

ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Diseases

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Serologic Markers in the Diagnosis and Management of IBD

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G&H What are the serologic markers that are currently in use in the diagnosis of Crohn's disease and ulcerative colitis?

SV There is a wide variety of antimicrobial peptides and antibodies that have been associated with inflammatory bowel disease (IBD) in the last several years (Table 1). The most thoroughly studied of these are antibodies against *Saccharomyces cerevisiae* (ASCA). In addition, a number of antibodies directed against other bacterial sequences or against yeasts or sugars that are components of the yeasts have been described. These include perinuclear antineutrophil cytoplasmic antibody (pANCA), outer membrane porin protein C (OmpC) to *Escherichia coli*, CBir1 (a bacterial flagellin), and anti-I2 (against *Pseudomonas fluorescens*). More recent research has revealed a set of antimannan antibodies, including antilaminaribioside carbohydrate antibodies (ALCA) and antichitobioside carbohydrate antibodies (ACCA).

In terms of diagnosis, none of the individual markers are sensitive enough for use alone. The greatest sensitivity is attributed to ASCA, at approximately 60%. The other markers are much less prevalent. It has been suggested that if a panel of these markers is used together, sensitivities of up to 80% can be achieved that may enter the range of diagnostic utility. However, the more markers that are added, the greater the loss of specificity. Further, tests for these markers are not always available in every laboratory, and some of these markers may not be stable over time. Finally, these tests, even when available, are expensive.

Table 1. Serologic Markers in IBD

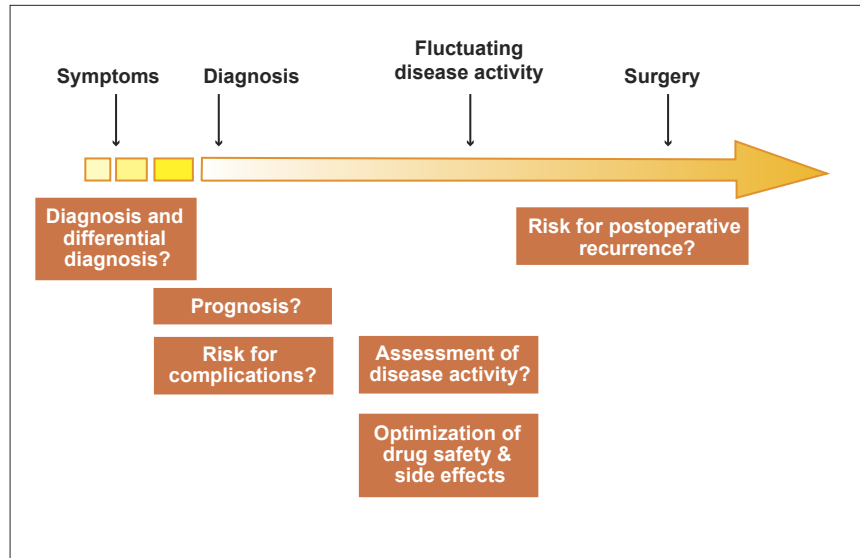
Antibody	Directed against	CD	UC
ASCA	Mannose of <i>Saccharomyces cerevisiae</i>	+ (40–60%)	-
pANCA	Neutrophils	+ (UC-like CD)	+ (40–60%)
PAB	Pancreas	+ (15–30%)	+
OmpC	Outer membrane porin	+ (20–40%)	+
I2	<i>Pseudomonas fluorescens</i>	+ (20–40%)	-
CBir1	Flagellin	+ (20–50%)	-
ACCA	Glycan (chitobioside)	+ (20–40%)	-
ALCA	Glycan (laminaribioside)	+ (20–40%)	-

All of these factors impede the practical use of serologic markers in diagnosis.

G&H Can other useful information be garnered from serologic marker testing after a diagnosis has been established?

SV As experience with these markers accumulates, we have learned from confirmed data and prospective studies that not only the number of antibodies but also the level of antibody response measured can be positively associated with the risk of a more complicated disease course, manifesting as stricture, development of fistulas, or the eventual need for surgical resection. Recent data have also demonstrated the possibility that these markers are a reflection of the genetic background of a patient. There is an association between mutations in the *NOD2* gene, for instance, and the presence of these markers. It is possible that a defect in the innate immune system can be traced to these genetic mutations and that these translate into a more aggressive adaptive immunity with more antibodies formed. The potential for the use of markers to provide

Figure 1. Proposed algorithm for the use of markers in the diagnosis and management of inflammatory bowel disease.



additional information in the diagnosis and management of IBD is outlined in Figure 1.

G&H How can general markers of inflammation provide further knowledge about the course of IBD?

SV In terms of general inflammatory markers, C-reactive protein (CRP) is the most useful. Over the years, studies have shown the strongest correlation between disease activity and CRP. The advantages of CRP include ease of measurement, wide availability, and a very short half-life, which means that levels increase very rapidly in the presence of inflammation and then drop immediately when the inflammation is controlled. All of this makes CRP a useful marker for follow-up during therapy to gauge efficacy. However, it is not a specific marker for Crohn’s disease. It is a marker of general inflammation.

Further, it should be noted that whereas CRP is an excellent marker for Crohn’s disease, it does not have the same utility in ulcerative colitis. The reason for this is not entirely clear. We know that production of CRP by the liver is triggered by inflammation and the resultant production of markers, including tumor necrosis factor and interleukin (IL)-6.

