Inflammatory Bowel Disease

Laboratory Support of Diagnosis and Management

CLINICAL BACKGROUND

Inflammatory bowel disease (IBD), which includes Crohn disease (CD) and ulcerative colitis (UC), is characterized by chronic inflammation at various sites of the digestive tract lining. IBD is diagnosed after ruling out alternative or co-existing conditions, including irritable bowel syndrome (IBS), ischemic colitis, infection, diverticulitis, and colon cancer. Diagnosis is based on history, examination, laboratory results, imaging (X-ray, CT, and/or MRI), and endoscopy and histology.

The inflammation associated with UC affects the mucosa and is thus relatively superficial. It involves continuous regions of the colon, usually beginning with the rectum and extending proximally. UC is generally confined to the colon, although in rare cases involvement may extend to the terminal portion of the ileum, and, even more rarely, into the proximal region of the alimentary tract. In CD, inflammation extends deeper into the tissue and can affect any portion of the digestive tract, often "skipping" regions. Both may present with severe bloody diarrhea, abdominal pain, fever, and malnutrition. Accurate differential diagnosis of UC and CD is critical, as their treatment and prognoses differ. Although they can usually be differentiated on the basis of clinical, radiographic, endoscopic, and histologic findings, they can be difficult to distinguish in about 10% to 15% of people with IBD.[1]

Laboratory tests can be used to help rule out other possible conditions, confirm the presence of inflammation, and help differentiate UC and CD. Additionally, they can be used to help differentiate active from quiescent disease and predict relapse in patients with IBD.

INDIVIDUALS SUITABLE FOR TESTING

- Individuals with unexplained severe bloody diarrhea, abdominal pain, fever, and/or malnutrition

TEST AVAILABILITY

Laboratory tests useful for IBD diagnosis and management include serum- and stool-based assays (**Table 1**).

TEST SELECTION AND INTERPRETATION

Differential Diagnosis

After ruling out other disorders, confirmation of inflammation is often the first step in the IBD differential diagnosis (**Figure**).[2] Four markers are available: C-Reactive Protein (CRP), erythrocyte sedimentation rate (ESR), fecal calprotectin, and quantitative fecal lactoferrin. When inflammation is present, anti-neutrophil cytoplasmic antibody (ANCA) and anti-*Saccharomyces cerevisiae* antibody (ASCA) tests can be used to help differentiate UC and CD.[2,3] If either test is positive, then radiology, endoscopy, and histology can be used to confirm the diagnosis of IBD and the differentiation of UC and CD. If both tests are negative in a patient with a moderate or high clinical suspicion of IBD, then radiology, endoscopy, and histology can be used to determine whether IBD is present and, if so, to differentiate UC and CD.

Inflammatory Markers

C-Reactive Protein

CRP is an acute-phase reactant released from the liver in response to infection, tissue injury, or other inflammatory conditions. Therefore, it is a general, nonspecific marker of inflammation. CRP levels rise early after the onset of inflammation and decrease rapidly after its resolution.[4] An elevated CRP result demonstrates the presence of inflammation and is consistent with active IBD.

An elevated CRP has moderate sensitivity (50%–87%) and specificity (76%–94%) for a diagnosis of IBD in symptomatic people.[5-7] Since the sensitivity is relatively low, a negative result does not rule out inflammation or IBD. The moderate sensitivity of CRP may be due in part to a genetic component; about 15% of normal healthy people don't mount a CRP response.[8]

In a meta-analysis of studies including people with IBD or IBS and healthy controls, a CRP level of 1.7 mg/dL or higher indicated a greater than 52% likelihood of IBD.[9] A CRP level of 2.7 mg/dL or higher indicated a greater than 90% likelihood of IBD and a less than 10% likelihood of IBS.[9]

Erythrocyte Sedimentation Rate

The ESR is another nonspecific marker of inflammation. Moderately elevated results are associated with inflammation, anemia, infection, pregnancy, and aging. Very high levels are associated with inflammation, vasculitis, severe infection, and multiple myeloma or Waldenstrom macroglobulinemia, even in the absence of inflammation. An elevated ESR has moderate sensitivity (58%–64%) and specificity (72%–94%) for a diagnosis of IBD in symptomatic people.[5,7] Thus, an elevated result in a patient with symptoms of IBD supports the diagnosis; however, a normal result does not rule out IBD.

