

Utility of IBD Serology Tests: Experience of an Academic Center

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Abstract

BACKGROUND: The diagnosis of inflammatory bowel disease (IBD) is based on clinical, radiographic, endoscopic and histological criteria. Recently, serology tests involving antibodies against microbial and auto-antigens have been increasingly used for the diagnosis and management of IBD. However, the clinical value of these tests is still being evaluated and debated. Therefore, we conducted a retrospective study in our academic center to evaluate the sensitivity and specificity of the IBD serological tests. **METHODS:** A retrospective study was done at the University of Missouri – Columbia from March 20, 1998 to February 22, 2008 involving all patients who underwent serology testing consisting of Prometheus IBD First Step Confirmatory System or IBD Serology 7. Patients were identified by a search conducted through Prometheus Laboratories and an extensive chart review was performed. Results of serology studies and final diagnoses (based upon all clinical criteria) were identified and recorded for each patient. Statistical analysis was performed in which the sensitivity and the specificity were calculated. **RESULTS:** The search identified 173 patients between the ages of 18 to 82 years, 100 females and 73 males. The sensitivity and specificity of the IBD First Step Confirmatory System was 54.8% and 86.5%, respectively. The sensitivity and specificity of the IBD serology 7 was 80% and 61.5%, respectively. **CONCLUSIONS:** The sensitivity and specificity of the IBD serology tests performed in our tertiary-care center was much lower than previously reported. Further studies into these factors may be helpful to further elucidate the role of IBD serology testing.

INTRODUCTION

Inflammatory bowel disease (IBD) is diagnosed based on several criteria including clinical, radiographic, endoscopic and histological evidence. Although the gold standard of diagnosis is histology, this is an invasive test. Serological markers are being used more and more in clinical practice to detect diseases and determine disease prognosis. They are especially beneficial due to their convenience and relative non-invasiveness. IBD is one of these diseases where panels of antibodies are being increasingly studied and used in clinical practice.¹⁻⁴

Serological markers being used in serological testing for IBD includes antibodies against microbial and self-antigens. Although new serological markers are constantly being discovered and investigated, there already are established and researched markers that are currently being used in clinical practice. These include the well known markers found predominantly in Crohn's disease (CD) and in ulcerative colitis (UC): ASCA IgG and IgA, Anti-OmpC IgA, Anti-CBir1 and the marker pANCA respectively.^{1,3,5}

In recent practice, these serological markers have been used in a variety of clinical circumstances. They are being used to help diagnose IBD; decide those patients who would benefit from a further diagnostic albeit invasive test such as colonoscopy; differentiate between UC and CD, especially for those patients with indeterminate colitis who need to undergo surgery; and to delineate prognosis of disease, surgical outcome, and treatment response.

The IBD First Step Confirmatory System is a panel that was the first panel offered in the 1990s and consisted of a two-part process where markers were detected or not detected and if they were detected, the markers would then be confirmed.^{6,7} The IBD Serology 7 was subsequently formulated which includes the First Step panel in addition to a new antibody, the Anti-CBir1, which is used to help differentiate pANCA-positive UC from UC-like CD, CD not detected by other markers, and those patients with CD with a more complicated disease course.^{1,3,6}

Although serological testing seems an enticing investigational modality in the scenarios described above,

there are limitations of this testing, such as knowing when these tests are best utilized to yield information with the highest sensitivity and specificity, resulting in the greatest clinical impact. Accordingly, in our own institutional experience, there seemed to be a discrepancy between the false positives of the IBD serology tests as reported in previous data and what seemed to be occurring in our institution. Therefore, we undertook a retrospective analysis with an aim to objectively evaluate the utility of IBD serology tests in our patient population.

MATERIALS AND METHODS

Study Design: IBD serology tests were retrospectively analyzed at the University of Missouri – Columbia using the institution’s own patient population specifically evaluating the test’s sensitivity and specificity. IRB approval was sought and approved prior to the start of study.

