

# ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Diseases

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## Serologic Testing in Inflammatory Bowel Disease

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### G&H What is serologic testing?

**EV** Serologic testing is a noninvasive way of detecting abnormalities that might be suggestive of an underlying disease process. In inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), serologic testing can reveal abnormalities directed against self or nonself proteins. Although these antibodies are not pathogenic and therefore not harmful, they serve as surrogate markers of immune dysregulation or disease susceptibility. Furthermore, antibody levels are relatively stable over time and are not present in non-IBD-colitis control subjects, implying that they are not nonspecific markers of colonic inflammation.

### G&H What specific serologic markers have been identified as effective indicators of IBD?

**EV** Among the first markers to be described in IBD were antineutrophil cytoplasmic antibodies (ANCA), which are seen in several immune disorders. While in some diseases, ANCA are associated with disease activity, they do not play an active role in UC or CD. The majority of UC patients are positive for perinuclear ANCA (pANCA). Serum pANCA in IBD have been shown to reflect pANCA production at the level of the gut mucosa. Interestingly, the subset of CD patients that expresses serum pANCA has many features typically associated with UC, indicating that this marker is associated with a certain UC-like inflammatory process.

Anti-*Saccharomyces cerevisiae* mannan antibody (ASCA), another marker, cross-reacts with brewers' or

bakers' yeast and is more common in CD than in UC. Another commercially available marker is OMP-C, which reacts to the cell wall of *Escherichia coli* bacteria and is associated more with CD than with UC. Two newer antimicrobial antigen markers that likewise are more often expressed in CD than UC are I2, an antibody to *Pseudomonas fluorescens*, and antibodies to flagellin (anti-CBir1).

The tendency to express markers appears to be hereditary, and does not necessarily represent a reaction to specific bacteria or pathogens but rather reflects an immune response. This theory is supported by the association of seroreactivity to several of these antibody markers with specific genetic markers. Studies have also demonstrated that serum immune markers may be present in family members that do not necessarily have IBD.

### G&H Can serologic testing distinguish IBD from other disease processes?

**EV** The described serologic markers are present in the majority of UC and CD patients and are infrequently present in non-IBD control subjects, including patients with irritable bowel syndrome, and as such are specific for IBD; the false-positive rate for each is low. Furthermore, individuals who have falsely positive serologies tend to have low levels of antibody marker expression. As such, serologic testing can serve as a useful screening tool in the primary care setting.

Abdominal pain and diarrhea might prompt a physician to test for CD or UC, and a gastroenterologist will generally be able to determine whether a referred patient has IBD. However a general practitioner to whom patients initially present may benefit more from such disease-specific tests.

### G&H Does serologic testing enable earlier detection of UC and/or CD?

**EV** Serologic testing does have the potential to enable earlier detection and subsequent intervention. Patients ultimately determined to have UC or CD often times present with a history of symptoms that have been going on for months or even years, or in the case of CD, even up to a decade or more. By this time, the inflammatory

process may already be advanced and more difficult to control. Alternatively, complications of the disease might already have developed, such as perforations, fistulas, deep ulcers, narrowing of the intestines, or strictures. In many such cases, earlier recognition and thereby earlier intervention could potentially have prevented or diminished the severity of the disease or its complications. Indeed, at our IBD center, which is a tertiary facility, we have observed a trend toward earlier referral of patients to establish or clarify the diagnosis. In many cases such referrals are coming directly from primary care physicians, pediatricians, internists, and family practice doctors because the blood tests, generally in the form of an IBD panel, are being used for disease detection.

### **G&H** Are serum immune markers alone enough to make the diagnosis of CD or UC?

**EV** As mentioned previously, serum immune markers may be present in family members that do not necessarily have IBD, the potential clinical relevance of which is currently under investigation. However, this observation, together with the infrequent expression of serum immune markers in individuals who do not have IBD, highlights the need to correlate the presence of these markers with other indicators of IBD.

### **G&H** If the typical symptoms of UC and CD are not yet present, what might trigger a physician to perform serologic testing for IBD?

**EV** It is well known that some patients with IBD initially present with nonintestinal manifestations of their disease and only later develop gastrointestinal symptoms. A good example of this is the pediatric population. Up to 50% of children and adolescents with CD do not initially present with predominant gastrointestinal symptoms but rather with growth problems, joint pain, fatigue, anemia, or other nonspecific symptoms. Furthermore, in many patients, particularly those with upper-tract or small-bowel CD, gastrointestinal symptoms may be more subtle and not at all “classic” for IBD.

In these types of cases, suspicious signs and symptoms may prompt for serologic testing. An appealing aspect of serologic testing is that it is a minimally invasive way to initially investigate the source of these problems, thereby serving as a useful initial alternative to the endoscopies and extensive x-rays typically used to diagnose CD and UC. Adding serum marker analyses to standard blood testing is simple and therefore attractive, particularly when trying to establish whether problems such as abdominal pain or diarrhea are related to irritable bowel syndrome infection or to IBD. A positive serologic test provides the impetus for further patient work-up.

### **G&H** Do serologic tests enable differentiation between UC and CD and why is this important?

**EV** In many cases, yes, and this is another key advantage. Although sometimes it is very clear whether a patient has UC or CD based on radiographic, endoscopic, and histologic findings, in perhaps up to 30% of patients the diagnosis is not so easily made. Importantly, recognition of the true diagnosis will influence surgical, standard medical, and experimental treatment options and choices. I estimate that approximately 20% of patients admitted or transferred to our center with a diagnosis of severe or fulminant UC are found to actually have CD or strong suspicion of CD upon further work-up. While initial treatments for UC and CD may be similar, in more refractory cases definitive distinction is important as surgical and medical therapeutic choices may differ. In addition, if a patient does not respond to initial therapy and clinical trial enrollment is being considered, it is essential to know whether the disease is CD or UC in order to ensure appropriate patients are enrolled in the trials and to ensure that the findings of clinical trials can be accurately interpreted.

### **G&H** Do serologic tests have a role in the management of IBD?

**EV** The serologic markers allow for patient stratification within a particular disease. It appears that certain marker patterns in CD are associated with more aggressive disease, which requires a different treatment approach to that for nonaggressive disease. High-level ASCA expression, particularly for the 2 variants of this antibody (immunoglobulins G and A) is associated with more aggressive small bowel disease, characterized by perforating, fistulizing, and stricturing complications. Patients with more aggressive disease are more likely to require not only small bowel surgery, but also surgery earlier in the course of their disease. While yet to be definitively demonstrated in a prospective manner, because of the higher likelihood of such complications such patients should be considered for more aggressive first-line intervention. Alternatively, if the disease requires surgery as the initial treatment, then postoperative therapy might be more aggressive in order to prevent CD recurrence, or postoperative follow-up might be more intensive, since careful monitoring and earlier intervention can help reduce the risk of requiring a second surgery in these patients.

Patients with UC who express high levels of pANCA prior to colectomy are more likely to develop chronic pouchitis than patients without high levels of this antibody. Studies are ongoing to evaluate whether treating UC patients who preoperatively expressed high levels of

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