Increasing Incidence of Pediatric Inflammatory Bowel Disease in France: Implications for Etiology, Diagnosis, Prognosis, and Treatment

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Abstract: The significant increase in pediatric-onset inflammatory bowel disease in recent decades appears to be a global phenomenon, with studies from multiple geographic areas noting an increase in Crohn's disease (CD) and ulcerative colitis (UC). In this large, population-based cohort from northern France, the rapid increase in pediatric CD and UC from 1988–2011 may be due to multiple potential etiologies including environmental factors and advancements in diagnostic capabilities. We should consider the clinical implications of this rise in incidence, including potential risk stratification approaches that may offer the ability to modify the disease course of patients with earlier diagnosis.

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Pediatric-onset inflammatory bowel disease (IBD) has significantly increased in incidence and prevalence in recent decades, with these shifts occurring in both developing and developed nations (1). Indeed, this appears to be a global phenomenon with studies from multiple geographic areas documenting an increasing incidence of pediatric Crohn's disease (CD) and ulcerative colitis (UC) (2–7). Despite recognition that these trends exist, the definitive explanations for such trends have not been established to this point. In addition, comparisons across studies have been difficult due to the heterogeneity in study design, data collections, and populations surveyed.

In this issue of *The American Journal of Gastroenterology*, Ghione *et al.* (8) describe a significant increase in the incidence of UC and CD in a large, population-based cohort from northern France. The source population for this study represents approximately 9% of the French population, and data regarding diagnoses of patients with IBD are collected from every adult and pediatric gastroenterology practice in the included geographic area. Incidence rates were computed, and divided into 3-year periods throughout the entire study period (1988–2011). The mean annual incidence rates were then calculated for the entire study period and for each 3-year interval period.

From 1988 to 2011, the authors noted a significant rise in both CD (from 2.1 to 4.7 per 100,000) and UC (0.8 to 2.1 per 100,000), whereas the incidence of IBD-undifferentiated remained stable. The findings among adolescents were particularly striking, with the overall incidence of IBD significantly increasing from 6.0 to 13.8 per 100,000. Among adolescents, the incidence of CD demonstrated an average yearly change of +4.3%. The incidence of UC among adolescents remained stable until 1999 and then demonstrated a dramatic increase from 2000 to 2011, with an average yearly change of over 11%.

The major strength of the study lies in the ability to study a large population over a period of 24 years, allowing for the identification of ~8% of all incident cases of pediatric IBD in France during the study period. This ability to perform population level analysis while maintaining granularity of clinical data for individual patients offers a unique opportunity for epidemiologic research. The final diagnosis of CD or UC was established by expert gastroenterologists, which adds further validity to the study design.

The striking increase in incidence of IBD among pediatric patients in this cohort from northern France is consistent with findings in other cohorts from other areas of the world (2–7,9). In a recent issue of *The American Journal of Gastroenterology*, Benchimol *et al.* (9) utilized provincial health administrative databases to study national trends in the epidemiology of pediatric

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IBD in Canada. These investigators described a marked incidence of very early onset IBD along with a more modest and not statistically significant increase in the overall incidence of pediatric IBD [annual percentage change +2.06% (95% confidence interval −0.64% to +4.76%)] (9). Although the age groups impacted were somewhat different between the Canadian and French studies, taken together, these and other studies raise multiple questions surrounding the potential drivers of these apparent increases in the incidence of pediatric IBD. We must first realize that the increased incidence demonstrated in this study (and others) occurs over too short of a time period to represent genetic shifts in populations. Thus, the increasing incidence of IBD is likely driven by environmental influences (10), including the hygiene hypothesis (11), the association between antibiotic exposure in childhood and increased risk of development of IBD (12–14), and appendectomy (15,16). In the present study, Ghione *et al.* (8) review many of these factors, and include an excellent discussion of temporal trends of antibiotic prescription patterns and utilization of appendectomy in France during the study period.

