A Critical Evaluation of Serologic Markers for Inflammatory Bowel Disease

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Clinical Scenario
A 44-year-old woman with abdominal pain of 4 months' duration is referred to your gastroenterology clinic from her primary care physician for evaluation of positive serologic markers for IBD. The patient denies diarrhea, bright red blood per rectum, melena, fevers, and weight loss. She has normal liver function test results, complete blood count, erythrocyte sedimentation rate, and C-reactive protein. There is no family history of IBD. She has undergone an upper endoscopy, a colonoscopy, and a small bowel series, all of which have been normal.

How do you proceed with evaluation and management of this patient? How should the information provided by the positive serologic markers be used? What is the role of serologic markers in the diagnosis of IBD?

Management Strategies and Supporting Evidence
To understand how gastroenterologists should interpret and use IBD serologic testing, it is important to briefly review the existing data regarding the currently available serologic tests. Numerous autoantibodies and antibodies against different bacterial components have been studied in patients with IBD. There are only 3 antibodies used in serologic testing for IBD that have been correlated with CD. These are (1) antibodies to the yeast Saccharomyces cerevisiae (ASCA); (2) antibodies to the outer membrane porin C of the bacteria Eschericia coli (anti-ompC); and (3) antibodies to the bacterial flagellin Cbir1 (anti-Cbir1). The reported prevalence of ASCA (either IgA or IgG) in CD has ranged from 35%–75%. ASCA has a high specificity for CD when compared with a population of normal, healthy controls. However, it is also found with fairly high prevalence in populations with celiac disease and has been described in unaffected family members of IBD patients. There are fewer data assessing the association of anti-ompC and anti-Cbir1 with CD compared with the existing evidence for ASCA. For anti-ompC, approximately 55% of individuals with CD have been found to have a positive serologic response. Approximately 50% of individuals with CD are positive for anti-Cbir1.

The primary serologic pattern associated with UC is the detection of atypical perinuclear antineutrophil cytoplasmic autoantibodies (pANCA), which are found in approximately 30%–83% of patients, depending on the assay. Some patients with CD, primarily those with disease activity confined to the colon, will also have a positive pANCA. Overall, the serologic tests available for IBD (ASCA, anti-ompC, anti-Cbir1, and pANCA) are relatively specific for IBD, generally around 90%, although the specificity is somewhat lower in terms of correctly differentiating CD from UC.

To maximize the sensitivity and specificity of these different serologic tests, the results might be collectively included in a

Abbreviations used in this paper: anti-Cbir1, antibodies to the bacterial flagellin Cbir1; anti-ompC, antibodies to the outer membrane porin C of the bacteria Eschericia coli; ASCA, antibodies to the yeast Saccharomyces cerevisiae; CD, Crohn’s disease; IBD, inflammatory bowel disease; pANCA, perinuclear antineutrophil cytoplasmic autoantibodies; UC, ulcerative colitis.
The most widely used panel in the United States is marketed by Prometheus Laboratories Inc (San Diego, CA). The Prometheus panel, named IBD Serology 7, was made commercially available in July 2006. The panel is composed of the following markers: ASCA IgA, ASCA IgG, anti-OmpC IgA, anti-CBir1, and IBD-specific pANCA. There are 3 separate components to the pANCA testing: (1) autoantibody detection by enzyme-linked immunosorbent assay; (2) perinuclear pattern detection by immunofluorescence assay; and (3) DNase sensitivity. The results for each of the individual tests are then analyzed in relationship to one another by using Prometheus’ proprietary Smart Diagnostic Algorithm. With a computer software program based on pattern recognition, the 7 different components of the IBD Serology 7 panel are analyzed and correlated with the pattern of serologies for patients in the database with UC or CD. If the results for an individual patient match a pattern known to the database to be associated with IBD, the computer predicts that the patient also has IBD. Interestingly, the Smart Diagnostic Algorithm can predict an IBD diagnosis even when all 7 of the parameters of the IBD Serology 7 panel would be considered normal on the basis of the reference ranges provided. As reported by Prometheus Laboratories Inc, the IBD Serology 7 panel has a sensitivity of 93% and a specificity of 95% for IBD. The predictive value of a positive test, according to Prometheus, is 96% in a population in which 59% of patients have the disease. Predictive value, however, depends on the prevalence of disease in the target population. When the prevalence (ie, prior probability) is low, the predictive value of a positive test will also be low. When the disease prevalence is very low, most of the positive tests are false positives.

The clinical scenario presented in this case involves a woman referred for further evaluation of positive serologic markers without any abnormal findings to support the diagnosis of IBD on traditional laboratory or imaging studies. In the setting of a normal endoscopic evaluation and with normal conventional blood work, the probability that a patient without typical symptoms or signs of IBD actually has CD or UC is quite low, and further testing is unlikely to be helpful. A wait and see approach would be reasonable with respect to IBD, and alternate causes of her chronic pain should be sought and treated.

When a patient has more typical symptoms of IBD (bloody stools, diarrhea, weight loss, anemia, elevated inflammation markers), a positive serologic test increases the probability that the patient has IBD, but the clinical suspicion is already high. As such, the utility of the serologic markers is low because they are unlikely to change the approach to imaging studies or the need for biopsy. Endoscopic and radiographic investigation is required to stage the extent and severity of disease, which will be important to direct therapy. The literature suggests that serologic responses in IBD (and possibly antibody titers) do not change substantially with disease activity. Thus, although serologic tests can support the diagnosis of IBD, they do not help the clinician guide therapy and determine treatment response.

