ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Diseases

Section Editor: Stephen B. Hanauer, MD

Emerging Diagnostic Methods in Inflammatory Bowel Disease

Edward V. Loftus, MD
Professor of Medicine
Division of Gastroenterology & Hepatology
Mayo Clinic School of Medicine
Mayo Clinic
Rochester, Minn.

G&H What is the unmet need in terms of diagnostic methods for inflammatory bowel disease?

EL When patients first present with gastrointestinal (GI) symptoms, the clinician must determine if they have irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), a GI malignancy, or another GI problem. Once the diagnosis of IBD has been established, the second, equally important, need is the assessment of disease activity. In order to treat effectively, it is important to gauge the level of inflammation (mild, moderate, or severe) and the extent of bowel involvement.

One of the challenges in IBD is that there is no single pathognomonic test to secure a diagnosis for either Crohn's disease or ulcerative colitis. These remain clinical diagnoses, which require the clinician to take a thorough history, quiz the patient for alarm symptoms, and perform a physical examination (specifically looking for an inflammatory mass, an abscess in the abdomen, evidence of perianal disease, anal stenosis on rectal examination, or any other complicating factor). Until recently, there were only two tests to arrive at a diagnosis: colonoscopy/ileoscopy and small bowel follow-through.

Colonoscopy/ileoscopy remains one of the most important tests, as it affords the opportunity for biopsy and tissue diagnosis of chronic inflammation. However, it is an invasive and expensive test, which requires considerable patient preparation. Less invasive methods to assess activity would be preferable. Small bowel follow-through can also provide important information, but it is becoming more and more apparent that it is relatively insensitive and can frequently miss milder forms of Crohn's disease.

G&H Could you describe the current advances in serologic testing for the diagnosis and evaluation of IBD?

EL Serologic testing, in the broadest definition of the term, encompasses any blood test, including antibody and serum measures of any substance. There are certain inflammatory biomarkers that might be helpful in determining how much systemic inflammation is present, but they cannot secure a diagnosis of IBD. These markers include C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Both of these tests have been around for many years. It has been recognized recently that CRP is a good test for detecting systemic inflammation, but it is not sufficiently sensitive or specific to rely on solely. It simply adds information in helping to gauge disease severity in patients with established IBD.

The evolving serologic tests that hold more promise for definitive diagnosis and prognosis measure antibodies. When serologies were first linked to IBD patients back in the late 1980s and early 1990s, only two tests were available: anti-neutrophil cytoplasmic antibody (ANCA) and antibodies to *Saccharomyces cerevisiae* (ASCA). ANCA tends to be present in patients with ulcerative colitis, and ASCA in Crohn's disease patients. When the two tests are combined in a panel, sensitivity decreases but specificity increases. The finding of negative ANCA and positive ASCA is reasonably specific for Crohn's disease but at a cost of slightly decreased sensitivity.

Recently, there has been increasing recognition of additional antibodies found to be positive in patients with IBD, mostly Crohn's disease. The immune system in the gut is as exposed to the outside environment as the

immune system in the skin. It needs to be active but to act selectively, recognizing what bacteria are helpful and harmful and deal with them accordingly. There is always some degree of inflammation in the GI tract, but it is for the most part controlled. In patients with Crohn's disease, and to some extent in patients with ulcerative colitis, that inflammation process has lost control and is dysregulated. The immune system in the gut seems to react to antigens that it should not, in a phenomenon called loss of tolerance. Over the years, we have recognized that patients with Crohn's disease develop a loss of tolerance to certain constituent bacteria that are ubiquitous. These are widely present bacteria to which, for whatever reason, Crohn's patients have developed antibodies. Some of these antigens include outer membrane porin C (OmpC) to *Escherichia coli*, the I2 constituent of *Pseudomonas fluorescens*, and CBir1, which is a bacterial flagellin. When these antibody tests are combined in a panel, the operating characteristics can again be increased such that, at least in unpublished studies, it has been suggested that sensitivity and specificity for Crohn's disease may be higher than 90%. However, the operating characteristics of this panel still need to be validated by independent third parties before they can be adopted for wide use.