Indirect support for environmental factors in the pathogenesis of IBD comes from studies of immigrant populations, where consistent evidence has demonstrated an increased risk of developing IBD among immigrants moving from a low prevalence area to a high prevalence area (17,18). Although many environmental factors have been associated with an increased risk of CD and UC, we should also consider that currently unidentified environmental risk factors that increase an individual's risk of developing IBD may also exist. Although the increase in the incidence of pediatric IBD demonstrated in the study by Ghione *et al.* (8) is striking, France has traditionally been viewed as a region of high IBD prevalence. Perhaps more impressive is the rising incidence of IBD in previously low incidence areas such as Asia (19). Future studies aimed at the identification of novel environmental triggers in each of these geographic areas has the potential to significantly impact our understanding of the pathophysiology of IBD, potentially leading to new methods to diagnose, risk stratify, or treat patients with CD and UC.

We should also consider whether the rising incidence of pediatric IBD may reflect an increased ability to diagnose CD and UC among children, and to make this diagnosis earlier in the disease course. This concept is supported by the study's finding of an increase in the percentage of patients with B1 (inflammatory) disease, which increased from 64% during the period from 1988 to 1990 to 87% during the period from 2009 to 2011 ($P<0.001$). This was accompanied by a significant decrease in B2 (stricturing) disease (33 to 11%). Traditionally, B1 disease has been viewed as an "earlier" phenotype of CD, with the potential to progress to more advanced phenotypes such as B2 and B3 (penetrating) disease over time. Improved and/or earlier diagnosis of pediatric IBD may be attributed to improved access to subspecialty care and/or more advanced diagnostic tools. In the population from France included in this study, the number of pediatric gastroenterologists increased from 3 in 1988 to 15 (currently). This increase in access to care by a pediatric gastroenterologist was also accompanied by major advances in our diagnostic capabilities and a likely increase in awareness of the signs/symptoms of IBD among pediatric patients during the 24-year study period. These diagnostic advances include, but are not limited to increased use of cross sectional imaging, capsule endoscopy, and laboratory markers such as fecal calprotectin. If some of the apparent increase in the incidence of pediatric IBD is due to earlier diagnosis, this should be applauded, as diagnostic delay has been a noted problem among patients with CD and UC (20).

The authors note that if improved diagnostics were the explanation for increasing incidence in the early to middle years of this study, incidence rates would have plateaued or possibly even declined in the later years of this study. This was not the case. Although a steady increase in incidence of CD was noted throughout the study period, the increase in UC was later. We speculate that improved access to care and advances in diagnostics improved over the entire course of this study and continue to evolve today. Therefore, incidence rates may not have "peaked" to this point. It will be interesting to continue to follow this population to see if the increases in incidence of CD and UC are sustained or if a plateau does in fact occur in the future.

We should also consider the clinical implications of these findings. On the one hand, it is possible that we may be detecting more mild patients (inflammatory CD or left-sided UC or proctitis) and perhaps a subset of these patients may not require lifelong immunosuppressive therapy at the time of diagnosis. On the other hand, perhaps we are detecting patients earlier in the course of disease, prior to the development of fibrostenotic, internal penetrating disease, and other complications. Perhaps there is a critical window in which early, aggressive therapy may be particularly impactful in altering the natural history of disease in such patients. These scenarios point to the urgent need for better prognostic markers and risk stratification tools, so that we can better identify the subset of patients who will benefit from early, aggressive therapy, and the subset for whom a "watch and wait" approach is most appropriate. New strategies such as those emerging from a recent multicenter inception cohort study of pediatric patients with IBD (21) will be critical to understanding the natural history of IBD among pediatric patients and guiding therapy choices in this population.

In conclusion, Ghione *et al.* (8) present a provocative study detailing a rapidly increasing incidence of CD and UC among pediatric patients in northern France. Their use of a prospective, population-based registry allows for a unique analysis of the epidemiologic patterns of IBD in this region over a 24-year study period. These findings, when placed alongside similar reports of an increasing incidence of IBD among pediatric patients worldwide, should spark further interest into the drivers of these epidemiologic trends and the prognostic and therapeutic implications if children are being diagnosed earlier in their disease and prior to the development of structuring/penetrating complications.

CONFLICT OF INTEREST

Guarantor of the article: Michael D. Kappelman, MD, MPH.

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