.076$) was similar in the UC (9.1; 4.6–12.0) and CD patients (9.6; 6.9–13.7) [51].

Pancolitis was the most frequent UC localisation both in Argentina (77%) and in Brazil (76%). Ileocolonic CD localisation was predominant both in the Argentine (46%) and Brazilian (37%) population. The most common phenotype of CD (77%) in the Argentine children was inflammatory. Penetrating CD was predominant in the Brazilian children (27%) [51].

3.5. Asia. The epidemiologic and clinical characteristics of IBD patients were assessed by Tozun et al. [16] in a large multicenter, countrywide hospital-based study in Turkey. Twelve centers distributed throughout the country registered all new IBD cases diagnosed between 2001 and 2003. The incidence in the referral population during the study period was 4.4/100,000 for UC and 2.2/100,000 for CD. The IBD incidence in Turkey was lower than that in North and West Europe and similar to that in the Middle East. The majority of the IBD cases were diagnosed in young adults (20 to 40 yrs). A characteristic biphasic age distribution was found with one peak between 20 and 30 and another between 50 and 70. Male predominance was noted in both diseases. Family history was positive in 4.4% in the UC and 8.3% in the CD patients. Extraintestinal manifestations were more frequent in the CD patients, with the exception of arthritis which was equally frequent in both the CD and UC patients. The rate of extraintestinal manifestations was lower than that reported in the literature [16] (Table 1).

Abdul-Baki et al. [17] found an age-adjusted prevalence of 53.1 per 100,000 persons for CD and 106.2 per 100,000 persons for UC in a representative Lebanese cohort. The mean annual incidence was 4.1 per 100,000 persons for UC and 1.4 per 100,000 persons for CD (range, 0–6.9/100,000 for both). The prevalence of IBD of this cohort fell in the intermediate range of that reported for white populations in Europe and North America. The mean age at diagnosis for patients with CD and UC was 28.8 ± 11.1 and 32.0 ± 13.4 years, respectively, and a slight female predominance was noted in the patients studied [17] (Table 1).

El Mouzan et al. [18] assessed the medical records of patients in Saudi Arabia younger than 18 who were diagnosed with IBD and monitored over a 10-year period. Fifty consecutive children were diagnosed with IBD between 1993 and 2002 resulting in an estimated incidence of 0.5 cases/100,000/year and prevalence of 5 cases/100,000 persons in the Riyadh region of Saudi Arabia. Most of the children (90%) were Saudi nationals and the female to male ratio was 1 : 0.6. Sixteen percent of the patients in the 5–18-year-old age bracket were younger than 12. Chronic UC was the most common form accounting for 48%, followed by CD and IBD-U in 38% and 16%, respectively. Although the incidence and prevalence of IBD in this report were lower than those in any other population, a comparison with data collected previously indicates that the incidence is increasing [18] (Table 1).

Together with urbanization and socioeconomic development, the incidence of IBD is increasing in China. A prospective, population-based incidence study was conducted by Zeng et al. [13] between July 2011 and June 2012 in Zhongshan, Guangdong, China. All newly diagnosed IBD cases in that region were included. Forty-eight new cases of IBD (17 CD and 31 UC) were identified over the 1-year study period. Age-standardized incidence rates for IBD, UC, and CD were 3.14, 2.05, and 1.09 per 100,000, respectively. Median ages at diagnosis were 38 for UC and 25 for CD. Disease localisation in the CD patients was defined as terminal ileum only (L1) in 24% of the cases, isolated colonic disease (L2) in 6% of the patients, and ileocolonic disease (L3) in 71% of the patients. Twenty-four percent of the CD patients had coexisting upper gastrointestinal (GI) involvement (L4) [30]. Inflammatory (B1), stricturing (B2), and penetrating (B3) behaviour was noted in 65%, 24%, and 12% of the CD patients, respectively. Fifty-nine percent of the CD and 26% of the UC patients had extraintestinal manifestations [13] (Table 1).

