

ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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Diagnosis and Treatment of Indeterminate Colitis

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G&H How is the term indeterminate colitis defined?

WJT The term indeterminate colitis is actually somewhat controversial. This term was originally used by pathologists to describe colectomy specimens in which no specific features for either Crohn's disease (CD) or ulcerative colitis (UC) were seen. Over the years, however, the term has been adopted by clinicians to describe patients in whom a diagnosis of UC or CD cannot be made based on standard clinical testing, including colonoscopy, imaging, laboratory tests, and biopsy. A different term, inflammatory bowel disease—unclassified, has also been proposed to describe these patients. However, the new ICD-10 index code that will soon be implemented will only include the term indeterminate colitis, so this term will likely continue to be used by clinicians.

G&H How many patients with inflammatory bowel disease are classified as having indeterminate colitis?

WJT Among patients with inflammatory bowel disease involving the colon, the frequency of indeterminate colitis is approximately 10%. This figure has not changed over the past 30 years, despite the introduction of newer diagnostic modalities.

G&H Is indeterminate colitis a distinct clinical entity, or do these patients simply have an unusual presentation that prevents them from being diagnosed with either CD or UC?

WJT There are certainly patients who later declare themselves as having either CD or UC, but there is also a group of patients who have durable indeterminate colitis. Patients in this latter group seem to persist in this in-between state, suggesting that indeterminate colitis may be a third disease entity. However, we do not have a way to determine whether indeterminate colitis is truly a unique disease.

G&H What is the significance of indeterminate colitis?

WJT Clarifying whether or not patients have indeterminate colitis is most important in patients who have failed medical therapy and are facing colectomy. The gold standard operation for treatment of UC is total proctocolectomy with ileal pouch–anal anastomosis (IPAA). Traditionally, this operation has been reserved for patients with UC because patients with CD have a higher risk of complications following the procedure. Specifically, CD patients who undergo colectomy with IPAA can develop CD in the pouch, which can necessitate pouch removal in some cases.

In retrospective case series, patients with indeterminate colitis do not do quite as well as patients with UC following surgery, but they fare better than patients with CD. Understanding the risk of postoperative complications is important for patients with indeterminate colitis who are contemplating surgery; they need to know that their risk of complications may be greater because they have indeterminate colitis instead of UC but that their risk of complications is lower than if they had CD.

G&H What research has been done to try to define or characterize indeterminate colitis? Are any future studies planned?

WJT Some of the best research in this area comes from natural history studies in which groups of patients with indeterminate colitis were followed over time to see how many patients manifest as having CD or UC and how many patients continue to have indeterminate colitis. The best such study is a multinational study from Europe, the results of which were first published in 1996. This is an ongoing study involving patients from France, Belgium, and Austria.

In addition, genetic studies have yielded tremendous advances in our understanding of genes associated with inflammatory bowel disease over the past 10 years, and that research eventually may help us to better understand indeterminate colitis. However, studying this group of patients is difficult since we do not know whether or not indeterminate colitis is a unique disease, and if so, how it should be defined. A definitive test that can positively diagnose indeterminate colitis is needed, rather than it being a negative diagnosis given to patients who do not fit the diagnostic criteria for either CD or UC.

G&H What diagnostic tools are available to evaluate patients with indeterminate colitis?

WJT In addition to the standard diagnostic tools—colonoscopy, biopsy, and radiographic assessment—the most reliable technique for evaluating patients with indeterminate colitis is serology. The serologic markers that have proven most useful for diagnosing indeterminate colitis are anti-*Saccharomyces cerevisiae* antibody (ASCA) and perinuclear antineutrophil cytoplasmic antibody (pANCA), also known as nuclear-specific antigen. Most patients with indeterminate colitis are negative for both of these markers.

While this finding is helpful, it is not diagnostic for indeterminate colitis because normal individuals are also usually negative for these markers. Instead, testing for these markers can help clinicians predict whether

patients will maintain a long-term diagnosis of indeterminate colitis. Typically, patients who lack these markers continue to have indeterminate colitis, whereas patients who have one or both of these markers will likely manifest with CD or UC over time.

