Current and Novel Uses of Intestinal Ultrasound in Inflammatory Bowel Disease

Michael T. Dolinger, MD, MBA,[1] Emma Calabrese, MD, PhD,[2] Fabrizio Pizzolante, MD,[3] and Maria T. Abreu, MD[4]

[1]Susan and Leonard Feinstein Inflammatory Bowel Disease Center, Mount Sinai Hospital, Icahn School of Medicine, New York, New York

[2]Gastroenterology Unit, Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy

[3]Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy

[4]University of Miami Leonard M. Miller School of Medicine, Miami, Florida

Corresponding author:
Dr Maria T. Abreu
UHealth
1120 NW 14th Street, Suite 1112
Miami, FL 33136
Tel: (305) 243-6404
Fax: (305) 243-6125
E-mail: mabreu1@med.miami.edu

Abstract: Intestinal ultrasound (IUS) is a patient-centric, noninvasive, real-time, point-of-care tool with the capability to aid in diagnosis and monitoring of disease activity in both Crohn's disease and ulcerative colitis without the need for bowel preparation. IUS can be used as a tool for precision monitoring of inflammatory bowel disease (IBD) treatment response. IUS as a cross-sectional imaging tool is as accurate as magnetic resonance enterography (MRE) for assessing the ileum and is more accurate than MRE for colonic assessment proximal to the rectum. Multiple simple ultrasound-based scoring systems have been internally validated with endoscopy in both Crohn's disease and ulcerative colitis, and changes in IUS parameters can be seen as early as 2 weeks after treatment initiation. IUS also plays a unique role in IBD activity monitoring of patients in whom avoidance of invasive testing is paramount, such as children and pregnant patients. Novel uses go beyond monitoring activity, with potential use of elastography to measure bowel wall stiffness to detect fibrosis and bowel damage for enhanced decision-making. Ultimately, IUS is likely to expand in the United States, facilitated by accessible expert training, access to equipment, and the development of a reimbursement model. This article provides a comprehensive review of the current and novel uses of IUS in IBD.

Keywords
Inflammatory bowel disease, ulcerative colitis, Crohn's disease, intestinal ultrasound, magnetic resonance enterography

Crohn's disease (CD) and, to a lesser extent, ulcerative colitis (UC) are transmural, resulting in progressive bowel damage requiring comprehensive monitoring strategies.[1-3] The current STRIDE-II treat-to-target goals for inflammatory bowel disease (IBD), however, include mucosal healing, not transmural healing.[4] At the time of STRIDE-II guideline development, transmural healing was only considered as an adjunct target for CD, not UC, because of the perceived limited ability to achieve transmural healing and limited evidence suggesting this prevented disease progression beyond what mucosal healing could already do. However, only assessing and monitoring the mucosa

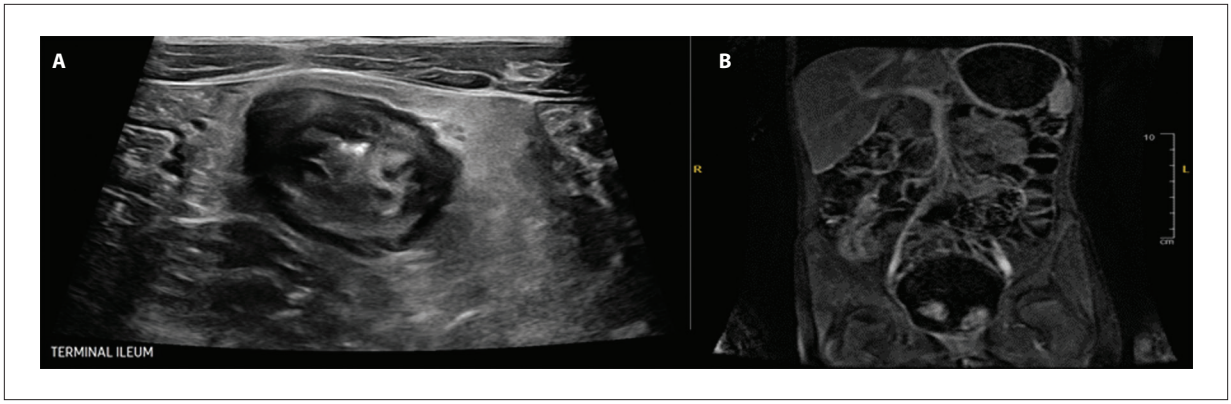

Figure 1. Inflammation in the terminal ileum seen on intestinal ultrasound (**A**) and magnetic resonance enterography (**B**) consistent with severely active Crohn's disease and characterized by increased bowel wall thickness to 7.1 mm, inflammatory fat stranding, and loss of bowel wall stratification.

with endoscopy limits the gastroenterologist's ability to visualize the entirety of disease burden, potentially contributing to a therapeutic ceiling conundrum. Cross-sectional imaging techniques such as magnetic resonance enterography (MRE) can view the totality of the bowel, are accurate for endoscopic activity, are able to measure treatment response, and have the unique ability to measure bowel damage.[5-7] Moreover, enhancements in ultrasound technology as a cross-sectional imaging technique and rising expertise among gastroenterologists have led to the emergence of intestinal ultrasound (IUS) as a noninvasive, real-time, point-of-care tool with the capability to aid in diagnosis and monitoring of disease activity in IBD.[8] This article reviews the current use of IUS in IBD for initial diagnosis and monitoring of disease activity, examines the role of IUS as a tight control measure of treatment response, discusses the use of ultrasonography with contrast, and explores novel uses of IUS to assess complications and further understand the nuances of transmural intestinal inflammation.