Another prospective study conducted between January and December 2010 by Zhao et al. [52] investigated the incidence of IBD in Wuhan, a major city in central China, using population-based methods. New IBD cases were identified in 17 central hospitals providing health care services in central Wuhan. Overall, 131 new cases of IBD were identified during the 1-year period, including 97 cases of UC and 34 cases of CD. The age-adjusted incidence of IBD, UC, and CD was 1.96 per 100,000 (range 1.62–2.30 per 100,000), 1.45 (range 1.16–1.75), and 0.51 (range 0.33–0.68), respectively. Disease was localized in the small bowel only (L1) in 15% of the CD patients, in isolated colonic disease (L2) in 24%, and in the ileo-colon (L3) in 61%. CD phenotypes were inflammatory in 44% of the cases, stricturing in 29%, and penetrating in 24%. In the UC patients 34.5% had proctitis, 44.6% had left-sided colitis, and 19.5% had extensive colitis [52].

According to the two latter studies, the incidence of IBD in China is similar to that in Japan and Hong Kong but lower than that in South Korea and countries of the Western Hemisphere [13, 52].

The Asia-Pacific Crohn's and Colitis Epidemiology Study, a large-scale population-based study, reported that although the incidence of IBD varies throughout Asia, it is still lower than that in the West. IBD can nevertheless be as severe or even more severe in Asia than it is in the West [20]. China has the highest incidence of IBD in Asia (3.44 per 100,000 individuals). The UC/CD ratio was 2.0 in Asia and 0.5 in Australia. Complicated CD (stricturing, penetrating, or perianal disease) was more common in Asia than in Australia (52% versus 24%; $P = 0.001$), and a family history of IBD was less common in Asia (3% versus 17%; $P < 0.001$) (Table 1).

A study conducted by Tsai et al. aimed to delineate the trend in incidence and clinical patterns of childhood IBD in Taiwan [19]. All children admitted to the National Taiwan University Hospital (NTUH) between 1979 and 2000 meeting the criteria for IBD were included. The clinical features and outcomes were analysed retrospectively. Seventeen children (9 females and 8 males, aged 2 months to 18 years) were diagnosed with IBD during the study period. Six (35%) of these had UC and 9 (53%) CD. The cumulative incidence of CD during 1979–1995 was 0.85% and increased to 2.6% during 1996–2000 ($P < 0.001$), while the incidence of UC did not change significantly between the two periods (from 0.85% to 0.99%, $P = 0.16$). The median interval from onset

to diagnosis was 7.7 months. Eighty percent of the patients showed moderate to severe disease activity at diagnosis [19].

Pinsk et al. [21] conducted a study which aimed to determine the incidence of IBD and disease subtype in the South Asian paediatric population living in British Columbia, Canada, compared with non-South Asian IBD patients living in the same area. A chart review was carried out with data collected for all patients ≤16 yr of age diagnosed with IBD from January 1985 to June 2005. Seventy-five South Asian patients were diagnosed with IBD, 48% with CD, 33.3% with UC, and 18.7% with IBD-U, as opposed to 71%, 18.8%, and 10.2%, respectively, in the non-South Asian population. The incidence rate for South Asian IBD patients for the 1996–2001 period was 15.19/10 (6.41/10 for CD, 6.70/10 for UC, and 2.08/10 for IBD-U) compared with 5.19/10 for the non-South Asian IBD group (3.69/10, 0.96/10, and 0.54/10, resp.). The South Asian male/female ratio was significantly different from that observed for the rest of the population. According to these data, there was a significantly higher incidence of IBD in the South Asian paediatric population compared with the rest of the BC paediatric population, as well as a different pattern of phenotypic expression, a male predominance, and more extensive colonic disease. Migration and environmental and lifestyle changes seem on the basis of these results to have an effect on the incidence of IBD and disease subtype [21] (Table 1).

