ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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Treating Inflammatory Bowel Disease in Children and Adolescents

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G&H What is the prevalence of pediatric inflammatory bowel disease, and why is it increasing?

JH We believe that the prevalence of pediatric inflammatory bowel disease (IBD) is increasing, but a practitioner needs to decide what his or her frame of reference is. If we look back 20 or 30 years, the data suggest an increase in the number of cases of pediatric IBD. I do not know whether that increase has continued over the past 10 years or so or whether the incidence rate may have leveled off a bit. There are difficulties in trying to determine both incidence and prevalence because IBD in children may not be diagnosed properly, and, depending on the type of practitioner a child goes to, the diagnosis may or may not be captured for data purposes.

One of the best studies on prevalence comes from Wisconsin, showing that we are probably seeing an increasing number of pediatric IBD cases now compared with the 1970s and 1980s. We continue to see more cases of Crohn’s disease than ulcerative colitis, which is a change from 30 years ago. At many centers, there are 3 or 4 patients with Crohn’s disease for every 1 new patient with ulcerative colitis, and this is certainly my experience as well. The cause for this shift is unknown.

One of the many theories for the increase in prevalence of IBD is increasing antibiotic exposure, which may be associated with intestinal dysbiosis. Another is the hygiene hypothesis, in which it is thought that diseases such as IBD emerge because children are not exposed, early in life, to a large antigenic stimulus, and so their enteric immune system does not develop tolerance. In my opinion, much of this remains speculative.

G&H What do we now know about dysbiosis in pediatric patients?

JH Children are the ideal population to study disease pathogenesis. They generally do not have multiple confounders, such as smoking, drinking, or use of birth control pills. They generally have less concomitant disease. Having said that, there is good information now to show that children with newly diagnosed IBD have an abnormal gut microbiome pattern. In fact, our Crohn’s and Colitis Foundation of America (CCFA) Risk study, published in the March 2014 issue of *Cell Host & Microbe*, is quite powerful. Using stool, rectal biopsy, and ileal biopsy samples, we examined the gut microbiome in the terminal ileum and rectum and showed that there is an abundance of Enterobacteriaceae, Pasteurellaceae, Veillonellaceae, and Fusobacteriaceae and a decreased abundance of Erysipelotrichales, Bacteroidales, and Clostridiales, which correlate with disease status.

Another fascinating finding is that this microbial dysbiosis seems to be aggravated in persons with prior antibiotic exposure. In fact, there have been other recent reports as well about a shift in the microbiome to a more “injurious” than benign one in adults who have been exposed to antibiotics. The finding is important given
the increasing exposure of our population, particularly our young population, to antibiotics at times when these agents are probably not needed.

The study also provided more insight on whether dysbiosis is a result of inflammation or vice versa. In this study, it was shown that, in treatment-naïve patients, dysbiosis was still present in areas of the bowel that were not inflamed, suggesting that dysbiosis may be a primary, and not a secondary, event. Why dysbiosis developed in these patients is still not clear. Further studies, including a National Institute of Diabetes and Digestive and Kidney Diseases study on newly diagnosed, treatment-naïve ulcerative colitis, will provide additional information.

**G&H What distinguishes pediatric IBD from adult IBD?**

**JH** The disease that we see in pediatric IBD, whether it is Crohn’s disease or ulcerative colitis, tends to be more severe and more extensive at the time of diagnosis. The reasons for this are unclear, but it has been hypothesized that early childhood IBD may be more driven by genetic factors, whereas, in adults, environmental factors may play a larger role. Again, this is speculative.

Pediatric patients have a greater need for corticosteroid therapy than adults, which seems to be associated with disease severity. At the same time, corticosteroids are very problematic for pediatric patients because of the effects of these agents on growth.

A study that appeared in *Gastroenterology* this past February looked at early treatment with anti–tumor necrosis factor (TNF) inhibitors compared with conventional early therapy with immunomodulators. We know that more than 80% of our pediatric patients require therapy beyond corticosteroids and aminosalicylates. In this particular study, in which we used an observational cohort and advanced statistical methods to develop very well-paired populations, we clearly show that early exposure to anti-TNF agents in children with moderate to severe Crohn’s disease is associated with significantly improved outcomes at 1 year, evidenced by the lack of disease activity and lack of need for continued corticosteroids. Importantly, normalization of growth was seen in those patients who had received anti-TNF therapy. The outcomes were significantly better than in children treated with early immunomodulators or those not treated with immunomodulators or anti-TNF agents in the first 3 months following diagnosis.