Table 1. Available Tests for the Differential Diagnosis and Management of Inflammatory Bowel Disease

Test Code	Test Name	Specimen Type	Clinical Use
70171	ANCA Screen with Reflex to ANCA Titer Includes titer for C-ANCA, P-ANCA, and/or atypical P-ANCA.	Serum	Diagnose IBD; differentiate UC and CD
16796	Calprotectin, Stool	Stool	Diagnose intestinal inflammation; differentiate IBD from IBS; monitor patients with IBD
4420	C-Reactive Protein (CRP)	Serum	Detect inflammatory disorders, including IBD; monitor patients with IBD
16503(X)	Inflammatory Bowel Disease Differentiation Panel Includes ANCA screen with reflex to P-ANCA, C-ANCA, and atypical P-ANCA titers; myeloperoxidase antibody; proteinase 3 antibody; and *Saccharomyces cerevisiae* IgG and IgA antibodies.	Serum	Diagnose IBD; differentiate UC and CD; differentiate IBD from vasculitides
17321(X)	Lactoferrin, Quantitative, Stool	Stool	Diagnose intestinal inflammation; differentiate IBD from IBS; monitor patients with IBD
8796	Myeloperoxidase Antibody (MPO)	Serum	Differentiate IBD from vasculitides
34151	Proteinase-3 Antibody	Serum	Differentiate IBD from vasculitides
10295	*Saccharomyces cerevisiae* Antibodies (ASCA) (IgA)	Serum	Differentiate UC and CD
17609	*Saccharomyces cerevisiae* Antibodies (ASCA) (IgA, IgG)	Serum	Differentiate UC and CD
10294	*Saccharomyces cerevisiae* Antibodies (ASCA) (IgG)	Serum	Differentiate UC and CD
809	Sed Rate by Modified Westergren	Whole blood	Detect inflammatory disorders, including IBD

ESR alone, unlike CRP, does not differentiate between IBD and IBS.[9] It also does not respond as quickly as CRP to changes in disease activity.[4]

Calprotectin

Calprotectin makes up about half of the cytosolic protein in neutrophils. Inflammation of the bowel results in an influx of neutrophils and release of calprotectin into the lumen. So an elevated level of fecal calprotectin indicates inflammation in the bowel.

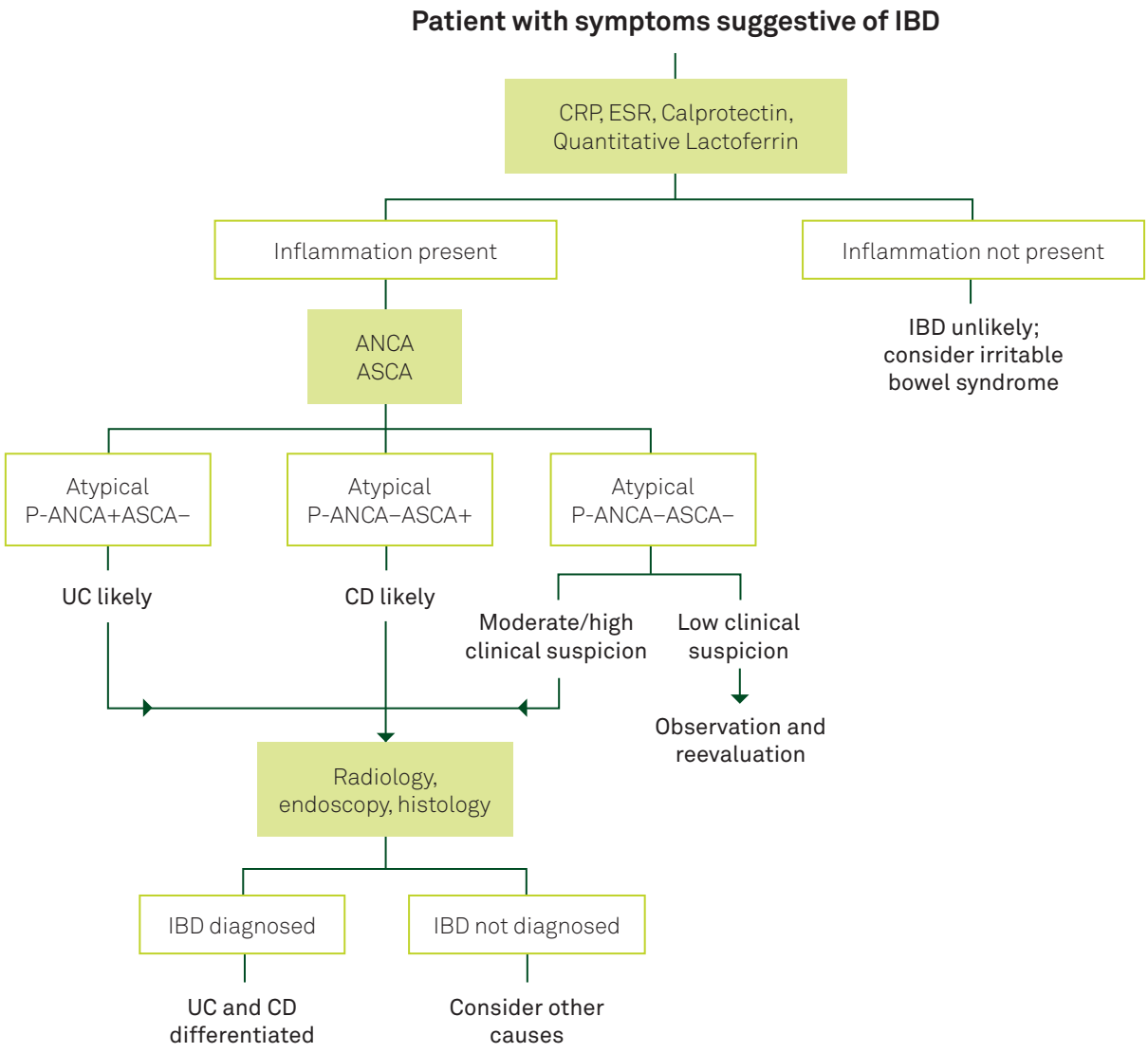
Elevated fecal calprotectin has a sensitivity of 93% (95% CI, 85%-97%) and a specificity of 96% (95% CI, 79%-99%) for differentiating inflammatory from noninflammatory bowel disease in symptomatic adults.[10] Similarly, in symptomatic children and teenagers, the sensitivity is 92% (95% CI, 84%-96%) and the specificity is 76% (95% CI, 62%-86%).[10] Thus, calprotectin may help identify patients who may benefit from more invasive testing. Furthermore, when the pretest probability of IBD is high, the test may be useful for differentiating IBD and IBS.[10,11]