G&H Are researchers looking for new biomarkers that could better identify patients with indeterminate colitis?

WJT Several different groups around the world have reported newer biomarkers. However, none of these biomarkers have shown convincing benefit over pANCA and ASCA. Nonetheless, efforts to assess newer biomarkers are continuing, both in Europe and the United States.

G&H Can biomarker testing help clinicians predict whether a patient with indeterminate colitis will progress to CD or UC, or do clinicians have to wait for the clinical presentation to change?

WJT Clinicians have to wait for the clinical picture to become clearer. Biomarkers are helpful, but they are not specific. For instance, 80% of patients with CD are positive for ASCA, so a positive ASCA test result is helpful in distinguishing between CD and UC. However, 20% of patients with CD do not have a positive ASCA test result; in these patients, distinguishing between CD and indeterminate colitis may be difficult.

G&H How could the diagnosis of indeterminate colitis be improved?

WJT Currently, indeterminate colitis is a diagnosis of exclusion, so a positive diagnostic test is needed. Perhaps a serologic test will fill this need, or maybe a genetic test will be developed if a specific gene pattern is found to be predictive of indeterminate colitis. Diagnostic testing for indeterminate colitis could also involve immunologic staining of biopsy samples, if an immune marker were identified for indeterminate colitis. I do not know what will ultimately be the best approach—it could be serologic, immunologic, or genetic testing—but some type of positive diagnostic test is needed.

G&H How are patients with indeterminate colitis typically managed?

WJT Patients with indeterminate colitis are often managed the same as patients who have UC; clinicians usually use the same drug regimen and surgical approach for both groups. A caveat to that statement is that some patients with indeterminate colitis have

backwash ileitis, and patients with CD can also have inflammation of the ileum, so telling those 2 groups apart is not always easy.

G&H How do patients with indeterminate colitis typically fare in terms of long-term outcomes?

WJT Patients with indeterminate colitis have more complications following colectomy than patients with UC, but they do better than patients with CD. Currently, longitudinal studies show that about half of patients with indeterminate colitis will eventually develop CD of the colon or UC, and the other half will continue to have indeterminate colitis.

G&H Would clinicians be able to treat these patients better if they could determine whether a patient was ultimately going to progress to UC or CD?

WJT We do not know the answer to that question right now. Currently, we cannot do prospective trials on patients with indeterminate colitis because we cannot really define this entity. Researchers have not been able to do a prospective treatment trial with new medications in patients with indeterminate colitis because the number of patients at any given medical center will be small and there is no definite diagnostic test to ensure that all patients in the study have indeterminate colitis. Currently, the standard

definition for indeterminate colitis is colitis that cannot be distinguished from UC or CD based on clinically available diagnostic tests; however, researchers cannot use a negative definition to do a valid prospective study. Given this limitation, we do not know whether some of our current therapies might be superior in patients with indeterminate colitis.

G&H What further research is needed in this area?

WJT I think the critical need is for a definitive diagnostic test. In order to move forward with this group of patients, we need to be able to precisely characterize indeterminate colitis; then, we can gather a homogeneous cohort of subjects in whom we can assess further diagnostic and therapeutic interventions.

Suggested Reading

Tremaine WJ. Review article: indeterminate colitis—definition, diagnosis and management. *Aliment Pharmacol Ther.* 2007;25:13-17.

Geboes K, Colombel JF, Greenstein A, et al; Pathology Task Force of the International Organization of Inflammatory Bowel Diseases. Indeterminate colitis: a review of the concept—what's in a name? *Inflamm Bowel Dis.* 2008;14:850-857.

Prideaux L, De Cruz P, Ng SC, Kamm MA. Serological antibodies in inflammatory bowel disease: a systematic review. *Inflamm Bowel Dis.* 2011 Nov 8. Epub ahead of print.

Mutar Mahdi B. Auto-antibodies in patients with inflammatory bowel disease unclassified. *Iran J Immunol.* 2011;8:189-194.

Zhou N, Chen WX, Chen SH, Xu CF, Li YM. Inflammatory bowel disease unclassified. *J Zhejiang Univ Sci B.* 2011;12:280-286.