Areas of Uncertainty

Data evaluating the role of serologic testing for IBD were obtained in individuals with a known diagnosis of either CD or UC. The controls in many of these studies were normal, healthy individuals. There are no prospectively validated data in which individuals (without a diagnosis of IBD) presenting with symptoms prompting serologic testing are then followed until either a diagnosis of IBD is made, or a satisfactory evaluation has concluded that IBD is not present. Another area of uncertainty about IBD serologic testing is the use of pattern recognition (of the serologic assays) as a method of predicting IBD. The data validating the use of the Smart Diagnostic Algorithm in predicting IBD are not published in a peer-reviewed journal. In addition, characteristics of the validation cohort, such as age, gender, and race, are not known. There is little evidence in the literature that addresses whether any of these patient characteristics could affect serologic markers. Furthermore, it is not clear that antibody patterns are the same for an individual at the time of diagnosis of IBD as it would be after several years of disease activity.

The greatest area of uncertainty is the precise role for serologic testing in the diagnosis of IBD patients. Although there are no prospectively validated data on the accuracy of IBD serologic testing in patients with suspected IBD, the presence of positive serologic markers likely does increase the probability that the person has IBD compared with the general population. However, when the physician has a reasonable index of suspicion that IBD might be present, more definitive endoscopic and imaging studies will be required to confirm or refute the diagnosis of IBD and to plan therapy, regardless of the results of serologies. If the physician has a low index of suspicion of IBD, then a positive serologic test is likely to lead to unnecessary evaluation, and a negative test simply adds additional expense for the patient without measurable benefit. Perhaps one role of serologic testing would be for patients with indeterminate colitis about to have surgery. Serologic results that supported a diagnosis of UC might increase enthusiasm for an ileal pouch procedure. Clearly, further research is necessary to develop the evidence base necessary for rational use of serologic testing.

Published Guidelines

There are no current guidelines that specifically address how gastroenterologists should use the results of serologic testing for IBD in the evaluation and management of patients. In 2004, the American College of Gastroenterology published its “Ulcerative Colitis Practice Guidelines in Adults” and concluded that: “while pANCA and ASCA assays at this stage of knowledge are neither a first step nor a definitive step in differential diagnosis or clinical-decision making, they may be useful in the patient in whom all other clinical features do not allow a distinction between UC and Crohn’s colitis.” The 2001 American College of Gastroenterology Practice Guidelines for the Management of Crohn’s Disease in Adults stated: “Serological studies such as antibodies against Saccharomyces cerevisiae are evolving to support the diagnosis of Crohn’s disease but may not be sufficiently sensitive or specific to be practical as screening tools.” Similarly, in the most recent European evidence-based consensus on the diagnosis of Crohn’s disease, the use of ASCA and pANCA is not recommended as a screening tool because predictive value was thought to be too low for routine clinical use.

In the absence of guidelines with specific recommendations about the use of serologic testing for IBD, the clinician must follow the same algorithm that existed before the advent of serologic testing. The clinician must perform a thorough history and physical examination. If indicated, routine blood work (including complete blood counts, liver function tests, erythro-
cyte sedimentation rate, and C-reactive protein) should also be obtained. If the suspicion for IBD is quite low after this evaluation, further investigation is likely to be of little value. If suspicion for IBD remains, endoscopic studies are necessary to establish the diagnosis and to plan therapy.

**Recommendations**

Practicing gastroenterologists are likely to be faced with increasing consultations for positive serologic testing for IBD. Although the test characteristics in regards to sensitivity and specificity are reasonably good for the most comprehensive serologic panel for IBD, the serologic tests should not be considered a diagnostic tool, and treatment for IBD should not be initiated solely on the results of serologic testing. For the case presented here, the positive serologic test result should be considered a false-positive result because the likelihood of IBD is very low on the basis of the clinical presentation and the negative endoscopic and radiologic studies. Because of the chronic nature of CD and UC and the potential toxicities of the treatments, serologic testing provides inadequate accuracy for the clinician to proceed with treatment on the basis of the results. Treatment needs to be individualized on the basis of the location, extent, and severity of disease as judged by endoscopic or radiologic examinations.

Serologic testing might have value in cases of indeterminate colitis, particularly before colectomy when the type of surgery might depend on whether the patient has CD or UC, but further prospective studies are needed to clarify the value of serology in this important clinical situation. There is a lack of prospectively validated data to justify the use of IBD serologic testing as an initial test in patients presenting with gastrointestinal symptoms, and current society guidelines do not support the use of serologic testing as a diagnostic test for IBD. Gastroenterologists will have to use their best judgment regarding further diagnostic testing when evaluating a patient with positive serologic markers, especially those without classic signs or symptoms of IBD. To proceed with an endoscopic and radiographic evaluation on every patient with positive serologic markers but no classic symptoms or signs of IBD is likely to lead to unnecessary (and invasive) testing, the very outcomes the serologies are designed to prevent.

**Suggested Reading**