Lactoferrin

Lactoferrin is an iron-binding protein found in neutrophils. Neutrophil levels increase in the intestinal lumen during inflammation, leading to elevated levels of fecal lactoferrin. So an elevated level of fecal lactoferrin indicates inflammation in the bowel.

Quantitative lactoferrin can help diagnose IBD and differentiate between IBD and IBS. Levels are relatively high in people with IBD compared to those in IBS and healthy individuals. The sensitivity for diagnosis of IBD in these populations is 80% (95% CI, 78%-83%) and the specificity is 82% (95% CI, 79%-84%).[12] Sensitivity and specificity are similar among people with UC and CD.[12]

Figure. Differential Diagnosis of Inflammatory Bowel Disease



IBD indicates inflammatory bowel disease; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ANCA, anti-antineutrophil cytoplasmic antibodies; ASCA, anti-*Sacharomyces cerevisiae* antibodies; P-ANCA, perinuclear ANCA; UC, ulcerative colitis; CD, Crohn disease.

This figure was developed by Quest Diagnostics based in part on references 2, 3, and 13. It is provided for informational purposes only and is not intended as medical advice. A physician's test selection and interpretation, diagnosis, and patient management decisions should be based on his/her education, clinical expertise, and assessment of the patient.

Serologic Markers

Two serologic markers, atypical P-ANCA and ASCA, are commonly used to help differentiate CD from UC (**Figure**).[13,14]

Atypical P-ANCA testing begins with an ANCA screen. A positive screen is followed by determination of the titer for the relevant pattern(s), eg, cytoplasmic pattern (C-ANCA), perinuclear pattern (P-ANCA), or atypical P-ANCA pattern. C-ANCA and P-ANCA are observed in vasculitis, whereas atypical P-ANCA is observed in IBD. Atypical P-ANCA is detected in about 55% to 80% of people with UC but only 5% to 25% of people with CD.[14,15]

Table 2. Sensitivity and Specificity of Atypical P-ANCA/ASCA Combinations for Ulcerative Colitis and Crohn Disease in Patients with Inflammatory Bowel Disease[a]

Marker	UC		CD	
	Sensitivity	Specificity	Sensitivity	Specificity
Atypical P-ANCA+/ASCA–	51%	94%	—	—
Atypical P-ANCA–/ASCA+ (IgA or IgG)	—	—	55%	93%

[a] Studies were largely retrospective, comprising patients in whom inflammatory bowel disease (IBD) had been classified as ulcerative colitis (UC) or Crohn disease (CD) on the basis of clinical, radiographic, endoscopic, and histologic findings.[14]

