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The Evolving Role of Serologic Markers in the Management of Pediatric IBD

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Abstract

Serologic markers are assuming a prominent role in managing many aspects of pediatric inflammatory bowel disease (IBD). Whereas approximately 10% of adult patients are diagnosed with indeterminate colitis (IC), up to 30% of children are labeled with this diagnosis. First generation serologic markers, such as anti-*Saccharomyces cerevisiae* antibodies (ASCA) and perinuclear antineutrophil cytoplasmic antibodies (pANCA), have not been specific enough to help the clinician differentiate between UC and CD in these cases. Newer markers such as anti-outer membrane protein C (OmpC) and anti-flagellin (CBir1) show promise in this area. In addition, recent research suggests that high serum levels of serologic markers can help clinicians identify those patients who will have an aggressive disease course and predict the likelihood of early surgery. In this roundtable discussion, the latest data on the role of serologic testing in the management of pediatric IBD are discussed, including diagnosis, prognosis, and medical and surgical management.

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Table of Contents

Challenges and Priorities in Diagnosing and Treating Pediatric IBD Patients
Carmen Cuffari, MD 3

Diagnostic and Prognostic Options in Pediatric IBD Patients
Marla Dubinsky, MD 6

Utilizing Predictive Serologies to Individualize and Optimize Therapy
Ernest Seidman, MDCM, FRCPC, FACG 8

Slide Library 12

Question and Answer Forum 14

Included in EMBASE

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Challenges and Priorities in Diagnosing and Treating Pediatric IBD Patients

Carmen Cuffari, MD

Ulcerative colitis (UC), Crohn's disease (CD), and indeterminate colitis (IC) are chronic idiopathic and heterogeneous inflammatory bowel diseases (IBD) that are commonly diagnosed among children and adolescents. Children account for approximately 20% of all cases of IBD. The median age of onset is 12 years and there is a slight male predominance in the younger age group.[1] New cases of IBD appear to be on the rise. One study published in 2003 found the incidence of IBD to be 7.05 per 100,000 among Wisconsin children. Interestingly, the incidence of CD was 4.56 per 100,000, over twice that of UC.[2] This trend in pediatrics may be explained in part by the general tendency of pediatricians to maintain a high index of suspicion for IBD in patients with chronic abdominal pain and a positive family history of IBD.

Concerns Particular to Pediatric IBD

Pediatric IBD, in particular CD, has been associated with growth failure, bone demineralization, and delayed puberty, all of which may influence ultimate adult height. It has been reported that as many as 85% of children and adolescents with CD show signs of growth failure as measured by weight loss at the time of the diagnosis.[3] Impaired linear growth is also observed in up to 40% of children with CD at the time of diagnosis; indeed, reduced height velocity is generally observed prior to the diagnosis of IBD in the majority of children with growth failure.[4] Therefore, growth failure may be an indicator of disease exacerbation. Although demineralization is sometimes observed in adult patients with IBD, it tends to occur with higher frequency in children due to inadequate nutrition, overuse of corticosteroids, and reduced physical activity. In terms of osteoporosis, a study of 73 children with IBD showed that despite a high prevalence of growth retardation, the majority had adequate bone mass after adjusting for bone size when interpreting data from a DEXA scan.

Although UC is less often associated with growth failure than is CD, UC is usually associated with more complications, and it is often refractory, which may necessitate a colectomy. Patients with longstanding UC are also at increased risk for colorectal cancer. A pivotal 2001 meta-analysis found that the cumulative probability of a colorectal cancer diagnosis among IBD patients was 2% by 10 years, 8% by 20 years, and 18% by 30 years.[5] Therefore, frequent surveillance colonoscopy is recommended after 8–10 years following the initial diagnosis.

IC is diagnosed in about 10% of adult patients with IBD, but the number is much higher in children. A study from Johns Hopkins University School of Medicine reported that, among 250 children diagnosed with IBD between 1996 and 2001, 50% had a diagnosis of CD, 20% had UC, and 30% had IC.[6] The mean age at diagnosis was younger among patients with IC and UC than it was for patients with CD. Among the patients with IC, 80% had pancolitis at diagnosis, and the remaining 20% had left-sided disease that progressed to pancolitis within 6 years. About two-thirds of the patients with IC maintained their diagnosis after a mean follow-up of 7 years. These data indicate that IC is a distinct pediatric subgroup of IBD with a prevalence that is higher than that observed in adults, and that children with IC have an aggressive and rapidly progressing disease phenotype, characterized by an early age of disease onset and a rapid progression to pancolitis.[6]