Intestinal Ultrasound in the Initial Diagnosis of Inflammatory Bowel Disease

Presentation of IBD is often insidious, leading to delays in diagnosis, albeit more commonly with CD than UC, which may result in advanced bowel damage.[9-11] Noninvasive, cross-sectional imaging can be valuable in expediting a diagnosis before the gold standard method of ileocolonoscopy and histology, which require bowel preparation, fasting, and sedation. Point-of-care IUS has the potential to accelerate IBD diagnosis because MRE requires an additional visit with radiology, often with long wait times. Thus, IUS could be used as a screening tool identifying transmural inflammation or complications consistent with IBD prior to diagnostic ileocolonoscopy. Above all else, IUS improves shared understanding and enhances clinical decision-making, enabling it as a comprehensive disease activity assessment tool.[12]

IUS and MRE are accurate for detecting inflammation in newly diagnosed small bowel CD. Figure 1 shows IUS and MRE images demonstrating inflammation consistent with terminal ileum disease activity in a patient with CD who underwent both tests. In a study by Castiglione and colleagues of 234 patients with suspected small bowel CD, IUS and MRE had comparable accuracy with a sensitivity and specificity to detect inflammation of 94% and 97%, respectively, for IUS, and 96% and 94%, respectively, for MRE. Compared with IUS, MRE was more accurate for defining small bowel disease extension (r=.69) and for detecting fistulas (κ=.67), but comparable for detection of strictures (κ=.82) and abscesses (κ=.88).[13] Overall, IUS, MRE, and computed tomography enterography (CTE) have similar accuracy for the diagnosis of abdominal complications of CD.[14] IUS is useful for initial evaluation of suspected complications and further delineation with MRE to guide management; MRE may be a more valuable tool to monitor bowel segment length in response to treatment compared with IUS.

Transmural Disease Activity Assessment With Intestinal Ultrasound vs Magnetic Resonance Enterography

Gastroenterologists evaluate the mucosa of the bowel by colonoscopy to understand the severity of IBD yet miss an important dimension of the disease process, that is, transmural inflammation and its response to therapy. The groundbreaking prospective multicenter study METRIC compared the accuracy of IUS with that of MRE for detecting CD presence, activity, and extent. This study demonstrated that IUS was accurate for assessment of

small bowel CD and could be positioned as a first-line cross-sectional imaging option.[15] Similar to previous findings by Castiglione and colleagues,[13] MRE was superior to IUS in assessing small bowel CD extent and MRE had a higher specificity for detecting small bowel CD presence compared with IUS.

One criticism of IUS compared with MRE or CTE has been its operator-dependent aspect. Analysis from the METRIC trial demonstrates that when IUS is performed by expert sonographers with IUS experience, there is less interobserver variability than with MRE. Interobserver agreement for small bowel disease presence on MRE was a modest 68% (κ=.36) for new diagnosis and 78% (κ=.56) for relapsed patients, and for colonic disease presence on MRE was only slight at 61% (κ=.21) for new diagnosis and 60% (κ=.20) for relapsed patients.[16] Interobserver agreement for IUS was higher than MRE in the small bowel, 82% (κ=.64) for new diagnosis and 81% (κ=.63) for relapsed patients, as well as in the colon, 64% (κ=.27) for new diagnosis and 78% (κ=.56) for relapse.[17] Furthermore, a retrospective study demonstrated that MRE is not accurate for colonic disease assessment in children, and that the simplified Magnetic Resonance Index of Activity missed most severe lesions in colonic segments.[18] Thus, in expert hands and especially in colonic disease, IUS has quite good interobserver agreement.

Intestinal Ultrasound as a Surrogate for Endoscopic Activity

By 2018, IUS indices for assessing disease activity in IBD had been developed with variable methodology and included 7 for CD and 4 for UC, 9 of which were benchmarked against endoscopy.[19] The IUS parameters used for these indices are bowel wall thickness (BWT), color Doppler signal (CDS), bowel wall stratification, haustrations, fat wrapping, contrast enhancement, strain pattern, compressibility, and peristalsis.[19] Over the years, several practical IUS scores have been developed and validated with high accuracy to detect endoscopic activity.[20-27] Despite their reported accuracy, limitations of IUS scores for both CD and UC persist, with many developed in single-center studies and subsequent adequate external validation still lacking.

Monitoring Disease Activity in Ulcerative Colitis

The Milan Ultrasound Criteria (MUC) scoring system is based only on BWT and CDS (1.4 × BWT [mm] + 2 × CDS). This score is accurate for detecting UC activity compared with endoscopy, with an area under the curve (AUC) for a MUC score greater than 6.2 of 0.891 (95% CI, 0.775-0.959).[22] On external validation, a MUC score greater than 6.2 also predicted a worse disease course (hazard ratio, 3.87; 95% CI, 2.25-6.64; P<.001), with a higher probability of requiring treatment escalation, corticosteroids, hospitalization, and colectomy.[23,28] Most recently, the UC-Ultrasound index with 0 to 7 points based on BWT (>2 mm = 1, >3 mm = 2, >4 mm = 3), CDS (spots = 1, stretches = 2), abnormal haustrations (1 point), and fat wrapping (1 point) was developed and correlated strongly with the Mayo score (rho=.83).[29] Both scores showed substantial interrater and intrarater agreement and were quickly calculated, demonstrating feasibility for real-time clinical utility.

Monitoring Disease Activity in Crohn's Disease

An ultrasonographic score for CD termed the Simple Ultrasound Score for CD (SUS-CD) has been developed. The score is from 0 to 5 based on BWT (<3.0 mm = 0, 3.0-4.9 mm = 1, 5.0-7.9 mm = 2, ≥8.0 mm = 3) and CDS (no or single vessel = 0, 2-5 vessels per cm^2 = 1, >5 vessels per cm^2 = 2). The SUS-CD score correlated well with the Simple Endoscopic Score for CD (SES-CD; r=.83) and accurately detected endoscopic activity, with an AUC equal to 0.920.[30] Similarly, a simple ultrasound score, developed by Ripollés and colleagues based on only BWT and CDS (0.957 × BWT + color Doppler grade × 0.859), of greater than 5.5 demonstrated high accuracy to detect active disease at endoscopy defined as SES-CD greater than 3 (AUC = 0.923).[24] Lastly, the International Bowel Ultrasound Segmental Activity Score (0-100), a recently developed IUS score based on expert consensus, has yet to be validated and is more complex, limiting its use as a point-of-care test, but may be useful in clinical trials and to better measure treatment response in the future.[25] These IUS indices will allow for uniform reporting of results much like what is done now for endoscopy.

Intestinal Ultrasound to Measure Treatment Response

The increasing use of IUS in IBD has introduced new challenges, including how to interpret lesion changes in response to anti-inflammatory therapies (corticosteroids, immunosuppressants, biologics, and small molecules) with different ultrasonographic techniques and how to define remission after treatments. The definition of transmural healing is an evolving concept, and several ultrasonographic parameters have been used to assess therapy response.

