ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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Antibiotic Use and the Risk of Crohn's Disease

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G&H Do antibiotics help or hinder in Crohn's disease?

CB Two issues need to be elucidated regarding this question. One is whether antibiotic therapy has any use in Crohn's disease, and the other is whether use of antibiotics predisposes patients to Crohn's disease. These are very separate issues that may be linked. There is no solid evidence that antibiotic therapy improves the course of Crohn's disease, particularly inflammatory Crohn's disease, except for some evidence that metronidazole can improve the course of ileal or ileocolonic Crohn's disease and that it or a related compound could improve or reduce the likelihood of disease recurrence after surgical resection of ileal or ileocecal Crohn's disease.

Few clinical trials that investigate the use of antibiotics in perianal Crohn's disease have been conducted. Metronidazole is commonly used, and in the past 10–15 years, ciprofloxacin has been added as a second antibiotic to treat perianal Crohn's disease. This approach has been taken in the absence of any definitive randomized controlled studies. Antibiotic therapy in this setting can be effective, but the reason why this is so is not exactly clear.

G&H Are antibiotics primarily of value to prevent or treat infection of fistulae?

CB When patients have an intra-abdominal abscess, fever, or an elevated white blood cell count and imaging confirms the presence of an abscess, antibiotics are used as adjunctive therapy to treat presumed infection. Antibiotics also are used to treat bacterial overgrowth. For example, when a patient has a stricture, some of the symptoms of bloating, excess gas, and diarrhea may be related to bacterial overgrowth. Metronidazole or ciprofloxacin is often given, and sometimes a reduction in symptoms is achieved.

G&H What have you learned in your research about the link between antibiotic use and Crohn's disease?

CB There is some evidence that the use of antibiotics may increase the risk of development of Crohn's disease. A handful of papers about this phenomenon have been published in the medical literature. A study by Card and colleagues, published in *Gut* in 2004, showed that when persons with a diagnosis of inflammatory bowel disease (IBD) were compared with controls, the cohort with IBD was more likely than the control group to have received antibiotic prescriptions a few years before the IBD diagnosis was made. The findings do not suggest cause and effect; rather, they suggest that an association exists between antibiotic use and development of IBD.

In light of the importance of the gut microbiome, my colleagues and I also asked whether antibiotic use prior to the development of IBD is an issue of concern. If it is, we wanted to know whether the timing of the antibiotic use is important in relation to the development of IBD. We questioned whether antibiotic use plays a role in the development of pediatric IBD. Of particular interest was whether antibiotic use in a child's first year of life is because the gut microbiome—as far as our current understanding

goes—is like a fingerprint. The gut microbiome begins to establish itself when we are young children of, maybe, 1 year or so of age. The gut microbiome is developing in that first year of life, but after this time, it stays pretty constant. Events, such as infections, may occur in that first year of life that impact the gut microbiome in such a way that some permanent changes occur.

With this in mind, we conducted a retrospective review using a database of all persons with a documented diagnosis of IBD—both Crohn's disease and ulcerative colitis—in Manitoba, Canada from 1984 to 2008. The database included information on every prescription drug every patient in it had been prescribed since 1995, so we extracted all the patients in the database whose first year of life began after 1995 and looked into their use of antibiotics in that first year of life. We matched these patients with a control group. Although the study set was relatively small—36 study subjects and 360 controls—we found that children who had an IBD diagnosis were about 3 times more likely than children without an IBD diagnosis to have received antibiotics in the first year of life.

We then looked into why the children in our database were prescribed antibiotics and found that most children were receiving antibiotic therapy for treatment of otitis media. We did not conclude that otitis media predisposes patients to IBD. Firstly, it is uncommon for otitis media to be diagnosed after the age of 6 years, and secondly, otitis media is unlikely to be an extraintestinal manifestation of IBD in the way that other chronic immune diseases in other organ systems can be. Rather, we thought otitis media would be a good proxy measure for antibiotic use during childhood in persons with IBD. We looked at all of our database subjects with IBD, compared them with the matched controls, and looked at diagnoses of otitis media by age 1 year, age 5 years, and ever. We found that subjects with IBD were significantly more likely than matched controls to receive a diagnosis of otitis media by the age of 5 years.

In another study, we examined antibiotic use prior to an IBD diagnosis in patients of all ages. We wanted to examine antibiotic use not just in the 6–12 months prior to an IBD diagnosis but in the 2–5 years prior to an IBD diagnosis because IBD develops over time, and the antibiotics prescribed within the several months of an IBD diagnosis may actually have been prescribed to treat gastrointestinal symptoms. We found an increased association between prior antibiotic use and an IBD diagnosis in adults just as we had in children. We found that the greater the antibiotic use, the stronger the association between antibiotic use and an IBD diagnosis.

Thus, these studies with our population database provide some circumstantial evidence of an association between antibiotic use and a diagnosis of IBD. The take-home message is that physicians need to be judicious and forward-thinking about the prescription of antibiotics, especially in young children. Pediatricians have been saying this for years.

G&H Have you identified whether certain antibiotics might be more problematic in relation to the risk of IBD?

CB The most common types of antibiotics that have been used are the penicillins, although macrolides are being used more frequently in recent years. We do not know whether a specific class of penicillin or another type of antibiotic is more problematic than others in relation to the gut microbiome and development of IBD. A study from a team at Pennsylvania State University in which a group of dermatology specialists collaborated with a group of gastroenterology specialists found an association between tetracycline use and IBD development. The finding suggests that some teenagers who receive tetracycline for treatment of acne may be put at risk for IBD.

G&H Might antibiotic use stimulate a latent predisposition?

CB No single factor likely causes IBD. For instance, back in 2001, the *NOD2* gene on chromosome 16 was the first gene to reportedly be associated with a chronic immunoinflammatory condition associated with Crohn's disease. *NOD2* was thought to account for about 25% of Crohn's disease, but its presence is neither necessary nor sufficient to cause Crohn's disease. Many people with Crohn's disease do not have this gene, and Crohn's disease does not develop in most people who have mutations on the *NOD2* gene.

If a person has a *NOD2* gene mutation, he or she either needs to have other genetic abnormalities or else environmental factors to set pathogenesis of IBD in motion. If antibiotic use were a risk factor for development of IBD because of changes it exerts on the gut microbiome, a susceptible person would also likely have to be genetically predisposed to mount a certain type of response to those changes. Therefore, IBD is not going to develop in most children who receive antibiotics. Risk is more relevant in the child who has an older sibling with IBD, suggesting a genetic predisposition. Attention should be given and care should be exercised regarding antibiotic use and the gut microbiome in such a child.

G&H What are the implications of current research, and what future research is planned?

CB Current research adds further circumstantial evidence to the importance of the gut microbiome. In examining the microbiome of young children, as we did, clinicians can better determine how IBD develops and why.

Further research is underway, including the Genes, Environment, and Microbes (GEM) study. Participating centers across Canada have been enrolling healthy siblings and children of persons with IBD into the GEM study. The microbiomes of these participants are being studied, and the expectation is that Crohn's disease eventually will be diagnosed in some of them. Although it is worthwhile to say that the gut microbiome is different in persons who have Crohn's disease compared with that of people who do not have Crohn's disease, if the cause is to be found out, the gut microbiome needs to be examined before Crohn's disease develops to examine what changes take place leading to pathogenesis.

Suggested Reading

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