Although Crohn’s disease and ulcerative colitis both cause inflammation and the production of IL-6, the message to produce CRP is delivered in cases of Crohn’s disease but not in ulcerative colitis. This may be related to the fact that Crohn’s is a transmural disease, whereas ulcerative colitis is a mucosal disease, although the precise explanation for this difference between these diseases is unknown.

Other inflammatory markers, including sedimentation rate, platelet count, and many other acute phase proteins have been studied, but none have been as consistently related to either form of IBD.

G&H Is there a role for stool markers in the evaluation of IBD?

SV The main stool markers for inflammation are fecal calprotectin and fecal lactoferrin. Other fecal markers, like faecal elastase, or novel markers in the S100 family of proteins, like fecal S100A12, are under study. Again, these markers are not specific to IBD, but they are limited to the bowel, as opposed to CRP, which can be triggered by an infection or inflammation anywhere in the body. The consequence of this nonspecificity for IBD is that patients with bowel infection, polyp, or colon cancer will find presence of stool markers. There is a need for further study with stool markers, and testing for these markers should be made more widely available, as well as internationally, because these tests are easy to perform and are noninvasive.

G&H Are any panels of markers currently under development with the promise of providing greater utility?

SV In my opinion, no single panel has shown itself to be superior to any other. For the serologic markers, sensitivity, regardless of the panel used, has been approximately 80%. Researchers have also examined panels of inflammatory markers but have only found that CRP is, in most of the studies, the most useful. In the future, more markers will

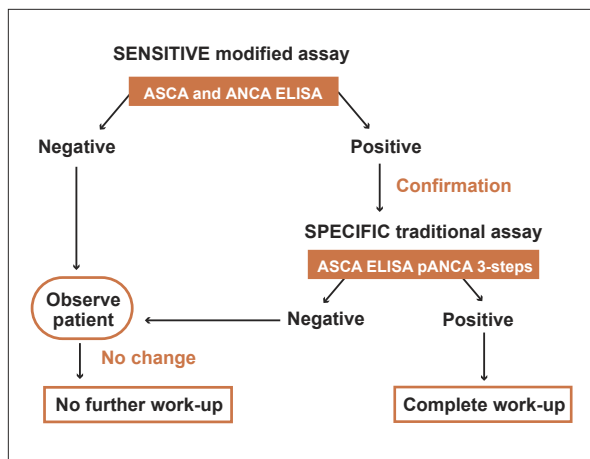


Figure 2. Serologic markers may prioritize diagnostic work-up in pediatric patients.

ANCA=antineutrophil cytoplasmic antibody; ASCA=antibodies against *Saccharomyces cerevisiae*; ELISA=enzyme-linked immunosorbent assay.

Adapted from Dubinsky M, et al. *Am J Gastroenterol.* 2001;96:758-765.

undoubtedly be discovered. However, I doubt they will improve overall clinical utility in terms of diagnosis. As discussed above, an increase of sensitivity with additional markers will inevitably lead to a loss of specificity, thus limiting use in clinical practice.

G&H How can the information garnered from marker testing be used to individualize therapy?

SV Hypothetically, the presence of serologic markers associated with a complicated disease course could lead a clinician to adopt a more aggressive therapeutic strategy. Of course, we have no definitive data showing that aggressive, or so-called “top down,” therapy can alter the course of disease. The only currently proven association is that between these markers and more severe course.

In the case of pediatric patients with suspected IBD, stool markers and serologic markers might play a more prominent role, as the use of colonoscopy should be minimized in these patients (Figure 2). Any endoscopic procedure performed on a child must be justified with a high level of evidence and pediatric gastroenterologists have been advocating the use of serum and fecal markers

to help prioritize these patients for definitive diagnostic procedures. As the worldwide prevalence of pediatric IBD rises, this becomes more critical.

G&H Are there any other specific populations where these markers might be of greater use?

SV Patients with indeterminate colitis (IBD-type unclassified) may benefit from this type of diagnostic information. These patients have confirmed IBD, but there is conflicting presentation in terms of determining Crohn’s disease versus ulcerative colitis. Most of the newer therapies seem to treat both disease states, but it is nonetheless important to confirm a specific phenotype because, if surgery becomes necessary, it may differ between Crohn’s disease patients and ulcerative colitis patients. Therefore, after endoscopy, if the clinician cannot differentiate and the pathologist cannot differentiate, these markers could be of potential use. However, in this subgroup, which makes up 10% of the overall IBD population, almost all markers come back negative upon testing. Nonetheless, if patients with colitis type unclassified do respond to marker testing, with a pANCA measure that is positive and ASCA that is negative, it would constitute a major positive predictor of ulcerative colitis. In cases of positive ASCA and negative pANCA, Crohn’s disease is highly probable.

In general, stool and serum markers can add information, but they cannot replace clinical judgement. Although there is a close correlation between levels of CRP and endoscopic findings, it is far from an exact correspondence. There is also good correlation between fecal calprotectin levels and endoscopy, perhaps better than with CRP, but these markers again cannot replace physician monitoring and examination.

Suggested Reading

- Riis L, Vind I, Vermeire S, et al. The prevalence of genetic and serologic markers in an unselected European population-based cohort of IBD patients. *Inflamm Bowel Dis.* 2007;13:24-32.
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- Dubinsky MC, Ofman JJ, Urman M, et al. Clinical utility of serodiagnostic testing in suspected pediatric inflammatory bowel disease. *Am J Gastroenterol.* 2001;96:758-765.
- Sandborn WJ, Loftus EV Jr, Colombel JF, et al. Evaluation of serologic disease markers in a population-based cohort of patients with ulcerative colitis and Crohn’s disease. *Inflamm Bowel Dis.* 2001;7:192-201.