Treatment Response in Crohn's Disease

Monitoring CD patients with IUS as a strategy for tight control during biologic therapy could be both a valuable method to assess lesion remodeling or healing and to determine whether to continue or change therapies.

Castiglione and colleagues evaluated the achievement of transmural healing (defined as BWT <3 mm) and mucosal healing (defined as the absence of ulcers in any segments) in 133 CD patients after 2 years of treatment with thiopurines or anti–tumor necrosis factor (TNF) agents. Transmural healing was observed in 25% of patients on biologics. Good agreement was found between transmural and mucosal healing (κ=.63; P<.001).[31]

A large multicenter German study has been conducted in CD patients receiving anti-inflammatory treatment. After 3 and 12 months, ultrasonographic examination showed significant improvements of nearly all ultrasonographic parameters, including reductions in BWT or stratification, decreased fibrofatty proliferation, and decreased signals in color Doppler ultrasonography (P<.01 for all parameters at months 3 and 12).[8]

Specifically looking at IUS changes after anti-TNF treatment,[31-35] transmural healing was achieved in 25% to 31% of CD patients treated with anti-TNF agents and was associated with a better clinical outcome; however, the definition of transmural healing was different for each study. In an Italian multicenter study, the authors demonstrated that after initiation of various biologic therapies in 188 patients with CD, transmural healing (defined as normalization of all bowel ultrasonographic parameters) was achieved in 53% after 3 months, in 62.5% after 6 months, and in 64% after 1 year. After 12 months of therapy, the average number of patients needed to be treated to have transmural healing was 3.6.[36]

In the STARDUST substudy, Kucharzik and colleagues evaluated the effect of ustekinumab (Stelara, Janssen) on transmural bowel inflammation in moderate-to-severe CD patients utilizing IUS. By using 4 ultrasound components (abnormally increased BWT, blood flow, loss of bowel wall stratification, and mesenteric inflammatory fat) to define IUS response and transmural remission, transmural healing rates with ustekinumab increased progressively through week 48 and reached up to 24.1%. IUS response was observed as early as week 4, improving over time through week 48. These data suggest that IUS could be a valuable objective tool to detect early response to treatment, potentially allowing for early treatment optimization.[37] In the future, a standardized IUS measure to define transmural healing that is linked to improved patient outcomes should be developed.

Treatment Response in Ulcerative Colitis

Endoscopic evaluation has long been considered the gold standard for assessing disease extent and severity in UC. The noninvasive nature of IUS renders it a potentially useful technique in monitoring patients with UC as well. The exception is rectal-only disease, which is not captured well during a point-of-care IUS but may be better captured by the transperineal approach.[38,39]

Various studies have demonstrated utility of IUS in UC. Different studies evaluated the role of IUS in moderate-to-severe UC before and after corticosteroid therapy. Parente and colleagues evaluated patients with moderate-to-severe UC treated with high-dose systemic corticosteroids who were subsequently monitored over 15 months using clinical, endoscopic, and ultrasonographic assessments. At baseline assessment, there was concordance between clinical and ultrasonographic evaluations; moderate-to-severe IUS parameters at 3 months were associated with a significantly higher risk of severe endoscopic activity at the 15-month follow-up visit (odds ratio, 9.1; 95% CI, 2.5-33.5).[40]

A large multicenter German study evaluated the response to a variety of induction therapies in patients with UC of differing extents who were experiencing a flare. At baseline, 88.5% of the patients had increased BWT in the descending or sigmoid colon. Even within the first 2 weeks of the study, a significant proportion of patients had an improvement in BWT with only approximately 40% continuing to demonstrate BWT (P<.001); these findings remained improved at week 6 and week 12 (P<.001). There was a high degree of correlation between normalization of BWT and clinical response after 12 weeks of treatment (P<.001).[41]

A recent study conducted by de Voogd and colleagues demonstrated that IUS was accurate in detecting treatment response in a small cohort of moderate-to-severe UC patients treated with tofacitinib (Xeljanz, Pfizer). BWT in the sigmoid colon after 8 weeks was lower in patients with endoscopic remission; a decrease in BWT was more pronounced in patients with endoscopic response after 8 weeks of treatment.[42] These studies support the utility of IUS for monitoring disease activity and treatment response in UC, possibly minimizing the need for repeated sigmoidoscopies or colonoscopies.

Transmural Healing and Effect on Disease Progression

Transmural healing in CD and histologic healing in UC are important aspirational goals in treatment response.[4] However, these targets are not achievable in most patients using currently available treatments. In CD, several studies using MRE and IUS report data on transmural healing. New combination therapy approaches for IBD may enhance the ability to go beyond mucosal healing to achieve this additional goal. Given the fact that IUS is noninvasive and can be performed as a point-of-care test, its repeated use may inform the kinetics of transmural healing. Furthermore, several studies have demonstrated the potential role of transmural healing assessed by IUS as a long-term prognostic factor.