In light of these concerns, it is no surprise that quality of life is often reduced in patients with pediatric IBD.[7] Anxiety and depression may occur due to feelings of difference from peers, the unpredictability of the disease course, and the possible risk of surgery.[8] Children with IBD may also have difficulty interacting with schoolmates because of delayed puberty, causing low self esteem.[9] Children with IBD may display behavior problems during adolescence, as they may not yet have developed skills to deal with the challenges of chronic disease.[10]

Current Challenges in the Diagnosis of Pediatric IBD

Early diagnosis is the goal in pediatric IBD in order to minimize symptoms and rapidly restore quality of life. A complete clinical evaluation will also increase physicians' awareness of potential complications including growth retardation and developmental delay. There are a number of imaging choices for evaluating children with suspected IBD, each with advantages and drawbacks. These modalities include upper GI small-bowel follow-through, enteroscopy (push enteroscopy), capsule endoscopy, computed tomography (CT) scanning, nuclear medicine imagining, ultrasonography, and magnetic resonance imaging (MRI).

Push enteroscopy has utility in evaluating pediatric patients with proximal small bowel disease[11]; however, there are a number of drawbacks to this technique. It can only access about a third of the small bowel, it is invasive, it usually requires sedation and analgesia, and it carries a danger of perforation.[12] Another, more recent choice is capsule endoscopy. Several studies in adults have suggested that capsule endoscopy has a superior diagnostic yield and sensitivity when compared with colonoscopy/ileoscopy, barium small bowel follow-through, CT enterography, or MRI enterography.[13-15] Drawbacks, however, include the inability of some patients to swallow the capsule, a risk that the capsule might become trapped within the GI tract and require surgical removal, and expense. It appears that adverse events are more likely to occur when capsule endoscopy is used in children than when used in adults.[16]

In comparison, CT scanning is widely available, well tolerated by children, and allows complete evaluation of the colon, but is, of course, associated with increased exposure to radiation. Radio-labeled white blood cell scintigraphy allows detection of inflammatory disease and can distinguish between CD and UC; however, it is unreliable as a screening test for proximal small-bowel disease.[17] Ultrasonography is another option. It does not involve radiation, and it can evaluate extraintestinal complications of IBD. In addition, disease activity can be assessed by monitoring for increased flow volume in the superior mesenteric artery.[18] MRI enterography also requires no ionizing radiation and yields excellent soft tissue contrast. It is often superior to ultrasound in identifying fistulae and stenosis and in localizing affected bowel segments, especially in patients with more proximal bowel involvement.[19]

Differential Treatment Response in Pediatric IBD

Responsiveness to medical therapy can differ between adults and children, although that is not always the case. In regard to corticosteroid use, a recently published study from the Mayo Clinic found that pediatric IBD patients are more likely to require corticosteroids than are adults. In this study, 50 children with CD and 36 children with UC were followed for 1 year.[20] Fifty-two percent of patients with CD and 39% of patients with UC required corticosteroids, compared with 43% and 34% respectively in adults in the same population.[21] Response rates, however, do not appear to differ significantly between children and adults. In the same study, 27% of children with CD and 29% of children with UC required surgery within 1 year after starting systemic corticosteroids, and an additional 31% of children with CD and 14% of children with UC were steroid-dependent.[20] Similar results have been found for adults in the same population.[21]

Because so many children with IBD are treated with steroids, there has been much interest in reducing steroid exposure. The early use of immunomodulators has been shown to reduce steroid use in pediatric patients with CD. In a landmark observational study by Punati and colleagues,[22] 247 patients with moderate-to-severe CD who were treated with an immunomodulator within one year of diagnosis were evaluated for outcomes of remission, corticosteroid use, infliximab therapy, hospitalizations, and CD-related surgery. A total of 150 of the 247 patients were treated with immunomodulators within 3 months of diagnosis (early group), and the remaining 49 patients received immunomodulator treatment between 3 and 12 months after diagnosis (late group). At 12 months, only 22% of the early group had required corticosteroids in the previous quarter, compared with 41% of the late group. The number of hospitalizations per patient was also noted to be significantly lower in the early group, although no difference was seen in the rates of remission, infliximab use over time, or surgery.

Infliximab is a monoclonal antibody to TNF-alpha, and is the first biologic therapy to be used in CD and UC. Higher response rates have been reported for infliximab use in children versus adults. In the REACH study of infliximab for children with CD, week 10 response was seen in 88% and remission was seen in 59%. At week 54, children who had received maintenance infliximab every 8 weeks demonstrated a response rate of 64% and a remission rate of 56%.[23] Compare this with results in adult patients with luminal CD in the ACCENT 1 trial and with fistulizing CD in the ACCENT 2 trial. In ACCENT 1, week 2 response was seen in 58% of adult CD patients, and week 54 response and remission rates were 50% and 38%, respectively.[24] In ACCENT 2, week 14 fistula response was seen in 65% and week 54 fistula response was seen in 38%.[25]

As with data from studies in the adult CD population, pediatric data suggest infliximab is most beneficial when used early in the disease course. In a study by Kugathasan and colleagues,[26] 15 children with medically refractory CD were given a single infusion of infliximab 5 mg/kg. Among the 14 patients who responded, 6 had had a disease duration of 2 years or less (early group) and 8 had had a disease duration of over 2 years (late group). At month 12, 50% of the early group maintained clinical response, but none of the late group maintained response.