Because children with IBD have a very long duration of expected disease, it may be particularly important in this population to prevent architectural changes to the bowel and avoid the complications of strictureing or perforation.

**G&H How should specialists work with the caregivers of pediatric patients with IBD?**

**JH** Caring for a child with IBD is multifaceted: we have the child, the family, and the physician. Every decision that is made as we move forward includes all of these parties, who need to be fully cognizant of the risk of therapy but also of the risk of poorly treated disease. A significant challenge is faced when a child with newly diagnosed IBD is found to have extensive disease. We know that this patient is at high risk for complications of their disease. As we discuss the benefits and risks of various treatment options, it is common for many patients and families to focus more on the risks than the benefits. This is unfortunate because these patients may wind up being undertreated and suffer the consequences of progressive disease.

I think the data are clear that anti-TNF agents are far superior to immunomodulators in maintaining remission and resulting in mucosal healing. In my mind, they have comparable, if not better, safety records. Nonetheless, there remains reluctance to use anti-TNF agents early in the disease course. Yet unanswered is whether combination therapy, in the form of an anti-TNF agent plus an immunomodulator, is superior to anti-TNF monotherapy with close monitoring of drug levels. From a safety standpoint, it would be preferable to use 1 agent rather than 2 agents. The development of a very rare and often fatal cancer, hepatosplenic T-cell lymphoma, appears largely driven by prolonged thiopurine exposure, although additional exposure to an anti-TNF may be important as well.

**G&H Do any special precautions need to be taken regarding immunizations in children with IBD?**

**JH** The only precaution is that any patient on immunomodulatory therapy, whether an adult or child, should not receive live viral vaccines. Every attempt should be made to complete the patient’s immunizations with live viral vaccines before starting the patient on immunomodulator therapy. Killed vaccines, such as the flu vaccine, are not an issue.

**G&H What prompts the pediatric IBD specialist to know that the patient will have a higher likelihood of surgical intervention in the future?**

**JH** This is an area of intense interest to us. We know that patients with small-bowel disease are more likely to require surgery than those with large-bowel disease. Deep ulceration at colonoscopy has been associated with a higher need for surgery in adults, but this has not been confirmed in children. We also know that serologic reactivity to microbial antigens is important. Patients with the highest antibody titers to microbial antigens tend to have
a markedly increased risk for development of complicated disease requiring surgery.

We expect that the CCFA Risk study, which began in 2008 and has recruited over 1000 patients with newly diagnosed Crohn’s disease, will provide robust new data that will allow clinicians to predict which patients are and which are not at high risk for complications requiring surgery.

**G&H** How can a smooth transition be made from pediatric to adult care?

**JH** The transition is often difficult for many of our patients. The mean age of diagnosis for the pediatric patient with IBD is approximately 12 years. In the United States, pediatric IBD specialists often follow patients until they graduate college, although the cutoff is age 18 years in Europe and Canada. This means that an average patient is going to spend 10 years with a pediatric IBD specialist. Most pediatric practices are very nurturing environments. The children grow up with the specialist and his or her staff. Many pediatric IBD specialists have coordinators who help patients and their families navigate through life with IBD. The adult IBD world may not have these additional resources. Appropriately, it is assumed that the young patient will take on an increasing amount of responsibility for his or her medical care. In my practice, the team introduces concepts of independence, ensuring that the patient has knowledge about his or her medicine and becomes responsible for making his or her own appointments.

Medication adherence is another important issue for both young persons and adults. Strong evidence shows that disease flares often correlate with poor medication adherence. Adherence in children may be compromised when they face transitions in their life, especially when they go from high school to college. Their mother is no longer there to ask them, “Did you take your medicine?” In the first semester of college, medication adherence often drops off, and patients begin to drink alcohol, stay up until 3 AM, and adopt other lifestyle habits that aggravate their IBD, so it is no surprise that we often see disease flares in patients at this stage.

**Dr Hyams has served on the advisory boards of AbbVie, Janssen Ortho-Biotech, and UCB and has served on the speakers bureau and received research support from Janssen Ortho-Biotech.**

**Suggested Reading**