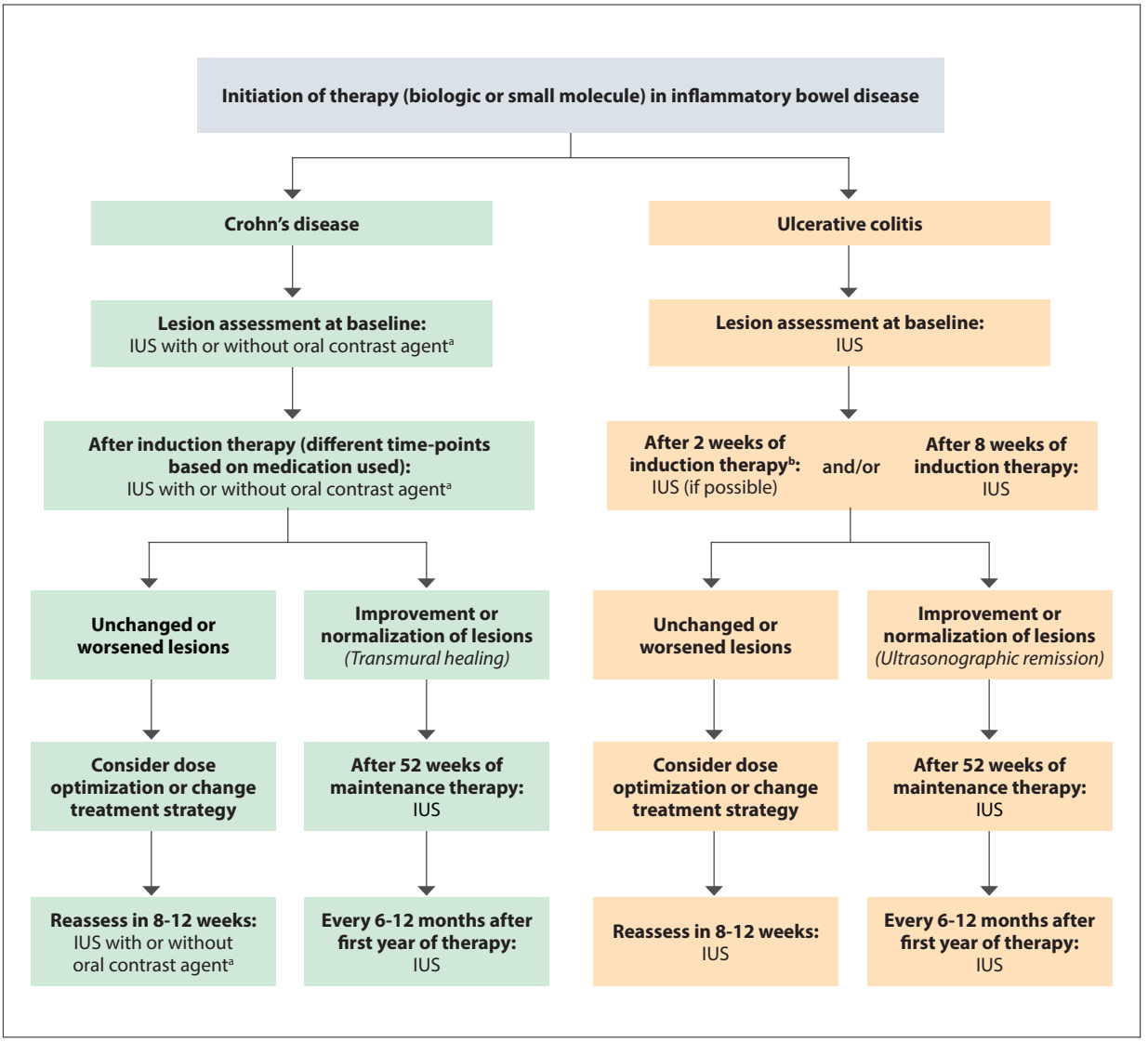

Figure 2. Algorithm for use of intestinal ultrasound as a tight control measure for monitoring treatment response in inflammatory bowel disease.

[a]The use of polyethylene glycol during IUS significantly increases accuracy in fibrostenotic Crohn's disease.[51,53]

[b]Consider early IUS at 2 weeks in patients with moderate-to-severe inflammation to monitor for improvement vs worsening in bowel wall thickness.[41]

IUS, intestinal ultrasound.

Ripollés and colleagues demonstrated that cross-sectional IUS response was seen in more than 50% of patients during induction anti-TNF therapy (at 12 weeks), and this response was a predictor of 1-year imaging response.[43] Castiglione and colleagues showed that normalization of BWT was associated with a higher rate of corticosteroid-free clinical remission and a lower rate of clinical relapse at 1 year compared with mucosal healing or no healing.[32] Zorzi and colleagues have demonstrated that ultrasonographic response was noted in more than 50% of patients after 1 year of anti-TNF therapy, and this response was associated with significantly reduced long-term risk (>3 years) of need for corticosteroids, hospitalizations, and/or surgeries in CD patients.[44] Lastly, Vaughan and colleagues demonstrated that CD patients in clinical remission who also have transmural healing on IUS have reduced disease progression compared with CD patients in clinical remission found to have transmural inflammation on IUS.[45] These data suggest that IUS can examine transmural healing and that transmural healing results in better intermediate-term outcomes.

Figure 2 presents an algorithm for use of IUS as a

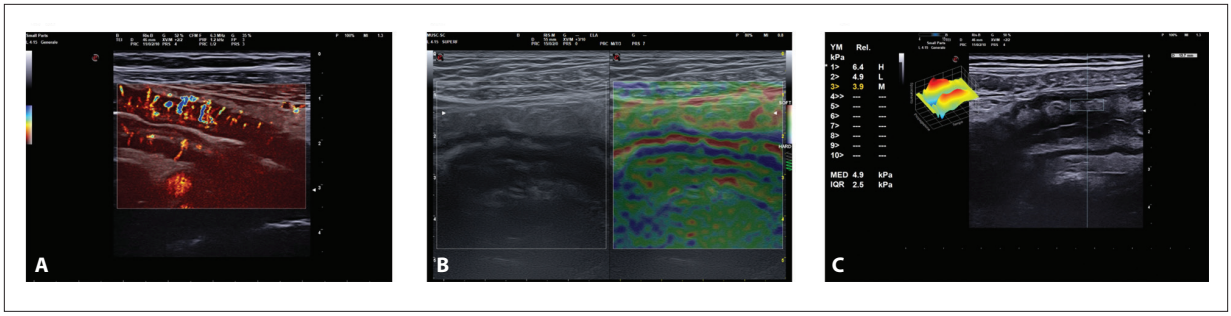

Figure 3. Evaluation of Crohn's disease activity in the terminal ileum on microvascular flow ultrasonography MicroV (MyLab X9, Esaote, Italy) shows evident transmural flows extending to the mesentery (grade 4 according to the Limberg score) (**A**). An elastogram produced from strain elastography (MyLab X9, Esaote, Italy) for acquisition of the terminal ileum affected by Crohn's disease is color coded according to the shear-wave speed and degree of the fibrosis, ranging from blue (harder tissue) to red (softer tissue) (**B**). Point shear-wave elastography (MyLab X9, Esaote, Italy), performed through the most severe bowel damage, shows quantitative measurements of bowel wall stiffness in the terminal ileum (**C**).

tight control measure for monitoring treatment response in patients with IBD receiving therapy with a biologic or small molecule. For Janus kinase inhibitor therapy (tofacitinib [Xeljanz, Pfizer], upadacitinib [Rinvoq, AbbVie]) or anti-TNF therapy (infliximab, adalimumab), we recommend IUS at 2 to 4 weeks after initiation. For vedolizumab (Entyvio, Takeda) or ustekinumab (Stelara, Janssen), we recommend IUS evaluation at 6 to 8 weeks after initiation. We recommend IUS evaluation at least annually to document ongoing response.

