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Incidence, Clinical Characteristics, and Natural History of Pediatric IBD in Wisconsin: a Population-based Epidemiological Study

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Abstract

Background—Epidemiological studies of pediatric inflammatory bowel diseases (IBD) are needed to generate etiological hypotheses and inform public policy; yet, rigorous population-based studies of the incidence and natural history of Crohn's disease (CD) and ulcerative colitis (UC) in the United States are limited.

Methods—We developed a field-tested prospective system for identifying all new cases of IBD among Wisconsin children over an 8-year period (2000–2007). Subsequently, at the end of the study period, we retrospectively reconfirmed each case and characterized the clinical course of this incident cohort.

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The authors have no conflicts of interest to disclose.

Results—The annual incidence of IBD among Wisconsin children was 9.5 per 100,000 (6.6 per 100,000 for CD and 2.4 per 100,000 for UC). Approximately 19% of incident cases occurred in the first decade of life. Over the 8-year study period, the incidence of both CD and UC remained relatively stable. Additionally, (1) childhood IBD affected all racial groups equally, (2) over a follow-up of 4 years, 17% of patients with CD and 13% of patients with UC required surgery, and (3) 85% and 40% of children with CD were treated with immunosuppressives and biologics, respectively, compared with 62% and 30% of patients with UC.

Conclusions—As in other North American populations, these data confirm a high incidence of pediatric-onset IBD. Importantly, in this Midwestern U.S. population, the incidence of CD and UC seems to be relatively stable over the last decade. The proportions of children requiring surgery and undergoing treatment with immunosuppressive and biological medications underscore the burden of these conditions.

Keywords

epidemiology; Crohn's disease; ulcerative colitis; IBD; children

Crohn's disease (CD) and ulcerative colitis (UC), collectively known as inflammatory bowel diseases (IBD), are life-long chronic inflammatory disorders of the gastrointestinal tract. It is estimated that 15% to 20% of all cases of IBD are diagnosed in the childhood and adolescent period. This period is a time of physical, emotional, and social maturation, and onset of this chronic disorder in childhood can seriously jeopardize health, growth, and education. The burden associated with this disease extends beyond that of simply physical symptoms. An increasing number of these children are being treated with immunosuppressive¹ and biological² medications. Although these medications can improve the short-term outcome and quality of life of children with IBD, they have been associated with opportunistic infections,³ malignancy,^{4,6} and lymphoproliferative disorders^{7,8} among IBD populations.

Descriptive epidemiologic studies are recommended to promote the development of new etiological hypotheses and to better define the public health burden of childhood-onset IBD. A number of observational reports from Europe suggest that the incidence of pediatric IBD is increasing from <4 per 100,000 in the 1970s and 1980s to >7 per 100,000 in the 1990s and 2000s.⁹⁻¹³ Because the majority of the North American population are of European origin, the speculation is that the incidence and prevalence of IBD in North America are equal to or even higher than that reported in Europe. Benchimol et al¹⁴ recently reported an increase in the incidence of IBD in Ontario, Canada, from 9.5 in 1994 to 11.4 in 2005. Epidemiological data of pediatric IBD in the United States are more limited. In a Northern California health plan, the annual incidence of CD per 100,000 increased from 2.2 to 4.3 from 1996 to 2006. The incidence of UC increased from 1.8 to 4.9 over the same period.¹⁵ To our knowledge, only limited epidemiological data from other regions of the United States are reported.¹⁶ Therefore, additional population-based studies are needed to accurately estimate the burden of IBD among children in North America.

To impart a greater understanding of the epidemiology of IBD in a population-based model among children in North America, we aimed to determine the incidence and time trends of

childhood IBD in Wisconsin and describe the clinical course and treatments in this cohort. We developed a system of capturing all possible cases of IBD presenting before the age of 18, occurring within a defined time period (the 8-year period between year 2000 and 2007 inclusive), and within the defined geographic locale of Wisconsin, an upper midwestern state in the United States (54,310 square miles, 5.5 million population). We then tested the hypothesis that the incidence of pediatric IBD has increased over this 8-year time period.

