

## Order of Presentation of Pediatric Siblings Inflammatory Bowel Disease

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### Abstract

**Aim:** To determine the birth order of presentation of pediatric siblings with Inflammatory Bowel Disease (IBD).

**Methods:** We selected all siblings from our data base of pediatric patients with IBD and determined which sibling presented with IBD first and then second.

**Results:** In 16 pairs of siblings, the second born sib presented first in 69% of the time.

**Conclusion:** Antibiotic exposure, or other environmental factor(s) may be responsible for the distribution of presentation we found.

Keywords: Crohn's disease; Ulcerative colitis; Siblings; Epidemiology

### Introduction

The Inflammatory Bowel Diseases (IBD) represent several diseases in which there is inflammation of various segments of the intestinal tract. In addition, there are many manifestations involving other systems of the body, i.e., extra intestinal manifestations. IBD is felt to be a disease of immune dysregulation. There has been great progress in elucidating the epidemiology, genetics, and pathophysiology of IBD during the past several decades. Yet the overall incidence of IBD has continued to increase. IBD has also become a more global as well [1,2]. There has also been a concomitant increase in cases of IBD presenting in the pediatric age group [3,4]. Numerous epidemiologic studies have searched for factors that may shed light on the etiology of IBD [5]. However, the specific etiology(ies) of IBD remain elusive. Familial occurrence of IBD is a well established risk factor. A patient with IBD has a significantly greater chance of having a first-degree relative who also has IBD [6]. This strong association of occurrence of IBD in families suggests the presence of genetic factors at play. Indeed, more than 30 genes have been identified that may play a role with respect to IBD [7,8]. However, studies of monozygotic and dizygotic and Materials in pediatric siblings with IBD. We also wanted to know the prevalence of siblings with IBD amongst a large cohort of children and adolescents (1–19 years) with IBD [9–11]. We wanted to determine the concordance rate of phenotype of IBD amongst these sibling pairs as well as the difference in time to present from one group to the other.

### Materials and Methods

We retrospectively reviewed our entire pediatric IBD database (1997–2010) and selected all siblings with IBD. The total number of pediatric patients in the IBD registry was 632. The study population is almost exclusively Caucasian located in an affluent area of Northern New Jersey in the United States. Siblings were selected by extracting those patients with the same family surnames and then verifying that

they were indeed biologic siblings with the same parent pair [12]. The diagnosis of IBD and phenotype was made based on standard clinical, radiographic and endoscopic criteria [13]. The overall prevalence of siblings with IBD was determined. We then examined the birth order of presentation of the siblings with IBD. We also examined the siblings for concordance of phenotype as well as for any family history of IBD.

### Statistical analysis

Descriptive statistical analyses were performed for the study sample. For continuous variables, measures of central tendency (e.g., mean, median) and standard deviation were provided. Proportions were used for categorical variables. The Chi-square test was used to analyze categorical data.

#### Results

Prevalence of siblings with IBD there were 16 families identified with more than one offspring with IBD. This is a prevalence of 2.5%. Of the 16 families, there were 4 families with three offspring (25%). There was 1 family in which all three siblings had IBD. Amongst the remaining 3 families with three offspring, the third sibling was free of IBD thus far. All of our sibling pairs with IBD were consecutive in birth order.

### Birth order of presentation

The second born (youngest) sibling was the first to present with IBD in 11 of the 16 families (69%). In the remaining 5 families, the first-born (older) sibling presented first (31%) (Table 1).

	First to present (%)	Second to present (%)
Youngest	11 (69)	5 (31%)

Oldest	5 (31)	11 (69)
Total (33)*	16	16

**Table 1 :**

### Incidence of Parental IBD

In 3 of the 16 families, one parent had IBD (19%). One parent had Ulcerative Colitis (UC) and two had Crohn's disease (CD).

### Gender

Of the total group of siblings with IBD, there were 12 females and 21 males. Seven of the females presented first (58%), whereas 9 males presented first (43%). This difference was not statistically significant ( $p = 0.39$ , by the Chi-square test).

### Time to presentation between siblings

Overall median time from presentation of the first sibling to the second sibling was 3.9 years (10–19 years of age). Median time of presentation from youngest to oldest was 3.3 years (10–17). Median time of presentation from oldest to youngest was 4.4 years (13–19) (NS).

### Concordance

In 6 of the families there were seven siblings with mixed phenotype. Amongst these families, UC presented first in six patients (86%) and CD in 1 (14%). In 10 families there was concordance of phenotype amongst the siblings. Six families were concordant for CD (60%) and four with UC (40%). In the remaining six families the siblings had discordant phenotypes (Table 2).