Ultrasonography With Contrast in Crohn's Disease

The use of power Doppler IUS to assess the vascularity of the bowel wall has been evaluated as a quantitative method for determining CD activity. Vascularity within the bowel wall has been evaluated using a subjective scoring system according to the semiquantitative intensity of color signals and/or by the analysis of Doppler curves obtained from vessels detected within the bowel wall. In most studies, vascularity evaluations and endoscopic/radiologic activity often correlated.[46]

Contrast-enhanced ultrasonography (CEUS) using an intravenously administered microbubble contrast agent can further assess CD activity through increased blood flow.[47-49] In a prospective study, Migaleddu and colleagues reported that CEUS showed 93.5% sensitivity, 93.7% specificity, and 93.6% overall accuracy in detecting inflammatory activity, using endoscopy/histology as the gold standard. The linear correlation coefficient for CEUS vs the Crohn's Disease Activity Index was 0.74 (P<.0001).[48] A retrospective study has demonstrated high diagnostic accuracy of CEUS in differentiation between intra-abdominal abscesses and inflammatory masses in CD. The use of CEUS in this specific setting of patients is extremely useful, rapid, and safe and allows for the evaluation of the presence and size of intra-abdominal abscesses.[50] Because CEUS involves intravenous injection, it is less likely to be used in everyday clinical assessment of IBD.

Another adjunct strategy to improve the accuracy of IUS is small intestine contrast ultrasonography (SICUS) accomplished with oral administration of polyethylene glycol (PEG) (generally 35 gm in 500 mL of water). Not surprisingly, this increases the procedure duration from 25 to 60 minutes.[51] The available evidence on this technique shows a clear increase in accuracy in detecting lesions in CD.[52] The accuracy for assessing lesions in the proximal small bowel and for defining the extent of diseased ileal walls can be significantly improved using SICUS. The sensitivity of SICUS for assessing anatomic disease site was 98.7% (95% CI, 95.2%-100%) for jejunal lesions and 97.4% (95% CI, 95%-99.8%) for ileal lesions. The specificity was 100% for both jejunal and ileal lesions.[52]

The use of an oral contrast agent also leads to a significantly greater accuracy in detecting the presence and number of stenoses. Parente and colleagues have compared conventional IUS with SICUS. Conventional IUS showed 74% sensitivity and 93% specificity in detecting at least 1 stricture. Distension of the lumen by PEG significantly increased the accuracy of IUS in identifying 1 or multiple strictures (sensitivity increased to 89%, and positive predictive value increased to 92% for 1 stricture and 77.7% for multiple strictures). SICUS was able to detect an additional 10% (if 1 stenosis) or 20% (2 stenoses) more stenoses than IUS without an oral contrast agent.[53]

The use of a PEG solution also increases the sensitivity of IUS for assessing recurrence in CD patients after

ileocolonic resection wherein the anatomy is distorted. IUS showed a high sensitivity (92.5%), positive predictive value (94%), and accuracy (87.5%) for detecting recurrent CD lesions using ileocolonoscopy as the gold standard. SICUS provides higher accuracy in determining severity of postoperative recurrence and in differentiating mild to severe lesions.[54] Although SICUS may add value over traditional IUS, data supporting its utility are still limited to single centers. Nevertheless, SICUS has no requirement for an intravenous injection and may be used in select special situations such as postoperative CD.

Novel Uses of Intestinal Ultrasound in Inflammatory Bowel Disease

Although ultrasonography, computed tomography, and magnetic resonance imaging show good sensitivity and specificity in the evaluation of transmural disease,[14,55-59] the key problem that remains is distinguishing inflammatory vs fibrotic transmural disease.[60,61] Often these coexist in affected stenotic segments. Conventional ultrasound and CEUS alone are not able to distinguish between the 2 patterns, although some key parameters have been identified such as submucosal thickening, hyperechogenic spiculates, and muscular hypertrophy.[62-64]

Shear-Wave and Strain Elastography to Assess Fibrosis

Chronic inflammation and fibrosis change the mechanical and elastic properties of the affected intestinal loop. The degree of fibrosis correlates with bowel wall stiffness; thus, tissue elasticity is a potential surrogate marker for intestinal fibrosis. Strain elastography (SE) and shear-wave elastography (SWE) can be measured with modern ultrasound machines and have been developed for parenchymal organs, especially the liver. These ultrasound-based elastography technologies can be used to evaluate the bowel as well.[65] SE provides a relative quantification; SWE (point or 2-dimensional) provides absolute quantification (Figure 3).

Several studies have been conducted using SE or SWE over the last several years showing heterogeneous data and sometimes conflicting results. These studies vary in methodology and have different endpoints or reference standards. Thus, it is currently not possible to set cutoffs that are immediately applicable to clinical practice. Nevertheless, the data show a positive correlation between SWE values and fibrosis.[66-70] Chen and colleagues suggested a classification of strictures in patients with CD based on SWE values and the Limberg score, suggesting severe fibrosis for SWE values greater than 22.55 kPa and mild fibrosis for SWE values less than 22.5 kPa.[61] Fraquelli and colleagues conducted a study of SE and documented elevated strain ratio values for patients with fibrotic strictures (2.4 ± 0.5) compared with those with moderate fibrosis (1.5 ± 0.5) or inflammation (1.2 ± 0.6).[69] The method is attractive because it is noninvasive, well-tolerated, easy to perform in most patients, reproducible, and not expensive. According to the European Federation of Societies for Ultrasound in Medicine and Biology guidelines, SE and point SWE can be used to characterize fibrosis in intestinal lesions even though ultrasound-based elastography may not be ready for widespread comparisons across centers in the absence of standardization.[65] Here, the variation between machines in the absence of a reference standard may hinder its use in studies, but for clinical practice, using the same machine in the same patient (SE or SWE) could be helpful to measure changes in fibrosis of a diseased segment.