As clinicians, it is important to always keep the long-term goals in mind. Although minimization of symptoms is the short-term goal, the ultimate goals for children with IBD are to restore quality of life, thereby normalizing emotional and social functioning, as well as to reduce long-term complications like hospitalizations, surgery, and cancer. As we move forward, making an accurate early diagnosis and producing a robust early response to therapy are critical

to achieving these goals. The emerging predictive role of serologic testing and interpretation may provide a crucial adjunct to standard laboratory testing and clinical observation in planning a course of effective treatment for these, our longest term patients.

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Diagnostic and Prognostic Options in Pediatric IBD Patients

Marla Dubinsky, MD

Standard Diagnostic Approach for Pediatric Patients

The classic presentation for UC, as is well known, consists of diarrhea, rectal bleeding, abdominal cramping, stool frequency, urgency, and tenesmus. CD, on the other hand, typically does not produce rectal bleeding unless there is involvement of the colon, particularly the left side of the colon. A more classic symptom presentation for CD is abdominal pain, intermittent diarrhea, fatigue, anemia, decreased intake, bloating, and weight loss.

One sign that pediatric physicians need to monitor closely is growth failure. Whereas less than 10% of patients with UC display linear growth failure, about 40% of patients with CD show linear growth failure at or even before the time of diagnosis.[1] Therefore, if a patient presents with a diagnosis of UC and yet has significant growth failure, the physician should strongly consider taking a close look at the small bowel and ruling out CD.

Three laboratory parameters that may be useful in evaluating presence of inflammation are the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and platelet count. Typically, an increased ESR, elevated CRP, and increased platelet count are more commonly seen in CD than in UC, but can be seen in both. These tests can be helpful when they are positive, but they can be overly sensitive or undersensitive, depending on the patient. There are certainly patients with a normal ESR who show an intense amount of inflammation on colonoscopy. On the other hand, there are patients who display an increased ESR that can be due simply to a mild respiratory illness. These tests do help the physician determine if there is a baseline level of inflammatory markers, but are not diagnostic in and of themselves.

From a diagnostic perspective, endoscopic and imaging evaluations still remain the gold standard, no matter what the laboratory tests might show. Most physicians would agree that patients should have some kind of small-bowel imaging as part of a complete work-up. As mentioned by Dr. Cuffari, CT enterography and MR enterography are increasingly favored options, and I think as the technology improves, MR enterography may become the standard for evaluating the small bowel. If small bowel disease is identified on small-bowel follow-through, CT enterography, or MR enterography, it is advisable to obtain tissue as well to get a microscopic and macroscopic evaluation of the extent of the disease. This is particularly important in light of the new interest in using immunomodulator or biologic therapy very early in the course of the disease.

Serologic Testing as a Non-Invasive Diagnostic Option

Colonoscopy and endoscopy certainly do play an important role in pediatrics; however, many patients that we see do not have IBD and might undergo invasive testing unnecessarily. We do have serologic markers that are useful in IBD diagnosis, including anti-*Saccharomyces cerevisiae* antibodies (ASCA), perinuclear antineutrophil cytoplasmic antibodies (pANCA), anti-CBir1 (anti-flagellin), and anti-outer membrane protein C (anti-OmpC). The most important thing to do when using serologic immune markers as a non-invasive diagnostic test is to not over- or under-interpret their diagnostic reliability.

The use of IBD serologic markers can be thought of as having 2 levels of diagnostic utility. If a physician is in a practice where the probability of a patient having IBD is very low, these tests have a good negative predictive value for ruling out disease and perhaps avoiding further invasive testing. For example, in a community gastroenterologist's office, it may be that only 1 out of 10 patients who present actually has IBD. In that case, a negative serological test is useful for ruling out the disease. At the next level, patients have a higher probability of having IBD, such as those seen at a secondary or tertiary referral center. In this setting, a positive test for serologic markers can help the clinician confirm his or her diagnostic suspicion of IBD, but a negative test does not necessarily rule out the disease.