ASCA, on the other hand, is detected in 60% to 70% of people with CD[15] but only about 6% to 15% of people with UC.[15,16]

Atypical P-ANCA and ASCA have the greatest sensitivity and specificity for UC and CD when used in combination. **Table 2**, based on a meta-analysis of 60 studies comprising 7,860 people with IBD, summarizes the sensitivity and specificity of atypical P-ANCA/ASCA combinations for UC and CD.[14] Practice guidelines note that the combination of these markers may be useful in patients with IBD that cannot be differentiated as UC or CD on the basis of traditional criteria (ie, indeterminate colitis; IC).[13]

Atypical P-ANCA and ASCA may also be helpful in stratifying CD: atypical P-ANCA-positive CD has been associated with colonic involvement and a clinical phenotype similar to that of UC (UC-like CD), whereas positivity for ASCA may be associated with non–UC-like CD.[16,17]

These markers may be particularly useful in children. Some reports have noted the potential utility of serologic testing, combined with other clinical and laboratory information, to identify children with suspected IBD who may not require invasive testing.[14,18]

Management

Quiescent vs Active Disease

Table 3 shows the sensitivity and specificity of elevated CRP levels in people with endoscopically verified active IBD. Owing to the high specificity in these people, an elevated CRP result strongly suggests active disease. In CD patients, CRP concentrations correlate with more severe endoscopic disease activity.[19] In UC patients, failure of CRP normalization should prompt consideration of further endoscopic evaluation, regardless of symptoms.[20]

Calprotectin and lactoferrin concentrations correlate with more severe endoscopic disease activity in both CD and UC patients.[19] They are more sensitive than CRP for this purpose and correlate better with colonic than ileal disease activity.[2,3] **Table 3** shows the sensitivity and specificity of elevated calprotectin and lactoferrin levels in people with endoscopically verified active IBD.

Mosli et al suggest that since fecal markers have relatively high sensitivity in patients with active IBD they can be used in some cases to manage symptomatic patients with high confidence that inflammation is present.[8] For instance, an

Table 3. Inflammatory Marker Sensitivity and Specificity for Endoscopically Confirmed Active Inflammatory Bowel Disease[8,a,b]

Test	Sensitivity, % (95% CI)	Specificity, % (95% CI)
CRP	49 (34-64)	92 (72-96)
Calprotectin	88 (84-90)	73 (66-79)
Calprotectin in ulcerative colitis	—	79 (68-87)
Calprotectin in Crohn disease	—	67 (58-75)
Lactoferrin	82 (73-88)	79 (62-89)

CI, confidence internal.

[a] Data derived from meta-analysis.

[b] Sensitivity and specificity depend on the cutoff used. Meta-analysis cutoffs used for calprotectin, lactoferrin, and CRP were 50 µg/g, 7.25 µg/g, and 5 mg/g, respectively.[8]

elevated fecal marker in a patient at high suspicion of active disease might allow an endoscopy to be avoided, whereas a negative result might not rule out active disease and thus result in an endoscopy.[8] On the other hand, a negative fecal marker result in a patient at lower suspicion of active disease might allow an endoscopy to be avoided, whereas an elevated fecal marker might provide enough evidence to proceed with an endoscopy.[8]

But other authors feel that in UC patients, failure of calprotectin normalization should prompt further endoscopic evaluation, regardless of symptoms.[20]

Relapse and Disease Course

An elevated CRP may predict relapse in some patients with CD.[3] Several studies have shown elevated CRP levels predict relapse among CD patients who had an elevated CRP at diagnosis[20] and among CD patients in medically induced remission.[3]

Fecal markers also play a role in predicting relapse. Gisbert et al showed that calprotectin levels were higher in patients who suffered a relapse than in those who remained in remission during a 12-month follow-up.[21] In this study, a cutoff of 167 µg/g had the best sensitivity (69%) and specificity (75%) for predicting relapse.[21] Calprotectin levels may be especially useful for predicting disease relapse shortly after remission.[3,21] They may also be particularly useful for predicting disease relapse in CD patients after surgical resection.[2]

An elevated lactoferrin level has a sensitivity of 62% and a specificity of 65% for predicting IBD relapse.[12,21] Elevated lactoferrin levels may be particularly useful to help predict early disease relapse in pediatric patients.[12]

Atypical P-ANCA and ASCA levels may predict complicated disease courses in children with CD.[2,3]

Response to Therapy

Normalization of CRP levels is associated with response to therapy in CD patients.[20] Roles for quantitative calprotectin, quantitative lactoferrin, atypical P-ANCA, and ASCA in predicting response to therapy are unknown at this time.

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