Disease Monitoring During Pregnancy

During pregnancy, biochemical parameters (C-reactive protein, hemoglobin, albumin) are not accurate to determine disease activity. Fecal calprotectin is accurate but lacks information about disease extent, lesion topography, and related complications.[65,71-73] Endoscopy and MRE are less comfortable or less feasible in pregnant IBD patients. IUS is radiation-free, noninvasive, and safe to use during pregnancy, compared with MRE and CT for monitoring disease activity.[14,52,74] IUS correlates well with clinical symptoms, therapeutic response, and fecal calprotectin.[75] Limitations include feasibility, particularly visualization of the terminal ileum and sigmoid colon, later in pregnancy.[75,76] Specificity of IUS is high during all 3 trimesters but significantly decreases in the third trimester compared with the first and second trimesters. Because of uterus expansion, evaluation of the rectum can be difficult; this may also be challenging from a perineal approach during the second and third trimesters. Nevertheless, IUS may be very useful in the setting of pregnancy to monitor disease activity, which can impact pregnancy outcomes.

Intraoperative Ultrasound Assessment of the Bowel in Crohn's Disease

Histologic involvement of surgical resection margins in CD is considered an important risk factor for postoperative recurrence. There is no consensus on the definition of margin involvement nor in the definition of a clinically meaningful postoperative recurrence.[77,78] The decision about the extent of the surgical resection is currently left to the surgeon's experience and preoperative investigations. The availability of new wireless devices has simplified the use of intraoperative ultrasound. The sonographic evaluation can be performed through a mini-laparotomy with extraction of the bowel loop to define the length of the resection and site of anastomosis. Use of intraoperative

ultrasound seems to be associated with a lower rate of histologically affected margins, with a comparable duration of the surgery and the length of the intestinal specimens removed.[79,80] We believe intraoperative IUS may allow for improved delineation of bowel for resection.

Identification of Other Pathologies

In Europe, performing a complete ultrasound scan of the bowel means studying the patient's entire abdomen. In the United States, a limited ultrasound of the intestines is performed by gastroenterologists. CD leads to pathologies not only of the intestine but also of the structures connected to it (mesentery, lymph nodes) and of other surrounding organs. Approximately half of CD patients develop hepatobiliary manifestations.[81] The most common manifestation is primary sclerosing cholangitis for which ultrasound would not be adequate to detect; other conditions such as fatty liver and gallstones may be detected easily on ultrasound. Another common manifestation is nephrolithiasis after ileal resection owing to predisposition to calcium oxalate stones.[82-84] These conditions can be recognized with ultrasound evaluation.

Incorporating Intestinal Ultrasound Into Practice

In the United States, most gastroenterologists, other than those who perform endoscopic ultrasound, have not had point-of-care ultrasound as part of formal training. To make IUS available to patients with IBD, gastroenterologists need to be trained to perform this technique. Ideally, training should begin during gastroenterology fellowship. Yet, how to support the education of practicing gastroenterologists to competently perform IUS for IBD must be considered. Relatively little has been studied with respect to the IUS learning curve because much of the literature has emerged from Europe where abdominal ultrasound is often part of general internal medicine training. Because of the lack of formal ultrasound training of American gastroenterologists, it would be difficult to predict the learning curve, which may vary significantly among individuals.

Rather than basing competency on a number of procedures that should be performed, a Delphi panel of experts has developed a list of knowledge, technical, and interpretation skills that someone performing IUS should be able to execute.[85] One study that examined the learning curve for IUS compared those with experience in abdominal ultrasound (>500 exams) with those without abdominal ultrasound experience. The study found that approximately 66 IUS examinations were necessary in the inexperienced group to have agreement with a highly experienced IUS physician whereas trainees with abdominal ultrasound experience needed 33 examinations for agreement with respect to BWT, pathologic dilatation, and enlarged lymph nodes.[86] The learning curve is reasonably steep. Presumably, a higher number will be needed for true proficiency—the ability to accurately detect disease activity and complications compared with gold-standard cross-sectional imaging tools such as MRE and CTE. Informally, most experienced IUS experts think at least 200 IUS examinations are needed before beginning to achieve competency.

Compared with visualization of the liver, the evaluation of the thin, pliable, shifting walls of the intestine requires a high level of resolution by ultrasound.[87] A full explanation of the characteristics of the different frequencies and probes used for IUS is beyond the limits of this article. A high-frequency (3-11 MHz) linear probe is typically used for evaluating the intestine; a low-frequency (1-8 MHz) convex probe is generally used for a broader view of the abdomen that complements the detailed view of the intestinal wall. In general, a mid-range ($40,000-$50,000) to high-range (~$100,000) general ultrasound machine is recommended. Entry level or portable ultrasound machines ($15,000-$25,000) can also provide general, useful information but may miss smaller subtle complications. In the United States, there is no specific Current Procedural Terminology (CPT) code for IUS, and this needs to be developed as the time needed to perform and interpret the examination is better understood. Instead, billing codes and procedure codes are available for limited abdominal ultrasound (CPT 76705). Ideally, images should be captured in the electronic medical record and are required for billing hospital-based procedures. In addition, documenting findings on a report should be included in the medical record for each IUS examination performed. Reimbursement will depend on the site of service. Obtaining privileges for IUS, like with any new endoscopic procedure, should follow the guidelines of local hospital systems. Although the International Bowel Ultrasound Group has developed a curriculum for providing a certificate of completion, there is still no recognition by national gastroenterology societies in the United States for what is needed to achieve a standardized accreditation and thus credentialing within institutions to perform IUS.[88] A systematic, practical way for American gastroenterologists to adopt this technique is being developed. As more American sites perform IUS, experience with this procedure will expand.

Conclusion

IUS should be considered an extension of the physical examination in a patient with IBD. IUS as a point-of-care test during an IBD patient visit allows for the immediate ability to see if there is evidence of inflammation or

a stricture, evaluate extent of disease, and can help guide therapeutic planning for the patient. It avoids the wait for a colonoscopy, MRE, or fecal calprotectin to evaluate activity of disease. Its applications are broad, including use in children and pregnant women in whom colonoscopy and MRE are usually avoided. However, there is no ideal model for organizing IUS during IBD visits. In Europe, most centers have days dedicated to IUS but also have it available as a point-of-care test to evaluate symptoms. As more centers in the United States adopt and incorporate this technique into fellowship training, IUS will likely become a valuable tool in the treat-to-target strategy for IBD.