Serologic Testing and Disease Prognosis

Recent evidence indicates that, among patients who already have a diagnosis of UC or CD, serologic marker testing can help define those who are at high risk of early complications and surgery. One case-control study published by Forcione

and colleagues in 2004 found that positivity for ASCA seems to define a subgroup of CD patients that are at risk for early surgery.[2] A total of 35 newly-diagnosed adult patients with CD who had surgery within 3 years of diagnosis (cases) were compared with 35 control patients with CD who did not undergo major surgery for CD within 3 years of diagnosis. Control patients were matched for age, sex, disease location, and smoking status. The authors found that ASCA IgA positivity was associated with over an 8-fold increased risk of early surgery, and that ASCA IgG positivity was associated with a 5-fold increased risk.

Similar findings have been reported in the pediatric population. Zholudev and colleagues[3] retrospectively studied sera from 81 children with CD, 54 with UC, and 63 controls, and they found that patients who were ASCA-positive were more likely to have disease of the ileum or ileum and right colon than patients who were ASCA-negative (58% vs 18%, $P<.001$). In addition, patients who were ASCA-positive were more likely to require ileocecal resection (36% vs 13%, $P<.05$).

Two prospective studies have been performed in the pediatric population. Dr. Seidman's group[4] obtained serum samples from 139 newly-diagnosed patients with CD and assayed them for ASCA IgA and IgG as well as for pANCA. They found that the time to occurrence of the first complication was shorter among patients with ASCA IgA or IgG positivity (hazard ratio (HR)=2.33; 95% confidence interval (CI)=0.99–5.50) and among those with higher ASCA IgA titers (HR=1.20; 95% CI=1.08–1.34). ASCA positivity did not appear to predict the time to undergoing surgery independent of complications, or the occurrence of recurrent surgeries, however.

Our group published a second prospective study in October of 2008. It was a national, multicenter collaborative study in which we looked at serum markers in 796 pediatric CD patients who were followed over time.[5] Serum samples were tested for anti-CBir1, anti-OmpC, ASCA, and pANCA. After a median follow-up of 32 months, 32% of the patients had developed at least one disease complication. Those with antibody positivity were more likely to develop a complication: 9% of the seropositive patients had internal penetrating/stricturing disease versus 2.9% in the seronegative group ($P=.01$). Twelve percent of the seropositive group underwent surgery versus 2% in the seronegative group ($P=.0001$). In addition, we found that the frequency of internal penetration, stricturing, and surgery significantly increased with increasing antibody levels.

Future Applications for Serologic Testing

Looking to the future, we are beginning to investigate the idea that various serologic markers may reflect different immune pathways in IBD. For example, there may be serologic markers that are associated with the secretion of high levels of tumor necrosis factor (TNF) or interferon-gamma in the intestines of a particular subpopulation of patients. These markers may then be correlated with a lack of response or a robust response to a particular medication.

One such study by Ferrante and colleagues[6] found that high levels of pANCA and low levels of ASCA are associated with a negative response to infliximab in patients with UC. A total of 100 patients who had received either one or 3 infusions of infliximab 5 mg/kg were included in the study. Of these, 44% were pANCA positive and ASCA negative, and these patients had a significantly lower rate of early clinical response (55% vs. 76%; $P=.049$). Future studies will further clarify the use of serologic markers for predicting response to therapy, and perhaps will tie in the genetic basis of these markers as well. The eventual goal is to be able to tailor IBD therapy based upon serologic and genetic test results in order to optimize patient response.

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Utilizing Predictive Serologies to Individualize and Optimize Therapy

Ernest Seidman, MDCM, FRCPC, FACG

Recent clinical trials have shown that there are few distinctions between CD and UC in terms of medical management. The main reason for clearly differentiating between UC and colonic CD is to guide surgical interventions and to predict clinical outcomes. When a child or young adult with a diagnosis of UC is referred for surgery to a colorectal surgeon, a colectomy with an ileoanal anastomosis will usually be recommended as a curative procedure. However, in approximately 5% of cases, the clinical course later reveals an ultimate diagnosis of CD. In such a circumstance, the pouch may require removal. This outcome then becomes a misfortune for the young patient, who no longer has a rectum and did not anticipate a lifelong ileostomy. Thus, when a patient is facing surgery for colitis, it is in their best interest for their physician to determine a diagnosis with as much accuracy as possible. Subsequently, a decision can be made whether to proceed with a complete proctocolectomy with the creation of an ileal pouch, or an ileostomy, leaving the rectum for a possible later reconstruction with closure of the ileostomy.