Patient/Chart selection: As Prometheus IBD serology tests were the only IBD serology tests ordered at our institution, Prometheus Laboratories was contacted for a list of all University of Missouri – Columbia patients that had undergone the IBD First Step Confirmatory System or IBD Serology 7 testing from March 20, 1998 to February 22, 2008. A list was then generated from Prometheus laboratories. The patients on this list comprised our initial patient population. These patients’ charts were then reviewed to determine if they met inclusion/exclusion criteria. Patients that were included in the study were those that were 18 years or older at the time the IBD serology test was performed, patients of the University of Missouri – Columbia Hospitals and Clinics, patients in whom there is a high suspicion of IBD who had also undergone serological testing with either the IBD First Step or Serology 7 to aid in diagnosis, and patients who underwent confirmatory testing with endoscopy. Table 1

Figure 1

Table 1: Inclusion and Exclusion Criteria

INCLUSION CRITERIA	EXCLUSION CRITERIA
Adults	Pediatric population
Patients at UMHC	Patients at other institutions
Clinical suspicion of IBD	IBD serology that is not performed at Prometheus
Prometheus Serology testing only	Confirmatory testing NOT performed
Confirmatory testing performed	

Patients that were excluded from the study were those who were 17 years or younger at the time of the serology test, those who had any IBD-specific serology performed that was not the IBD First Step or the IBD Serology 7, anyone who had the serology ordered but not resulted, and any patient who has not undergone confirmatory testing with

endoscopy. Table 1

Chart Review: For every patient who met inclusion criteria, an extensive chart review was performed. Results of the serology studies and final diagnoses were identified and recorded for each patient. Of note, final diagnoses of IBD was determined predominantly by endoscopy with biopsies but was supported by clinical and radiological investigations. Several other factors were also evaluated and recorded during the retrospective chart analysis including: Age, gender, ethnicity, clinical symptoms and signs at time of presentation leading up to the IBD serology test being performed, other investigational modalities used for achieving diagnosis, the medical or surgical specialty of the ordering physician and the reason for ordering the serology test.

Statistical Analysis: After the chart review was completed, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were all calculated.

RESULTS

PROMETHEUS IBD FIRST STEP CONFIRMATORY SYSTEM

Study Population: Of the 139 patients who underwent the Prometheus IBD First Step serology test during our study period, 94 met inclusion criteria. Forty-five patients were excluded because they were pediatric patients, those who had not undergone colonoscopy, and those who in whom a complete chart review was not able to be performed.

Patient Demographics: The mean age was 37.4 ± 14.2 years with an age range of 18-75 years. The study population consisted of 59 females and 35 males with 75 Caucasians, 6 African-Americans, 3 Hispanics, 1 Indian, and 2 Asians. Ethnicity was not documented in 7 patients. GI symptoms at the time of the serology testing were highly variable. Ordering physicians included gastroenterologists (67 cases), medicine internists (8 cases), general surgeons (3 cases), family medicine (1 case), and unknown (15 cases). Table 2

Figure 2

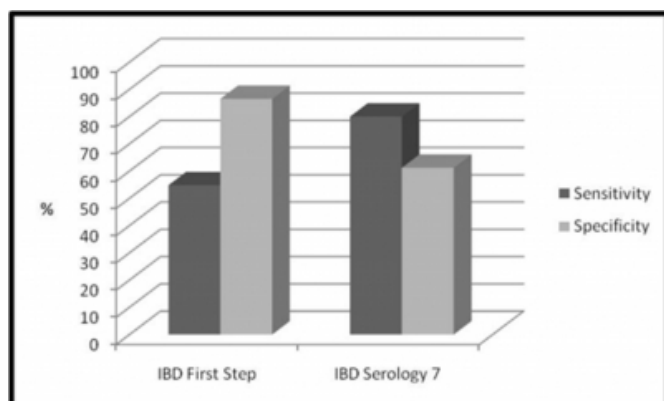
Table 2: Patient demographics

Characteristics/Serology test	IBD First Step	IBD Serology 7
Total #	139	115
Those that met inclusion criteria	94	79
Age range	18-75	19-82
Sex		
Female	59	41
Male	35	38
Ethnicity		
Caucasian	75	40
Black	6	2
Hispanic	3	0
Indian	1	0
Asian	2	0
Other	0	0
Unknown	7	37
Ordering Physician		
Gastroenterologist	67	61
Internist	8	6
General Surgeon	3	0
Family medicine	1	2
Unknown	15	10

Data Analysis: Within this population, 23 patients experienced a positive test and were confirmed to have IBD (true positives) while 45 patients experienced a negative test that did not have IBD (true negatives). However, 7 patients experienced a positive test and did not have IBD (false positives) and 19 experienced a negative test and found to have IBD on further testing (false negatives). Based upon these findings, the calculated sensitivity was 54.8% and specificity 86.5%. Figure 1

Figure 3

Figure 1: Sensitivity and Specificity of the IBD First Step and IBD Serology 7



The positive predictive value was 76.7% and negative predictive value was 70.3%. The prevalence of IBD in this patient population was 45%. Of note, of the 23 true positives, the serologies of 4 patients were not accurate as to whether a patient had UC or CD. There were 3 patients in whom this could not be differentiated and one patient who endoscopically and clinically had UC but the serology

testing diagnosed Crohn's disease.