Disclosures

Dr Dolinger is a consultant for NeuroLogica, a subsidiary of Samsung Electronics. Dr Calabrese has received lecture fees from MSD, Janssen, Takeda, and AbbVie. Dr Pizzolante has no relevant conflicts of interest to disclose. Dr Abreu has consulted and/or served on an advisory board for AbbVie, Arena Pharmaceuticals, Bristol Myers Squibb, Celsius, Eli Lilly Pharmaceuticals, Gilead Sciences, Helmsley Charitable Trust, Janssen, Microba, Pfizer, Prometheus Biosciences, UCB Biopharma, and WebMD Global. She has done teaching, lecturing, or speaking for Alimentiv, Janssen, Prime CME, and Takeda.

References

1. Torres J, Mehandru S, Colombel J-F, Peyrin-Biroulet L. Crohn's disease. *Lancet*. 2017;389(10080):1741-1755.
2. Torres J, Billioud V, Sachar DB, Peyrin-Biroulet L, Colombel J-F. Ulcerative colitis as a progressive disease: the forgotten evidence. *Inflamm Bowel Dis*. 2012;18(7):1356-1363.
3. Le Berre C, Ananthakrishnan AN, Danese S, Singh S, Peyrin-Biroulet L. Ulcerative colitis and Crohn's disease have similar burden and goals for treatment. *Clin Gastroenterol Hepatol.* 2020;18(1):14-23.
4. Turner D, Ricciuto A, Lewis A, et al; International Organization for the Study of IBD. STRIDE-II: An update on the selecting therapeutic targets in inflammatory bowel disease (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD): determining therapeutic goals for treat-to-target strategies in IBD. *Gastroenterology.* 2021;160(5):1570-1583.
5. Ordás I, Rimola J, Alfaro I, et al. Development and validation of a simplified magnetic resonance index of activity for Crohn's Disease. *Gastroenterology*. 2019;157(2):432-439.e1.
6. Hanžel J, Jairath V, Ma C, et al. Responsiveness of magnetic resonance enterography indices for evaluation of luminal disease activity in Crohn's disease. *Clin Gastroenterol Hepatol.* 2022;20(11):2598-2606.
7. Pariente B, Mary JY, Danese S, et al. Development of the Lémann index to assess digestive tract damage in patients with Crohn's disease. *Gastroenterology.* 2015;148(1):52-63.e3.
8. Kucharzik T, Wittig BM, Helwig U, et al; TRUST study group. Use of intestinal ultrasound to monitor Crohn's disease activity. *Clin Gastroenterol Hepatol*. 2017;15(4):535-542.e2.
9. Walker GJ, Lin S, Chanchlani N, et al. Quality improvement project identifies factors associated with delay in IBD diagnosis. *Aliment Pharmacol Ther*. 2020;52(3):471-480.
10. Schoepfer A, Santos J, Fournier N, et al. Systematic analysis of the impact of diagnostic delay on bowel damage in paediatric versus adult onset Crohn's disease. *J Crohns Colitis.* 2019;13(10):1334-1342.
11. Nahon S, Lahmek P, Paupard T, et al. Diagnostic delay is associated with a greater risk of early surgery in a French cohort of Crohn's disease patients. *Dig Dis Sci.* 2016;61(11):3278-3284.
12. Friedman AB, Asthana A, Knowles SR, Robbins A, Gibson PR. Effect of point-of-care gastrointestinal ultrasound on decision-making and management in inflammatory bowel disease. *Aliment Pharmacol Ther*. 2021;54(5):652-666.
13. Castiglione F, Mainenti PP, De Palma GD, et al. Noninvasive diagnosis of small bowel Crohn's disease: direct comparison of bowel sonography and magnetic resonance enterography. *Inflamm Bowel Dis.* 2013;19(5):991-998.
14. Panés J, Bouzas R, Chaparro M, et al. Systematic review: the use of ultrasonography, computed tomography and magnetic resonance imaging for the diagnosis, assessment of activity and abdominal complications of Crohn's disease. *Aliment Pharmacol Ther*. 2011;34(2):125-145.
15. Taylor SA, Mallett S, Bhatnagar G, et al; METRIC study investigators. Diagnostic accuracy of magnetic resonance enterography and small bowel ultrasound for the extent and activity of newly diagnosed and relapsed Crohn's disease (METRIC): a multicentre trial. *Lancet Gastroenterol Hepatol.* 2018;3(8):548-558.
16. Bhatnagar G, Mallett S, Quinn L, et al. Interobserver variation in the interpretation of magnetic resonance enterography in Crohn's disease. *Br J Radiol*. 2022;95(1134):20210995.
17. Bhatnagar G, Quinn L, Higginson A, et al; METRIC study investigators. Observer agreement for small bowel ultrasound in Crohn's disease: results from the METRIC trial. *Abdom Radiol (NY).* 2020;45(10):3036-3045.
18. Lepus CA, Moote DJ, Bao S, Mosha MH, Hyams JS. Simplified magnetic resonance index of activity is useful for terminal ileal but not colonic disease in pediatric Crohn disease. *J Pediatr Gastroenterol Nutr.* 2022;74(5):610-616.
19. Bots S, Nylund K, Löwenberg M, Gecse K, Gilja OH, D'Haens G. Ultrasound for assessing disease activity in IBD patients: a systematic review of activity scores. *J Crohns Colitis*. 2018;12(8):920-929.
20. Allocca M, Craviotto V, Bonovas S, et al. Predictive value of bowel ultrasound in Crohn's disease: a 12-month prospective study. *Clin Gastroenterol Hepatol*. 2022;20(4):e723-e740.
21. Allocca M, Craviotto V, Dell'Avalle C, et al. Bowel ultrasound score is accurate in assessing response to therapy in patients with Crohn's disease. *Aliment Pharmacol Ther*. 2022;55(4):446-454.
22. Allocca M, Fiorino G, Bonovas S, et al. Accuracy of Humanitas ultrasound criteria in assessing disease activity and severity in ulcerative colitis: a prospective study. *J Crohns Colitis*. 2018;12(12):1385-1391.
23. Allocca M, Filippi E, Costantino A, et al. Milan ultrasound criteria are accurate in assessing disease activity in ulcerative colitis: external validation. *United European Gastroenterol J.* 2021;9(4):438-442.
24. Ripollés T, Poza J, Suarez Ferrer C, Martínez-Pérez MJ, Martín-Algíbez A, de Las Heras Paez B. Evaluation of Crohn's disease activity: development of an ultrasound score in a multicenter study. *Inflamm Bowel Dis*. 2021;27(1):145-154.
25. Novak KL, Nylund K, Maaser C, et al. Expert consensus on optimal acquisition and development of the international bowel ultrasound segmental activity score [IBUS-SAS]: a reliability and inter-rater variability study on intestinal ultrasonography in Crohn's disease. *J Crohns Colitis*. 2021;15(4):609-616.
26. Wang L, Xu C, Zhang Y, Jiang W, Ma J, Zhang H. External validation and comparison of simple ultrasound activity score and international bowel ultrasound segmental activity score for Crohn's disease. *Scand J Gastroenterol.* 2023;58(8):883-889.
27. Dragoni G, Gottin M, Innocenti T, et al. Correlation of ultrasound scores with endoscopic activity in Crohn's disease: a prospective exploratory study [published online April 6, 2023]. *J Crohns Colitis*. doi:10.1093/ecco-jcc/jjad068
28. Allocca M, Dell'Avalle C, Craviotto V, et al. Predictive value of Milan ultrasound criteria in ulcerative colitis: A prospective observational cohort study. *United European Gastroenterol J.* 2022;10(2):190-197.
29. Bots S, Nylund K, Löwenberg M, Gecse K, D'Haens G. Intestinal ultrasound to assess disease activity in ulcerative colitis: development of a novel UC-Ultrasound index. *J Crohns Colitis*. 2021;15(8):1264-1271.
30. Sævik F, Eriksen R, Eide GE, Gilja OH, Nylund K. Development and validation of a simple ultrasound activity score for Crohn's disease. *J Crohns Colitis*. 2021;15(1):115-124.
31. Castiglione F, Testa A, Rea M, et al. Transmural healing evaluated by bowel sonography in patients with Crohn's disease on maintenance treatment with biologics. *Inflamm Bowel Dis*. 2013;19(9):1928-1934.
32. Castiglione F, Imperatore N, Testa A, et al. One-year clinical outcomes with biologics in Crohn's disease: transmural healing compared with mucosal or no healing. *Aliment Pharmacol Ther.* 2019;49(8):1026-1039.
33. Fernandes SR, Rodrigues RV, Bernardo S, et al. Transmural healing is associated with improved long-term outcomes of patients with Crohn's disease. *Inflamm*