4. The Natural History of Paediatric IBD

4.1. The Natural History of Crohn's Disease. Although the natural history of paediatric CD is characteristically unpredictable [53], the following factors are fundamental in determining disease evolution [54]: disease activity, the rate of recurrence and complications over time, the need for surgery, and its impact on quality of life.

In terms of growth impairment, approximately 50% of adults with CD presenting in developmental age reach a final height that is 10% lower than that in the general population, and in 25% of cases 5% lower than the established target [55].

Representing an important consideration in 28–36% of cases after the first year of treatment, the risk of corticosteroid dependency is similar in adults and children, regardless of concomitant administration of immunosuppressants. While the use of corticosteroids is efficacious in treating an acute phase of IBD, prolonged use should be avoided or limited [55].

Intestinal surgery is required in as high as 80% of CD patients, and a permanent stoma is required in more than 10% [27]. The risk is higher in patients with genotype NOD2-CARD15 and fibrostenosing disease and in those with serum positivity for anti-ASCA antibodies [55].

Postsurgical relapses occur in 20–30% of adult CD patients, and they are endoscopically documented in 43–79% of cases. In children, the global recurrence rate after 5 years is estimated at 50% and varies, depending on disease localization [53].

Patients with CD have higher mortality rates with respect to the general population [44]. Only precocious aggressive therapeutic strategies focusing on treating early recurrent lesions in asymptomatic individuals seem to have a significant impact on progression of this chronic disease [44].

Four hundred and four CD children (<17 years at diagnosis) forming a geographically derived incidence cohort were diagnosed between 1988 and 2002, by Vernier-Massouille et al. [54] and monitored for approximately two years. The most frequent disease location at diagnosis was the terminal ileum-colon (63%). Disease progression was noted in 31% of the children during the followup. Complicated behaviour was observed in 29% of the children at diagnosis and 59% at followup. Kaplan-Meier survival estimates of the cumulative incidence of surgery were 20% at 3 years and 34% at 5 years after diagnosis. Multivariate Cox models showed that both stricturing behaviour at diagnosis and treatment with corticosteroids were associated with an increased risk for surgery, while treatment with azathioprine was associated with a decreased one. Azathioprine was introduced earlier in the course of disease in patients not undergoing surgery than in those patients requiring surgery. The authors concluded that paediatric CD was characterized by frequent recurrences and severe complicated disease behaviour. Immunosuppressive therapy seemed to improve the natural history of the disease and to reduce the need for surgery [54].

4.2. The Natural History of Ulcerative Colitis. Both the clinical presentation at the time of diagnosis and the disease course of UC are heterogeneous and variable over time, and colectomy is one of its major risks [56].

The clinical characteristics of UC that influence its course include the extent and the severity of the disease at diagnosis, both of which correlate with a higher rate of colectomy [56]. While colectomy is required in approximately 10%–30% of UC patients [57], mortality in these patients has not been found to be higher with respect to that in the general population [57].

Just as in adult patients, the response to corticosteroid therapy plays an important role in defining the natural history of the disease in the paediatric population [56].

A short-term remission has been found in 75–80% of children and a long-term one in 60% of patients according to a recent report on the efficacy of biological drugs in UC patients [56, 57].

Gower-Rousseau et al. [58] identified 113 UC children (<17 years at diagnosis) in a geographically derived incidence cohort between 1988 and 2002 who were monitored for at least 2 years. At diagnosis, 28% of the patients had proctitis, 35% left-sided colitis, and 37% extensive colitis. Forty-nine percent of the patients showed disease progression. A delay in diagnosis longer than 6 months and a family history of Inflammatory Bowel Disease were associated with an increased risk of disease progression. The cumulative rate of colectomy was 8% at 1 year, 15% at 3 years, and 20% at 5 years following diagnosis. The presence of extraintestinal manifestations at diagnosis was associated with an increased risk of colectomy. In the patients with limited disease at diagnosis, the risk of colectomy was higher in those who

experienced disease progression with respect to those who did not [58].