Several population-based studies demonstrated that in 4–10%[1,2] of adult patients having IBD involving the colon, it is impossible, with available diagnostic tools, to distinguish between CD and UC. As mentioned, establishing a definitive diagnosis has crucial implications in clinical practice, impacting decisions regarding medical and surgical therapy, and ultimately, clinical outcome. The term indeterminate colitis (IC) was initially proposed in 1978[3] to describe patients undergoing colectomy in which the subsequent surgical specimen showed overlapping features of CD and UC. This label of IC was eventually adopted by clinicians to widely classify any patient with IBD in whom it was impossible to reach a definitive diagnosis of either UC or CD, even when surgical specimens were unavailable.[4] In 2006, an international working group[5] recommended that the term IC should be reserved for those cases where colectomy has been performed without reaching a definitive histopathological diagnosis. The same group proposed a new term, "IBD type unclassified" (IBDU), to classify patients in whom there is evidence for chronic inflammatory bowel disease affecting the colon, without small bowel involvement, and no definitive histology or other evidence in favor of either CD or UC. Using this terminology, IBDU is generally seen in approximately 10% of IBD cases. As mentioned by Dr. Cuffari, it has recently been diagnosed in up to 30% of pediatric IBD patients.[6]

What, then, can be done in cases of diffuse colitis and presurgery diagnosis of IBDU, where endoscopic, imaging, and histologic results do not allow for a definitive diagnosis of UC or CD? There is considerable interest in the clinical utility of serologic tests to assist with decisions preoperatively.

Interpreting Serologic Tests to Differentiate UC and CD

Diagnosing CD is fairly straightforward if granulomas are found in the colon or if there is small bowel involvement. What is less straightforward is the patient with homogeneous colitis, without "skip" areas and in whom granulomas are not found in biopsies. In this case, we can be fooled into thinking that the patient has UC when in fact, over time, it will become clear that the correct diagnosis is CD. According to the literature, about 3–9% of patients with a diagnosis of UC or CD will have a switch in diagnosis within 5 years.[7,8]

In the early years of serologic testing, there was much hope that these tests would be able to definitively differentiate CD from UC for the patient with IBDU. Using the first generation of IBD serology (ASCA and pANCA only), clinicians were often disappointed, and understandably so, about their performance for this intention. For example, although ASCA positivity is about 95% specific for CD, it is highly associated with small bowel CD. Relatively few patients with colonic CD are ASCA positive. On the other hand, although pANCA positivity is seen in about 60% of UC patients, it can be seen in 8–23% of patients with CD.[9] These patients are also typically the ones who have a UC-like presentation clinically, endoscopically, and histologically.

One of the most important studies in this field was published by Joossens and colleagues.[10] They identified 97 patients with IC from 3 European centers, analyzed their sera for pANCA and ASCA, and then followed them

prospectively for up to 6 years. A definitive diagnosis was reached in only 32% of the patients. Of these, 80% of the ASCA+/pANCA- patients were diagnosed with CD, and 64% of the ASCA-/pANCA+ patients were ultimately diagnosed with UC. Interestingly, 48.5% of the total 97 patients were negative for both ASCA and pANCA. Most of these patients remained with a diagnosis of IC during their further clinical course. What have we learned from this study? Primarily that the first generation of IBD serology is often not clinically helpful in terms of predicting the ultimate diagnosis in IC and probably IBDU as well. With almost one third of ASCA-/pANCA+ patients actually having a diagnosis of CD in this study, and two thirds with UC, the clinician simply does not have a means of accurately diagnosing utilizing these two markers alone.

Newer markers have shown more promise. The flagellin CBir1 has been identified as a dominant antigen capable of inducing colitis in mice and eliciting a humoral immune response in a significant subpopulation of patients with CD. Targan and colleagues[11] tested sera from 484 patients in the Cedars Sinai Medical Center repository for anti-CBir1. The authors found that the presence and level of IgG anti-CBir1 were independently associated with CD. Anti-CBir1 expression was also independently associated with small-bowel, internally penetrating, and fibrostenosing disease features. Targan's group then assayed anti-CBir1 antibody titers in a cohort of 50 "reagent grade" pANCA+ IBD patients, 25 of whom had UC, ultimately, and 25 who had CD. They found that patients who were both anti-CBir1 and pANCA-positive almost invariably had a final diagnosis of CD.

Although these data are promising, there are no studies available that have prospectively examined the ability of the combined results from anti-CBir1, ASCA, and pANCA to differentiate between UC and CD in patients with IBDU. Such studies are going to be very important to this field.