MATERIALS AND METHODS

We performed a prospective population-based study to ascertain all new cases of pediatric IBD occurring in the state of Wisconsin between the years 2000 and 2007. We have previously published our initial experience from the first 2 years.¹⁷ To improve our case ascertainment rate and the quality of the data collection, a subsequent, retrospective chart review was performed to further characterize the presenting features and clinical course of these incident cases.

Study Setting

All pediatric gastroenterologists providing care for Wisconsin children were invited and agreed to participate in this study. Because of its geographic location, Wisconsin is the ideal state to conduct a population-based study. Almost all Wisconsin children receive their medical care within the Wisconsin borders, with only a small subset being cared for in Minnesota, the state just west of Wisconsin. Wisconsin children are limited as to where they can seek medical care because Lake Michigan borders the eastern edge of Wisconsin, and Lake Superior and the upper peninsula of Michigan (where there are no pediatric gastroenterologists) share the northern border of Wisconsin. Few children seek gastroenterology care in Illinois, as the Medical College of Wisconsin operates a number of satellite clinics in southern Wisconsin and northern Illinois. Those children who did seek care outside of Wisconsin were easily able to be identified with the help of pediatric gastroenterology centers in Minnesota. Data from 6 pediatric gastroenterology practices in Wisconsin (1 large academic center and 5 either small academic centers or private practices) and 3 pediatric gastroenterology practices in Minnesota (2 large academic centers and 1 private practice) were collected on all new diagnoses of pediatric IBD and was forwarded to a central registry at The Medical College of Wisconsin. Permission to do the research and/or approval from the institutional review board was obtained at each individual center.

Recruitment of Patients and Data Collection Methods

As previously described, beginning in January 2000, all new diagnoses of IBD in children <18 years, whose postal address zip code was Wisconsin, were prospectively identified at each participating practice and reported to the central registry at The Medical College of Wisconsin. The date of the definitive procedure was used as the date of diagnosis. The gastroenterologist caring for the patient completed a data collection form including diagnosis, date of diagnosis, age at the time of diagnosis, gender, ethnicity, postal zip code at the time of diagnosis, family history of IBD, duration of presenting symptoms, extraintestinal manifestations (EIMs), and extent of disease at the time of diagnosis.

To verify and maximize case ascertainment and evaluate the clinical course and treatments in this incident cohort, a subsequent retrospective chart review was performed at each participating center in 2007. In addition to verification of IBD diagnosis, additional clinical features, surgery, medication exposure, and length of follow-up time were reported.

Criteria for IBD Diagnosis

All diagnoses of IBD were confirmed by endoscopy and histology. New pediatric diagnoses were categorized into 3 clinical groups: CD, UC, and indeterminate colitis, defined according to established clinical, biochemical, radiologic, endoscopic, and histologic criteria. Children with nonspecific chronic inflammation without firm evidence of IBD were excluded from the study.

CD was defined as the presence of histologically documented discontinuous chronic inflammation of the gastrointestinal tract confirmed by endoscopy and supported by clinical, biochemical, or radiologic evidence of CD. UC was defined as the presence of continuous inflammation limited to the colon, extending proximally from the involved rectum, with histologically typical chronic inflammation limited to the mucosa and not extending beyond the muscularis mucosa. Indeterminate colitis was defined as inflammatory colitis in the setting of histopathological changes indicative of chronic IBD colitis, containing both endoscopic and microscopic findings that were consistent with both CD and UC. UC cases with inflammation limited to the left side of the colon and not extending proximally beyond the splenic flexure were categorized as left-sided colitis. Pancolitis was defined as gross and microscopic evidence of chronic inflammation extending proximally beyond the splenic flexure. All participating gastroenterologists received telephone training in the classification of disease type and extent.

