ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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Risk Assessment in Crohn's Disease

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G&H In your opinion, what might be the cause of the emergence and increase in prevalence of Crohn's disease since the Industrial Revolution?

MD The hygiene hypothesis says that as regions become more industrialized or westernized, an increase in diagnoses of inflammatory bowel conditions, among other autoimmune diseases, is seen. The idea is that, with increased hygiene comes less opportunity to build immunity against pathogens. Being in a more hygienic or sterile environment impacts gut flora so that certain bacteria may be treated as foreign in some people. Genetics plays a strong role, and so those individuals with a genetic susceptibility to gut disorders are most vulnerable. If we look at India or other Asian countries as an example of westernization and industrialization, we see an increasing incidence of inflammatory bowel disease (IBD) in these advancing countries. Interestingly, the pattern of IBD emergence in many countries as they industrialize is one in which increased incidence of ulcerative colitis is seen that then is overtaken by more Crohn's disease–like forms of IBD. This phenomenon may be because flora change as a region becomes more westernized.

We classify IBD into being either ulcerative colitis or Crohn's disease, but 110 of the 163 genes that have been identified as playing a role in IBD overlap between the 2 disease entities. The same genes, therefore, can go in either direction to cause a person to be at risk for development of ulcerative colitis or Crohn's disease. The flora likely influence in which direction the genes go. Perhaps, early on, a change in the environment or hygiene predisposes certain people in a newly industrialized region to a gene-bacterial interaction that gives rise to a more ulcerative colitis–like phenomenon. As industrialization of the region progresses, a gene-bacterial interaction that selects a more Crohn's disease–like phenomenon emerges.

G&H Since factors in addition to genetics determine emergence of Crohn's disease, is there a role for genetic testing?

MD This is not a concern. Gene testing is not ready for prime time in any way. As I mentioned, there are 163 genetic loci. We do not know what these genes actually do, though. Discovering the function of all of the gene defects that are associated with IBD is important, but identifying a gene is only part of the story. Having a gene mutation is not necessarily predictive of disease development.

The positive predictive value of a single genetic locus in predicting IBD development is low. Perhaps when scoring begins to be developed and genetic pathways begin to be explored—that is, when the 163 loci are consolidated into perhaps 20 or 50 different pathways—then we will have a better predictive value of disease risk. For example, the presence of the *NOD2* gene, which was identified in 2001, has been shown to be highly associated with the development of Crohn's disease, but this genetic variant is only present in about 35% of patients with Crohn's disease. If a person is *NOD2*-negative, this does not predict that IBD will not develop in that person. Likewise, IBD will not necessarily develop in patients who are *NOD2*-positive. The gene may simply be passed down through families.

Also of interest in regard to the genetics of IBD is that some genetic loci that are associated with IBD overlap as markers for other autoimmune diseases. For example, the interleukin (IL) 23 receptor gene also is a marker for psoriasis. There also have been reports showing overlap between genetic loci associated with IBD and type 1 diabetes.

G&H How should the siblings or children of patients with Crohn's disease be dealt with to possibly minimize disease risk?

MD An unaffected person who might be at risk for sharing some genetic homology with a sibling or parent who has Crohn's disease might be counseled about lifestyle habits and changes that might be wise to initiate. A clinician may, for instance, suggest that a parent make sure that exposure to nonsteroidal anti-inflammatory drugs is minimized in the sibling of an affected child and that the sibling is taking vitamin D supplements and perhaps omega 3 supplements or probiotics. Siblings of patients with IBD might also even minimize exposure to isotretinoin if their parents or physicians are concerned about a suspected link between isotretinoin use for acne and the development of IBD. Although siblings and children of patients with IBD can take preventive measures, there are no data to support the idea that a genetically at-risk person can prevent IBD by altering his or her lifestyle. The rationale behind interventions for relatives of patients with IBD is speculative.

G&H What are the risk factors for Crohn's disease, and what is the best way for a physician to assess whether a patient is at risk?

MD Risk prognostication is a discipline onto itself. Research suggests that carriage of the *NOD2* and the IL-12–beta genes is associated with increased likelihood of stricturing Crohn's disease and need for surgery. To date, no other genes have been shown to be associated with outcomes as strongly as these 2. There are a few genome-wide association studies that have shown other genes but not consistently across studies.

Other investigators have looked at developing models of clinical variables, meaning clinical factors that predict which patients may progress to complications or surgery. These variables include the level of C-reactive protein elevation, the role of disease location (such as the small vs large bowel), and the presence of perianal disease. All of these factors have been shown, from a clinical perspective, to influence the likelihood of progressing to a complication or need for surgery.

In addition, investigators have looked at the role of serologic immune markers that are targeted against bacterial microbial antigens in the gastrointestinal tract. Serologies have been shown to very strongly influence prognosis and risk of surgery. Also, models are being developed that combine genetics, clinical variables, and serology in an effort to predict an outcome.

G&H Once identified, how is risk of progression of Crohn's disease intercepted?

MD The goal is to get an at-risk patient on the right therapy early. Of concern is the patient at risk for rapid disease progression—that is, someone whose disease rapidly progresses, with complications requiring surgery, in the first year or 2 after diagnosis rather than the patient who requires surgery 10 years after diagnosis. It is important to identify these patients early so that an effective treatment intervention can be initiated. Risk prognostication, in this way, prepares the patient and also provides physicians with the data needed to explain to a patient why one course of treatment is being used instead of another. It is very important that patients understand that risk prognostication helps balance the risks and benefits of therapy vs the risks of the disease itself and helps patients who are at very high risk understand that living with their disease in an untreated state is far riskier than any medication that might be prescribed.

Also, although safety issues are associated with drugs used in Crohn's disease, adverse effects of treatments are more amplified in patients whose disease is more progressed and are, thus, more debilitated. When therapy is delayed so long that complications develop, sometimes the complications are blamed on therapy when, in reality, the physician and patient may have waited too long to initiate therapy.

Physicians and patients procrastinate and often do so based on concerns about adverse effect profiles, although the adverse effects may actually be related to the disease activity itself. For example, in the literature on rheumatoid arthritis, it has been shown that patients in whom more infections developed were those who began using biologic therapies later than earlier.

Young patients typically have a very healthy and hearty immune system, but if a young patient has chronic untreated inflammation, the outcome will never be good regardless of what therapy is used. About 25% of cases of Crohn's disease are diagnosed in children—patients younger than 18 years—and it has been suggested that this population is the fastest growing in terms of Crohn's disease diagnoses. It is so very important for physicians to understand that, when markers for a high risk of disease progression are present in a certain subgroup of patients, those patients need to be treated more aggressively than other patients.

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Suggested Reading

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