Interpreting Serology Post-Ileoanal Anastomosis

If one looks at studies in patients with a diagnosis of UC who have already undergone an ileoanal anastomosis procedure, it is reported that up to 10% of cases will eventually have their diagnosis changed to CD. Melmed and colleagues[12] prospectively enrolled 238 consecutive patients with UC or IC (more properly IBDU) who then underwent ileal pouch-anal anastomosis. Serum drawn preoperatively was assayed for ASCA, pANCA, anti-CBir1, and anti-outer membrane porin-C (Omp-C) by ELISA. After a median of 19 months, 7% of the post-surgery patients were diagnosed with CD. The predictors of a diagnosis change were family history of CD (HR=8.4; 95% CI, 2.96–24.1; $P<.0001$) and ASCA IgG positivity (HR=3.14; 95% CI, 1.1–9.81; $P=.04$). The cumulative risk of CD among patients with these two risk factors was higher than in patients with either risk factor or neither risk factor. A second case-control study from this group looked at 21 patients whose diagnosis had changed from UC to CD and compared them with 52 age-matched UC controls and 56 CD controls.[13] Sera were analyzed for ASCA, ANCA, anti-CBir1, and anti-Omp-C by ELISA, and charts were reviewed for possible "red flags." Three red flags significantly differed between cases and UC controls. At initial colonoscopy, cases were more likely to have extensive colonic involvement, were more likely to have non-bloody diarrhea at initial presentation, and were more likely to have weight loss of more than 10% of body weight at presentation than were UC controls. In this cohort, serologic markers did not add to the contribution of these clinical factors in predicting a change in diagnosis from UC to CD.

Based on the available data, I recommend that patients scheduled for elective colectomy for UC or IBDU undergo a gastroscopy with routine biopsies of the esophagus, stomach, and duodenum to look for granulomas, as recommended by the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN).[14] Furthermore, I would also recommend requesting IBD serology, using the tests with the highest clinical validity, which include the anti-CBir1 test. I might reconsider the pouch procedure as a first-line intervention for patients with UC who have a family history of first-degree relatives with CD, who have pre-operative ASCA positivity, high titer anti-CBir1 levels, who present with non-bloody diarrhea, or who present with significant weight loss. These appear to constitute red flags that we should consider before assuming that what looks like UC is, in fact, UC. The surgeon can leave the rectum and a decision regarding pouch procedure can be delayed. Again, further studies to validate this approach are much needed to guide clinicians.

Interpreting Serologic Tests to Predict Disease Phenotype and Avoid Surgery for CD

We commonly see young CD patients who have terminal ileal disease with or without cecal or right colonic involvement. These patients' CD appears mild to moderate at onset. The question then becomes, which of these patients are going to present soon afterwards with complications requiring hospitalization, antibiotics, and an eventual resection within a year or 2 of diagnosis? In this situation, serology has been shown to be very helpful in predicting a penetrating or fibrostenosing CD phenotype.

As described by Dr. Dubinsky above, several studies in both adult and pediatric populations have found that high titers of ASCA are associated with the fibrostenosing and

penetrating CD phenotypes as well as with the need for early small bowel surgery.

More recent studies have looked at the newer markers and combinations of markers and have found that the higher levels of ASCA, anti-OmpC, and anti-CBir1 are associated with an early onset of disease, early need for surgery, and fibrostenosing or internal penetrating disease. Based on the accumulating evidence, serological tests, such as the PROMETHEUS IBD Serology 7, can be clinically useful in predicting which patients with benign-appearing ileitis or ileocolitis at diagnosis have an unfavorable antibody profile and therefore should be considered as candidates for more aggressive treatment.

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Notes

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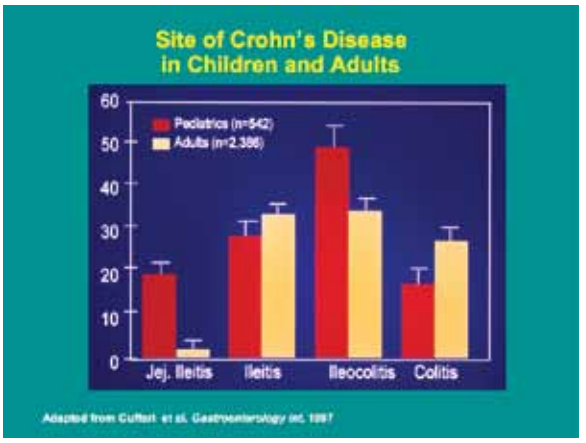