Phenotype	No. Families	No. Sibs	Sibs with CD	Sibs with UC
Concordance	10	20	16	4
Discordance	6	13	6	7
Total	16	33	22	11

**Table 2 :** Distribution of IBD phenotype among siblings.

**Discussion** The major finding in this study was that, in the vast majority of cases of pediatric siblings with IBD, the second-born (youngest) sibling presented before the first-born (oldest) sibling. This is not what one would expect if the disease distribution of birth order were random. Hugot et al. studied 10 sibling pairs with IBD using the CAST statistical model and found that the distribution of disease onset was not random and that birth order had an influence on disease. They concluded that environmental factors contribute to the observed familial aggregation of disease [14]. Hampe et al. found that higher birth rank was associated with a lower risk of IBD [15]. Our findings support the existence of environmental factor(s) resulting in the distribution of the birth order of presentation of IBD that we observed. What could be responsible for the distribution we observed in patients who were raised in a very similar milieu? One factor may be an alteration in the gut microbiome. For this to explain our findings, the youngest sibling would have to be affected by factors that would alter the microbiome more frequently than the older sibling. Recently, there

has been great interest in the gut microbiome and the role it may play in IBD. It is felt that perturbation of the gut microbiome may, in turn, alter host immunity. When this occurs in the presence of an at-risk genetic host, IBD may follow.

In fact, this dysbiosis in IBD has been described in detail in patients with IBD [16,17]. Ponsonby et al. examined perinatal risk factors and their relationship to the development of IBD and found that delivery by Cesarean (elective or emergent) was associated with a higher risk of developing IBD. The microbiome in newborns differs markedly between those delivered vaginally versus by Cesarean section [18]. Furthermore, the resultant dysbiosis associated with antibiotic treatment may last long after the antibiotics have been discontinued. There is also evidence to support that there may be a slow and incomplete recovery of the microbiome in infants treated with antibiotics [19]. Shaw et al. showed that there is an association between the risk of IBD in children and the occurrence of otitis media prior to age 5 years [20]. Otitis media may indeed represent a proxy for antibiotic use. More specifically, it has been shown that antibiotic use in early childhood is a risk factor for the development of IBD [21–23]. The use of broad-spectrum antibiotics has significantly increased during the last four to five decades. The increased incidence of IBD and other disorders of immune dysregulation has paralleled the increasing use of antibiotics since the first introduction of amoxicillin in the UK in 1972 [24,25]. This trend in aggressive, non-specific antibiotic use has likely caused a perturbation of the intestinal microbiome and hence changes in both the mucosal and systemic immune systems.

Another trend that has become widespread during the past several decades is attendance in some form of “school” at a very early age. The resultant risk of acute illness in daycare attendees is greatest during the first three years of life and decreases with advancing age. In a large Danish cohort, it was shown that the second-born sibling had a greater number of acute illnesses and received a greater number of courses of antibiotics when compared to the first-born sibling [26]. Furthermore, there is a significant increase of antibiotic use among second-born siblings versus first-born siblings that has been confirmed by Koppleman et al. [27]. Our study is notable for describing certain trends. The prevalence of IBD of 2.5% in siblings with IBD in pediatrics is roughly half of that shown in siblings with IBD over a lifetime, which is 4.8% [28,29]. We also found that the onset of IBD in the second-born sibling preceded that of the older siblings in about 70% of the sibling pairs. Our findings are consistent with studies showing that exposure to antibiotics in early childhood is a risk factor for IBD. Furthermore, the younger sibling is more likely to contact common illnesses and receive a course of antibiotics as compared to the older sibling. This may indeed account for our findings. The primary limitations of this study include a relatively small number of pediatric sibling pairs with IBD to power this analysis. This is unavoidable in any one institution given the low prevalence of pediatric siblings with IBD. Furthermore, we did not have access to specific antibiotic regimen(s) amongst our patients. This study is, however, a first step and should be confirmed by other studies.

### Conclusion

The more we know about the epidemiology of a disease, the closer we get to elucidating the etiology. The ultimate goal is to find ways to prevent the disease from occurring. This study is the first to examine certain trends in children and adolescents who are siblings and have been diagnosed with IBD. Our most striking finding was that in the majority of cases, the onset of IBD in pediatric siblings occurred in the

second-born sibling first. The age of onset for the next sibling to present was approximately four years no matter what combinations of phenotype we examined. Our findings lend support to the potential role of antibiotic use and the potential role in the increasing incidence of disorders of immune dysregulation. Finally, it should add further support to the judicious use of antibiotics in the pediatric age group. This study was approved by the institution's IRB.

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