5. Discussion

IBDs are an example of pathological entities having a multifactorial etiology. Over the past several decades, advances have been made in understanding the epidemiology of IBD. At the same time, the incidence and prevalence of both CD and UC have been increasing worldwide across pediatric and adult populations and its epidemiology is evolving. It is to be remembered, however, that the rising pattern may also be due to advances in disease detection and recognition and continued environmental alterations and exposures impacting disease onset. At the same time, the disease is emerging in previously low prevalence areas such as the developing world and among emigrant populations moving to industrialized Westernized societies. Genetic mutations that have been detected can explain a number (about 20–30%) of diagnosed cases but the evidence of IBD's rising frequency in industrialized areas of the world also implicates environmental risk factors [1, 29, 30]. The geographical variability in IBD incidence and prevalence may, in turn, reflect a variety of underlying genetic patterns in different populations [31]. As IBD's prevalence and incidence vary among different ethnic groups and the disease's clinical spectrum is still evolving, environmental factors may continue to contribute to its pathogenesis. Industrialization and globalisation seem, in any case, to be associated with the disease's spreading, rising pattern. In view of these considerations, a growing number of gastroenterologists and paediatricians have become interested in the disease's underlying epigenetic mechanisms.

Some gastroenterologists are particularly concerned about exposure to antibiotics in childhood and specific diets such as the "Western" one containing processed, fried, and sugary foods or low in omega-3 fatty acids may be linked to IBD presentation and the common mechanism may be through an alteration of the gut flora [30]. Greater discretion in prescribing antibiotics to children and ensuring that diets are high in omega-3 fatty acids may be appropriate measures especially in high risk families (positive family history for IBD). Future strategies may aim to modulate gut flora either with antibiotics targeting identified noxious microbes or with selective probiotics that can rebalance the gut dysbiosis [30].

Until now study findings have primarily been retrospective and subject to recall bias and for the most part they have been carried out in richer countries that have the means to do so. As IBD is a relatively rare disorder, with complicated interactions between potential inciting agents, very large cohorts with detailed, prospectively collected, environmental exposure data are needed. At the same time large, well-phenotyped cohorts of IBD patients are likewise necessary if we are to study the effects of environmental exposures on disease course.

In view of these considerations and in particular of the disease's ever evolving epidemiology and impact on quality of life, epidemiologic data must be gathered and analyzed following a systematic, rigorous process. As demonstrated in this review, the process of diagnosing and enrolling patients, be they adults or children, is a complex endeavor. Incidence and prevalence figures extrapolated from published studies regarding paediatric patients have, in particular, been found to be extremely heterogeneous. Establishing multicenter national and international registers and networks would be a step forward in the direction of constructing a shared database system utilizing an established, homogeneous criteria.

This review has attempted to examine the quality of epidemiologic data found in the principal studies carried out on the general and paediatric populations and to identify the weaknesses and gaps existing in the information that is presently available. Implementing a shared database system will hopefully lead the way to well-designed studies and to new, important treatment breakthroughs.

6. Conclusions

The highest incidence rates of IBD are in Europe and North America, although the overall prevalence of both CD and UC is increasing throughout the world. Assessing the incidence of IBD is, nevertheless, complicated, especially in the developmental age.

Geographical variability in IBD incidence and prevalence might reflect different underlying genetic patterns within different populations. As there are important differences in the prevalence of IBD between different racial and ethnic groups it is possible that the disease's clinical spectrum is still evolving and that environmental factors might be involved in its pathogenesis. Industrialization and globalization seem nevertheless to be associated with a spreading increasing incidence of IBD.

IBD has a significant impact on patients' quality of life and is generally associated with a high financial burden due to elevated medical costs in particular with regard to biologic drugs.

An analysis of data emerging from multicenter national registers and international networking can provide information on IBD epidemiology and lead to hypothesis about its causes and possible management strategies.

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