Statistics

Categorical data were analyzed by the χ^2 or Student's *t* test, where appropriate, to determine statistical difference between groups. A statistical significance (alpha) of 0.05 was used throughout, and SPSS version 18.0 (SPSS Inc., Chicago, IL) was used to perform all statistical analyses. For any missing data (i.e., race), we assumed it was missing completely at random. We compared type of IBD and use of immunosuppressive and biological medications using a Pearson chi-square test.

RESULTS

Age of Onset and Gender

The average age of diagnosis of IBD was 12.3 years (CD: 12.3 years, UC: 12.5 years, indeterminate colitis: 10.4 years) (Fig. 1). The highest age-related incidence occurred at 14 years for CD and at 15 years for UC. Almost one-fifth (19%) of all CD and UC diagnoses were made in children <10 years. More males than females were diagnosed with CD (57% males, 43% females); in UC, both genders were equally represented. The median length of symptoms before diagnosis was 4 months for CD (range: 0–108) and 2 months for UC (range: 0.2–36).

Incidence and Trends of IBD in Children

From the 2006 U.S. Census Bureau data, the Wisconsin population was 5.5 million persons, with 26% of the population <18 years (pediatric population 1.3 million). There were 992 confirmed new diagnoses of IBD in children residing in Wisconsin during the 8-year period between January 1, 2000 and December 31, 2007. The overall incidence of IBD among children was 9.5 per 100,000 children (CD: 6.6 per 100,000 [6.3–6.9]; UC: 2.4 per 100,000 [2.1–2.7]; indeterminate colitis: 0.5 per 100,000 [0.09–0.91]), with CD almost 3 times as common as UC. Reviewing this 8-year period for any trends showed that although the incidence of IBD (and the subcategories CD and UC) fluctuated, the overall incidence of both CD and UC remained stable (Fig. 2).

Race and IBD

Eighty-eight percent of the Wisconsin state population were Caucasian, 6% African American, 2% Asian, and 4% other (Native American or others). Race was determined by self identification, as per the guidelines followed by the U.S. Census Bureau. Therefore, White Hispanic and Middle Eastern origins were also included in the Caucasian category. Reliable self-reported data on race were available in 86% of the patients in this Wisconsin pediatric IBD cohort. Among those with data, 92.8% were Caucasian, 4.2% African American, 0.8% Asian, and 2.2% other. The racial diversity of this pediatric IBD cohort was not significantly different from that of the Wisconsin state population ($P=0.868$).

Familiarity of Pediatric-Onset IBD

A family history of IBD (defined as a first-degree or second-degree relative) was present in 21% of the newly diagnosed IBD cases; this was a consistent finding in both CD and UC. Of those patients with a positive family history of IBD, 21% had multiple family members affected (4.4% of all IBD cases). The relationship of the affected family member was known in 94% of cases. Of these, 44% were first-degree relatives and 56% were second-degree relatives. In the two-thirds of cases where the diagnosis of the affected family member was known, for both CD and UC, the affected family member had the same diagnosis 70% of the time, whereas in the remaining 30% of cases, the affected family member had the opposite diagnosis, indicating that a significant proportion of the families in our cohort had both diagnoses.

Extraintestinal Manifestations of Pediatric-Onset IBD

EIMs were reported to be present at diagnosis in 26% of children with IBD. EIMs were more commonly seen in children with CD compared with children with UC (30% CD versus 21% UC, $P<0.001$). In both CD and UC, joint pain was the most frequent EIM (20% CD, 14% UC), followed by oral ulcerations (13% CD, 6% UC), rash (erythema nodosum or pyoderma gangrenosum, 2.6% CD, 1.2% UC), and sclerosing cholangitis or autoimmune hepatitis (0.3% CD, 1.2% UC).