In terms of prediction of treatment response, the data with respect to serologic testing are conflicting. Clinicians have begun looking retrospectively at patients taking biologic therapies and considering what factors may predict response. One subgroup of patients, who have colonic involvement that mimics ulcerative colitis but who are actually perinuclear ANCA–positive, tends to be treatment-resistant. Ultimately, these patients are found to have Crohn's disease. Thus, there are vague ideas that different phenotypes can be associated with specific therapeutic response, but these relationships are difficult to characterize.

It has also been found that pediatric Crohn's disease patients can be tested for antibody levels, and this information can help forecast their prognosis in terms of intestinal complications including fistula, stenosis, obstruction, and need for small bowel resection. The more antibodies patients test positive for, the more likely they are to have intestinal complications. Further, the higher these antibody titers are, the greater the likelihood of complications. Our hope from these findings is that, ultimately, we will be able to predict the level of severity early in a patient's disease course and develop a risk score based on clinical features, serologic testing, and other demographic information. This will allow us to formulate a treatment plan that is more or less aggressive, based on informed prognostic concerns.

Fecal markers of inflammation, including lactoferrin and calprotectin, can also provide diagnostic information. These proteins are found in the secondary granules of neutrophils. If elevated levels of these proteins are found in the stool, they provide indirect evidence of an inflammatory process in the GI tract. A number of studies have correlated levels of fecal lactoferrin or calprotectin for successful discrimination of IBD from IBS and, among IBD patients, to discriminate between active and inactive disease. Both of these markers have reasonably good operating characteristics, but calprotectin has the added advantage of relative stability at room temperature, whereas stool samples must be frozen to test for lactoferrin if the test is not performed soon after collection. These markers are already in use among some pediatric gastroenterologists because they provide a noninvasive way to assess inflammation. I suspect that their use will grow in adult practice as well. Fecal markers are also under examinations as prognostic tools in gauging the likelihood of disease flare or relapse.

G&H What new endoscopic techniques are being utilized in IBD diagnostics?

EL Capsule endoscopy is a recent tool that has proven valuable in assessing the mucosa of the small bowel, which had not previously been accessible through conventional endoscopy. In patients that have unexplained abdominal pain along with some other symptom that indicates organic disease (eg, weight loss, anemia), elevated levels of inflammatory markers such as CRP, or a strong family history of IBD, it is reasonable to consider capsule endoscopy if conventional testing yields negative results. In a patient with lower quadrant abdominal pain and weight loss, who has undergone colonoscopy/ileoscopy and small bowel follow-through and no abnormality has been detected, capsule endoscopy can be utilized to confirm a negative diagnosis or uncover previously undetected evidence of inflammation and IBD.

Multiple studies have shown that capsule endoscopy provides a higher diagnostic yield than standard endoscopic procedures. These studies have generally been designed for patients in whom Crohn's is suspected but conventional testing has been negative. However, there are several concerns. The finding of erosions or an ulcer in the small bowel mucosa is not specific for Crohn's disease. We know from studies of cyclo-oxygenase (COX)-2 inhibitors that Crohn's-like erosions can be mimicked in the general population when patients are taking these medications. Even asymptomatic normal subjects not on nonsteroidal anti-inflammatory drugs can have small bowel erosions detected on capsule endoscopy. Because there is no way to biopsy with capsule endoscopy, it is difficult to make a confirmed diagnosis. Further, it can be difficult to orient the capsule in the bowel and know where a lesion is

located, even when it has been visualized. There is also the issue of capsule retention. In patients with known Crohn's disease, the retention rate in some studies has been as high as 10–13%. Clinicians need to be cautious in ordering capsule endoscopy in these patients. Nevertheless, it is a very powerful tool, and in some indications, very helpful.

Another new endoscopic technique is the evolving practice of double-balloon enteroscopy, which is performed by specialized, therapeutic endoscopists in patients under heavy sedation or general anesthesia. It involves the use of two balloons on one scope, alternating between inflation and deflation to maneuver the instrument through the GI tract for direct visualization of the small bowel. It is an effective technique but very time-consuming and fairly invasive. Further, there have been reports of perforation. Therefore, I would reserve this technique for selected individuals who require tissue sampling in a specific area that is inaccessible via colonoscopy.