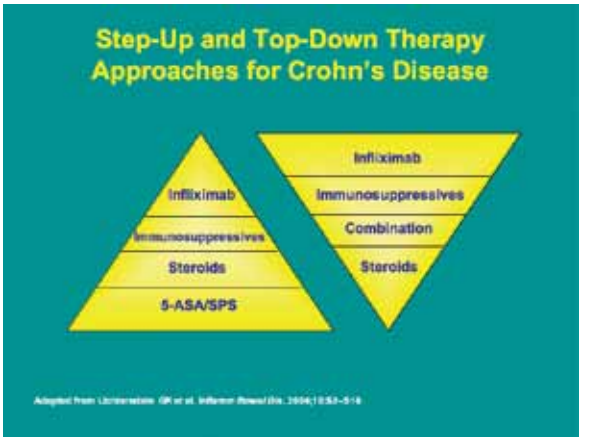

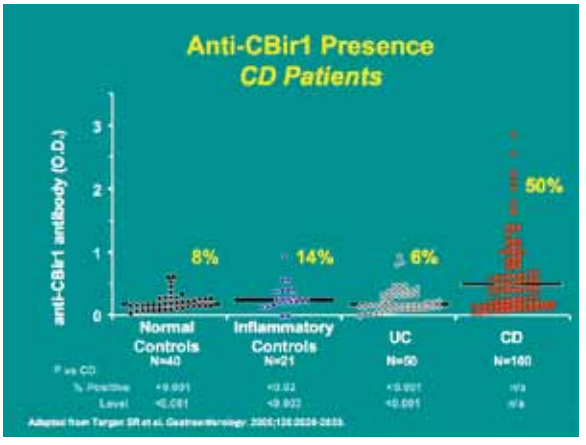

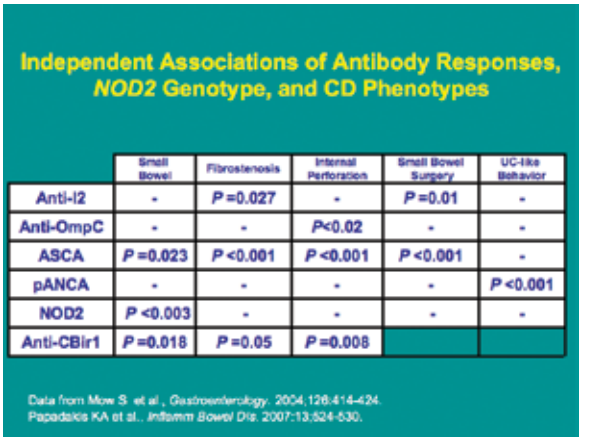

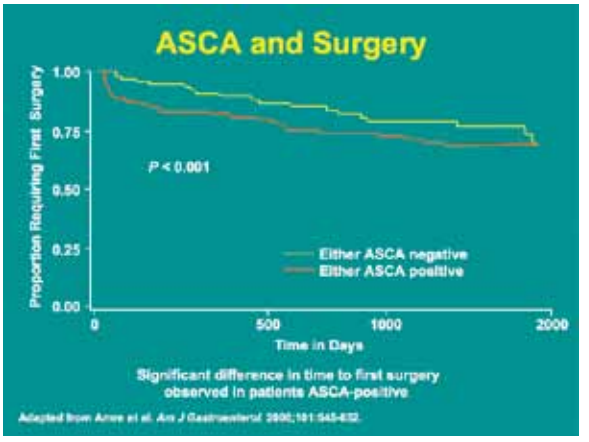

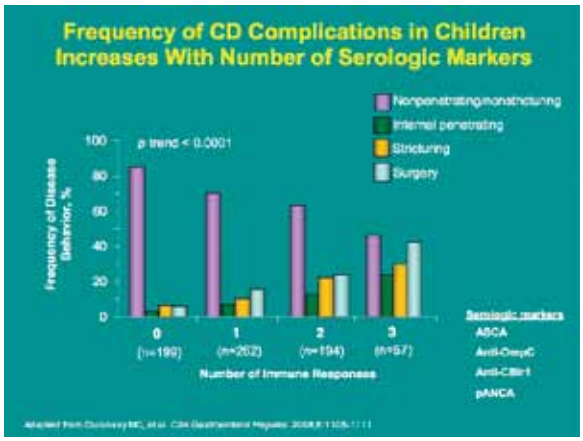

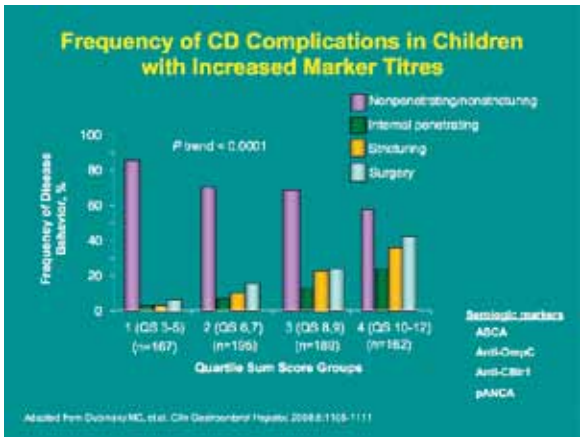

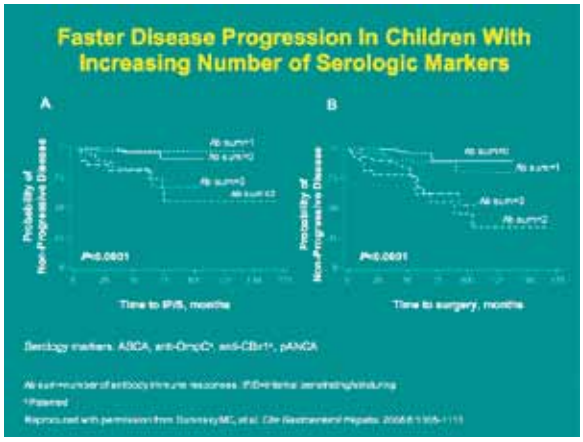

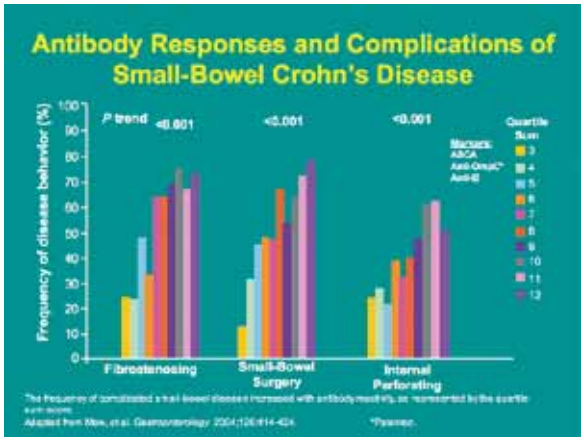

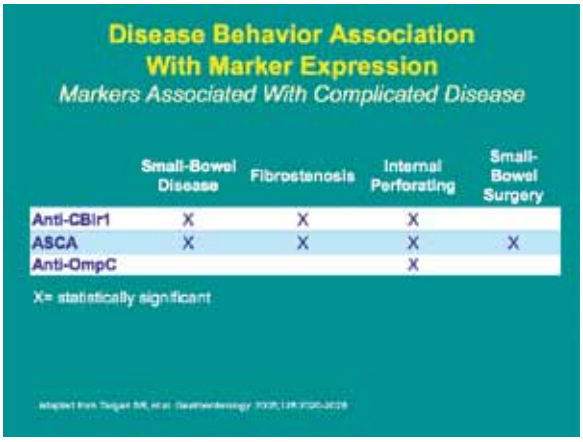

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Question and Answer Forum

Drs. Seidman and Dubinsky discuss further specific topics in the management of pediatric IBD.

In distinguishing between CD and UC, what is the significance of a finding of histologic gastritis on endoscopy? What is the significance of a finding of rectal sparing?

Marla Dubinsky Last year, the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition, and the Crohn's and Colitis Foundation of America published an algorithm that clinicians can follow for differentiating childhood UC from CD. The guideline notes that focal gastritis is more typical of CD, but that it is seen in patients with UC with some frequency.[1] One study in pediatric patients found focal gastritis to be present in 65% of patients with CD and 21% of patients with UC, compared to 2.3% of controls without IBD and 2.6% of patients with *H. pylori*.[2] So, I typically diagnose a patient who has colitis, a normal terminal ileum, and gastritis as having UC with gastritis, as long as there is an absence of granulomas in the stomach.

Ernest Seidman In regard to rectal sparing, the classical teaching, of course, is that a completely normal rectal biopsy would exclude the diagnose of UC. That being said, there are patients who initially present with rectal sparing who do actually have UC. Typically, as the disease progresses, the rectum becomes involved.