PROMETHEUS IBD SEROLOGY 7

Study Population: Of the 115 patients who underwent Prometheus IBD Serology 7 serology testing during our study period, only 79 met inclusion criteria with 36 being excluded because they either did not have a colonoscopy (25), had unclear diagnoses (7), were out of the IRB approved data collection range (2), or were less than 17 years of age (2).

Patient Demographics: The mean age was 40.6 ± 16.8 years with an age range of 19-82 years. The study population consisted of 41 females and 38 males with 40 Caucasians and 2 African-Americans. Ethnicity was not documented in 37 patients. GI symptoms at the time of the serology testing were highly variable. Ordering physicians included gastroenterologists (61 cases), medicine internists (6 cases), family medicine (2 cases), and unknown (10 cases). Table 2

Data Analysis: Within this population, 32 patients experienced a positive test and were confirmed to have IBD (true positives) while 24 patients experienced a negative test that did not have IBD (true negatives). However, 15 patients experienced a positive test and did not have IBD (false positives) and 8 experienced a negative test and found to have IBD on further testing (false negatives). Based upon these findings, the calculated sensitivity was 80% and specificity 61.5%. Figure 1 The positive predictive value was 68.1% and negative predictive value was 75%. The prevalence of IBD in this patient population was 50.6%. Of note, of the 32 true positives, 6 patients' serology was not accurate as to whether a patient had UC or Crohn's disease. There was one patient whose diagnosis remained unclear, 3 patients who endoscopically and clinically had UC but the serology testing diagnosed Crohn's disease, and 2 who endoscopically and clinically had CD but serological testing diagnosed UC.

DISCUSSION

The diagnosis of IBD is made by the overall assessment of clinical presentation and radiological, endoscopic and, more recently, serological investigations. As a general rule, the less invasive a test is, the more appealing it is for clinical use. However, the test also needs to be sensitive, specific, and impact a patient's diagnosis or disease course for it to be clinically applicable. We undertook a retrospective evaluation of our IBD serology tests further evaluating the way they have been used in our institution and the results as

they correlate with each patient's clinical picture.

We found that the IBD First Step Confirmatory System and its successor the IBD Serology 7 both yielded lower sensitivities and specificities than that noted in previous data.^{1,3,5,8} We also found that with the addition of an antibody in this newest serology panel (IBD Serology 7), the increase in the sensitivity of this panel was at the sacrifice of its specificity. Figure 1 This then begs the question of how this antibody panel should be utilized. Given its sensitivity and specificity, this antibody panel should not be used for diagnosis, but would be of most benefit as an adjunct in diagnosing those cases of indeterminate colitis or possibly as a prognostic marker for disease course or for therapeutic response. Even then, there were discrepancies found in our patient population between the diagnosis of CD or UC based on the IBD serology test compared to the diagnosis made based on clinical, radiological, and endoscopic investigations.

Surprisingly, at our institution, the predominant medical personnel ordering the IBD serology tests were gastroenterologists for patients with clinical symptoms and signs suggesting IBD and less so for disease classification or prognostic aid. This further emphasizes the need for clarification in the gastrointestinal community of the utility of these tests.

Of course, our study had several limitations including a limited sample size, subjective interpretation of endoscopic and histopathologic findings (by the endoscopist, pathologist, and gastroenterologist), and the lack of follow-up on several patients who either had undifferentiated IBD or false positives where further disease manifestation was

not able to be followed.

Although the antibody panels do not seem to be a reasonable diagnostic test, serological testing has great potential to become a beneficial aid in IBD. However, the question at this point is which specific antibodies are useful for what portions of a patient's disease course (diagnosis versus prognosis versus surgical outcomes versus therapeutic response) and when exactly is testing indicated. Further studies will need to be performed to further establish the exact role of both more established antibodies and newly diagnosed ones.

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