Disease Location and Disease Behavior

The anatomical location of CD involvement at the time of diagnosis was categorized using the Vienna classification for CD.¹⁸ At the time of diagnosis of CD, the extent of disease was

small bowel only in 18%, large bowel only in 26%, and both small bowel and large bowel in 55%. Approximately 26% had perianal disease, with a fistula present in 8% of all patients with CD at the time of diagnosis. Among the children with UC, 66% had pancolitis at the time of diagnosis and 34% had left-sided disease only. No attempts were made to look at the progression of CD or UC with disease behavior, as the available data were insufficient.

Need for Surgery

Surgery was required in 17% of children with CD, with the mean follow-up of nearly 4 years. A partial bowel resection secondary to a stricture, perforation, or abscess was the most common surgery performed (11% of all patients with CD), followed by abscess incision and drainage (4.4%), fistulotomy (1.7%), and colectomy (1.3%). A similar percentage of patients with UC required surgery (total 13% of all patients with UC), with the mean follow-up of 4 years. In all but one of these UC cases, the surgery performed was a colectomy.

Exposure to Immunosuppressive and Biological Medications

Overall, approximately 85% of all children with CD were exposed to an immunosuppressive medication. Biological medications were also used frequently, with 40% having undergone treatment with a biological medication. In comparison, lower numbers of children with UC were exposed to immunosuppressive and biological therapies (62% and 30%, respectively, $P < 0.001$).

In a subset of the cohort that had received care at The Medical College of Wisconsin (approximately half of the cohort), medication data were further analyzed. Overall, 95% of these patients with CD had been treated with an immunosuppressive and 43% with a biological medication (Fig. 3). The mean time between CD diagnosis and the start of immunosuppressive therapy was 2.5 months (median: 1 month), and the mean time between CD diagnosis and the start of biological therapy was 16 months (median: 9 months). By 1 year after diagnosis, 90% of all patients with CD had been exposed to an immunosuppressive and 23% to a biological medication; by 2 years after diagnosis, 93% and 30% had been exposed to immunosuppressive and biological therapies, respectively. We also determined the exposure of corticosteroids and mesalamine medications in this data set. Although 88% were exposed to steroids, only 29% were exposed to the mesalamine group of drugs, indicating that 5-aminosalicylic acid medications are decreasingly being used in pediatric-onset CD.

For patients with UC, 70% had been treated with immunosuppressive and 38% with biological medications (Fig. 3). The average time between diagnosis of UC and the start of immunosuppressive and biological therapy was 5 and 11 months (median: 3 and 8.5 months), respectively. At time point 1 year after diagnosis, 60% were exposed to an immunosuppressive and 26% exposed to a biological medication. By 2 years after diagnosis, 65% and 36% had been exposed to immunosuppressive and biological therapies, respectively. Mesalamine exposure was available on 100% and steroid exposure was available on 98% of patients. Of those patients with data available, 77% and 94% were exposed to mesalamines or steroids, respectively.

DISCUSSION

In this population-based study covering the entire state of Wisconsin, we determined that the overall annual incidence of pediatric IBD was 9.5 per 100,000 (6.6 per 100,000 CD and 2.4 per 100,000 UC), and that the incidence rates remained relatively stable over the 8-year period of this study. Childhood IBD affected all racial groups equally. Over a mean follow-up of 4 years, approximately 17% of patients with CD and 13% of patients with UC required surgery. Approximately 85% and 40% of children with CD were treated with immunosuppressive medications and biologics, respectively, compared with 62% and 30% of patients with UC.

The incidence of pediatric-onset IBD reported here is similar to that reported by Benchimol et al¹⁴ in Ontario, and Abramson et al¹⁵ in the Kaiser Permanente Northern California health plan, the only recent study of IBD incidence in the United States. A number of population-based studies in Europe and Canada have suggested that the incidence of IBD among children has increased over the past 40 years, with this increase primarily because of an increase in CD, with the incidence of UC remaining stable.^{13,19,20} Additionally, the Ontario and Kaiser Permanente Northern California studies^{14,15} suggested continued increases in pediatric IBD incidence over the last decade. In contrast, we did not observe an increased incidence of IBD over time in our population, mirroring the leveling off of incidence observed in a recent primarily adult study based in Olmsted County, Minnesota.²¹ We speculate that this might reflect the stability of Midwestern U.S. populations versus the relatively higher population of immigrants in Northern California, Ontario, and other parts of Canada.