Endoscopy has also advanced in the surveillance of IBD patients for dysplasia. New techniques include chromoendoscopy, where the lining of the colon is sprayed with methylene blue or indigo carmine to highlight abnormal tissue and allow for targeted biopsy rather than random sampling. Several studies, including at least one randomized trial, have shown that dysplasia detection rates can be tripled or even quadrupled by using this technique. Current investigators are looking at certain forms of light and optics, or autofluorescence, to perform narrow-band imaging, which would highlight the same tissue by pressing a button on the endoscope rather than requiring the administration of dye. However, this technique is very experimental and cannot currently be recommended for wide use.

G&H What other advances in imaging techniques play a part in examining IBD patients?

EL Computed tomography (CT) and magnetic resonance imaging (MRI)-based techniques are steadily improving and allowing more detailed detection of small-bowel abnormalities. CT scans currently have the ability to obtain thinner slices at higher resolutions and can be performed more quickly than ever before, so patients are not required to stay still for as long a period as previously. With these advances, various radiography techniques can be employed to accurately image the small bowel. Patients ingest a large volume of an oral contrast. However, instead of a positive oral contrast like barium, they take a negative or neutral oral contrast to highlight the difference between the lumen and the actual bowel wall. At the same time, intravenous (IV) contrast is administered and the scan is performed at a specific time to again highlight the differences. Areas that are inflamed will have engorged blood vessels and therefore be further enhanced by the IV contrast. In combining all of these principles, CT enterography can be performed, where the patient comes in 1 hour and 15 minutes before their actual scan, drinks 1.5 L of neutral or negative contrast, receives IV contrast dye in a protocolized fashion, and the scan is performed on a fast 16-, 32-, or 64-slice scanner. The scanner protocol is performed in a way that provides images that far surpass those achieved with small bowel follow-through.

The added advantage with this technique is that it provides information outside of the bowel lumen, showing the full thickness of the bowel wall and any abscesses or fistulas. In many centers, CT enterography has essentially replaced the small bowel follow-through procedure in patients with known or suspected Crohn's disease. This is allowing us to base treatment decisions less on symptoms and more on the degree of inflammation seen on the scans. Whether or not this will affect the natural history of the condition remains to be seen, but we are hoping to study these outcomes both prospectively and retrospectively.

Certain patients, those with renal insufficiency, iodine allergy, or illness that prohibits the ingestion of 1.5 L of oral contrast, cannot undergo CT enterography. Further, there is radiation exposure involved, anywhere from 4 to 10 times more than with small bowel follow-through. MR enterography has been proposed as an alternative to address radiation concerns. It utilizes the same principles as CT enterography. Patients come in early, drink a large-volume contrast, and receive IV gadolinium before undergoing MRI. The images are not quite as good as those achieved with CT enterography, but the technology is improving and it is hoped that MR will one day surpass CT in terms of overall diagnostic accuracy while removing concerns regarding radiation exposure.

Suggested Reading

Bruining DH, Loftus EV. Evolving diagnostic strategies for inflammatory bowel disease. *Curr Gastroenterol Rep*. 2006;8:478-485.

Solem CA, Loftus EV Jr, Tremaine WJ, et al. Correlation of C-reactive protein with clinical, endoscopic, histologic, and radiographic activity in inflammatory bowel disease. *Inflamm Bowel Dis*. 2005;11:707-712.

Paulsen SR, Huprich JE, Fletcher JG, et al. CT enterography as a diagnostic tool in evaluating small bowel disorders: review of clinical experience with over 700 cases. *Radiographics*. 2006;26:641-57; discussion 657-62.

Leighton JA, Triester SL, Sharma VK. Capsule endoscopy: a meta-analysis for use with obscure gastrointestinal bleeding and Crohn's disease. *Gastrointest Endosc Clin N Am*. 2006;16:229-250.

Sabery N, Bass D. Use of serologic markers as a screening tool in inflammatory bowel disease compared with elevated erythrocyte sedimentation rate and anemia. *Pediatrics*. 2007;119:e193-e199.