I think that the future of classifying patients is truly to do so at an immune and genetic level, instead of trying to fit patients into a catch-all diagnosis. Once we look at it from an immunological and genetic perspective, questions about focal gastritis or rectal sparing will no longer be an issue.

If a diagnosis has already been confirmed through endoscopy and colonoscopy, what is the role of serologic testing?

MD I find it useful in helping me gauge prognosis of my patients, and also for managing patient expectations about the likelihood of response to infliximab. If the patient is pANCA positive and is somewhat early in the disease course, I can advise that patient that there is about a 50% chance of early response to anti-TNF therapy. If the patient is pANCA positive and has more severe disease, is failing steroids, and needs to make a decision between infliximab and surgery, for example, I tell him or her that the probability of primary response to infliximab may be closer to 25%.

What is your opinion on the management of a patient who presents with a positive serologic test but has no symptoms?

MD When the parents of a patient come to us and say that the patient's sibling has a positive serologic test but does not have symptoms, we must decide how to manage the situation. My general approach is to explain to the parent that the serologic markers indicate a genetic defect that is present in both children, but it is not at all certain that the child without symptoms will ever encounter the trigger to actually manifest IBD.

There are some data from a study done on Israeli army soldiers that indicates that ASCA positivity may have been seen before symptom development in some patients who are eventually diagnosed with CD, and that pANCA positivity may been seen before diagnosis in some patients who are eventually diagnosed with UC.[3] That being said, I would not endoscopically evaluate a child with only a positive serologic test unless some symptoms did manifest, or if there were growth failure.

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