Most of the data we present summarizing the clinical characteristics of pediatric IBD, including the mean age of diagnosis, gender distribution, proportion of children with a family history of IBD, presence and type of EIM at diagnosis, disease location at diagnosis, and the percentage of children with IBD requiring a major surgical procedure are consistent with previous reports.^{9,13,22} However, the ratio of CD to UC of 3:1 among children has not been previously reported.

One of the surprising findings of our study was the high rate of the immunosuppressive and biological exposure in children with IBD in this unbiased population-based incidence cohort. Although these treatments lead to better disease control and mucosal healing, they also increase the risk of hepatosplenic T-cell lymphoma,⁴⁻⁶ lymphoproliferative disorders,^{7,8} and other unintended effects. Careful population-based longitudinal cohort studies are needed to fully evaluate the risks and benefits of this evolving medical paradigm in the pediatric IBD population.

The strengths of this study include the population-based design and robust efforts to ensure near complete capture of all cases occurring in the state of Wisconsin, including (1) complete participation of all pediatric gastroenterologists in the state and in the neighboring areas of Minnesota; (2) the geographic situation of Wisconsin making it unlikely that patients with IBD would be treated outside of our catchment area; (3) the relative abundance and access to pediatric gastroenterologists in Wisconsin making it unlikely for children to be

diagnosed and followed by adult gastroenterologists; and (4) the combination of prospective reporting and retrospective case identification at each site to capture any inadvertently missed cases. Nevertheless, we acknowledge the possibility of incomplete reporting at each center, that some children may have sought care in Illinois, and that some older adolescents may have been cared for by adult gastroenterologists. However, this underreporting is likely stable over time and would not affect incidence trends; the actual incidence may be slightly higher than that reported here. Another strength of this study was the confirmation and classification of each case by strict clinical, radiographic, endoscopic, and pathologic criteria by pediatric gastroenterologists specifically trained for this purpose. This effectively eliminated the possibility of misclassification that is always possible with studies using administrative, rather than clinical data. Efforts were also undertaken to avoid duplication of cases, in the situation where children were treated at multiple different practices. A final strength was the long duration of case ascertainment, spanning an 8-year time period, thus sufficient time to evaluate trends in incidence.

In conclusion, we implemented a population-based rigorous pediatric IBD case identification system covering the entire state of Wisconsin, determined the disease incidence, and characterized the presenting features, clinical course, and medical and surgical utilization over a follow-up period with a mean of 4 years. As there are few other population-based studies of childhood IBD in North America, these data should help providers, epidemiologists, policy makers such as federal drug administrators, pharmaceutical companies, insurance companies, and others quantify the burden of IBD among children in the United States.

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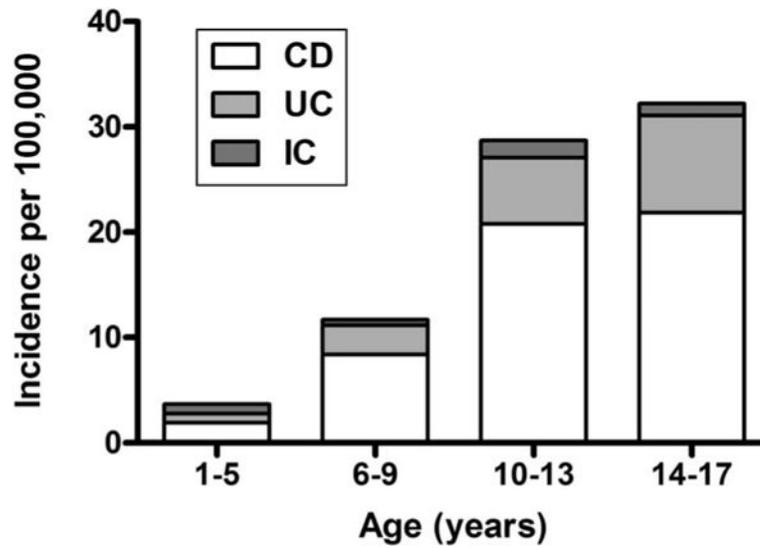


FIGURE 1.

Incidence of pediatric IBD by age group. Incidence of IBD is depicted here along with the subgroups of CD, UC and indeterminate colitis. Overall, the incidence of CD was almost 3 times more common than UC. This difference was most apparent in the older age groups.

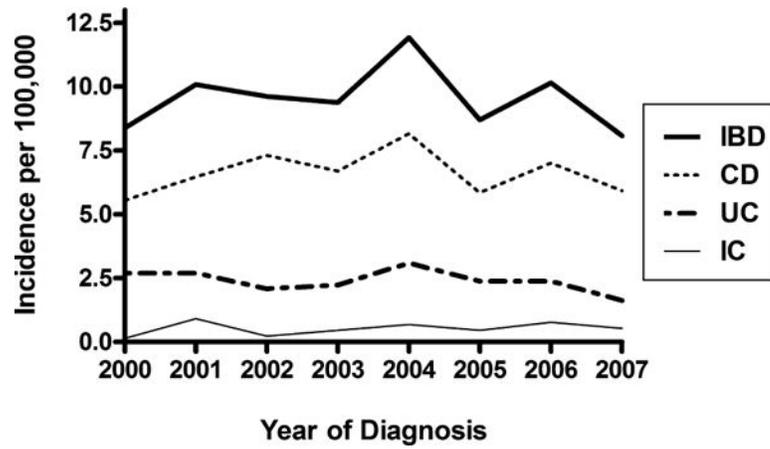


FIGURE 2.

Incidence of pediatric IBD by year. Incidence of IBD per year is shown here along with the subgroups of CD, UC and indeterminate colitis (IC). There was no overall increase in incidence occurred over the 8-year period studied.

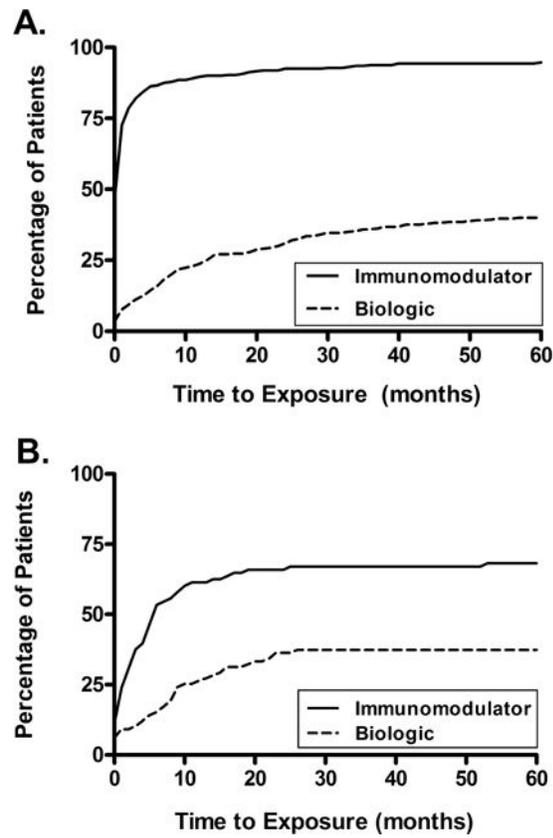


FIGURE 3. Cumulative medication exposure among the IBD patients. Patients with CD (A) were significantly more likely to be exposed to immunosuppressive medications compared with patients with UC (B). Patients with CD and UC were equally likely to be exposed to biological medications.