Bowel Dis. 2017;23(8):1403-1409.
34. Paredes JM, Ripollés T, Cortés X, et al. Abdominal sonographic changes after antibody to tumor necrosis factor (anti-TNF) alpha therapy in Crohn's disease. *Dig Dis Sci*. 2010;55(2):404-410.
35. Paredes JM, Moreno N, Latorre P, et al. Clinical impact of sonographic transmural healing after anti-TNF antibody treatment in patients with Crohn's disease. *Dig Dis Sci.* 2019;64(9):2600-2606.
36. Calabrese E, Rispo A, Zorzi F, et al. Ultrasonography tight control and monitoring in Crohn's disease during different biological therapies: a multicenter study. *Clin Gastroenterol Hepatol.* 2022;20(4):e711-e722.
37. Kucharzik T, Wilkens R, D'Agostino MA, et al. Early ultrasound response and progressive transmural remission after treatment with ustekinumab in Crohn's disease. *Clin Gastroenterol Hepatol*. 2023;21(1):153-163.e12.
38. Sagami S, Kobayashi T, Miyatani Y, et al. Accuracy of ultrasound for evaluation of colorectal segments in patients with inflammatory bowel diseases: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2021;19(5):908-921.e6.
39. Sagami S, Kobayashi T, Aihara K, et al. Transperineal ultrasound predicts endoscopic and histological healing in ulcerative colitis. *Aliment Pharmacol Ther*. 2020;51(12):1373-1383.
40. Parente F, Molteni M, Marino B, et al. Are colonoscopy and bowel ultrasound useful for assessing response to short-term therapy and predicting disease outcome of moderate-to-severe forms of ulcerative colitis?: a prospective study. *Am J Gastroenterol*. 2010;105(5):1150-1157.
41. Maaser C, Petersen F, Helwig U, et al; German IBD Study Group and the TRUST&UC study group. Intestinal ultrasound for monitoring therapeutic response in patients with ulcerative colitis: results from the TRUST&UC study. *Gut*. 2020;69(9):1629-1636.
42. de Voogd F, van Wassenaer EA, Mookhoek A, et al. Intestinal ultrasound is accurate to determine endoscopic response and remission in patients with moderate to severe ulcerative colitis: a longitudinal prospective cohort study. *Gastroenterology*. 2022;163(6):1569-1581.
43. Ripollés T, Paredes JM, Martínez-Pérez MJ, et al. Ultrasonographic changes at 12 weeks of anti-TNF drugs predict 1-year sonographic response and clinical outcome in Crohn's disease: a multicenter study. *Inflamm Bowel Dis*. 2016;22(10):2465-2473.
44. Zorzi F, Ghosh S, Chiaramonte C, et al. Response assessed by ultrasonography as target of biological treatment for Crohn's disease. *Clin Gastroenterol Hepatol*. 2020;18(9):2030-2037.
45. Vaughan R, Tjandra D, Patwardhan A, et al. Toward transmural healing: sonographic healing is associated with improved long-term outcomes in patients with Crohn's disease. *Aliment Pharmacol Ther*. 2022;56(1):84-94.
46. Calabrese E, Zorzi F, Lolli E, Pallone F. Positioning ultrasonography into clinical practice for the management of Crohn's disease. *Gastroenterol Hepatol (N Y)*. 2015;11(6):384-390.
47. Serra C, Menozzi G, Labate AM, et al. Ultrasound assessment of vascularization of the thickened terminal ileum wall in Crohn's disease patients using a low-mechanical index real-time scanning technique with a second generation ultrasound contrast agent. *Eur J Radiol.* 2007;62(1):114-121.
48. Migaleddu V, Scanu AM, Quaia E, et al. Contrast-enhanced ultrasonographic evaluation of inflammatory activity in Crohn's disease. *Gastroenterology*. 2009;137(1):43-52.
49. Ripollés T, Martínez MJ, Paredes JM, Blanc E, Flors L, Delgado F. Crohn disease: correlation of findings at contrast-enhanced US with severity at endoscopy. *Radiology.* 2009;253(1):241-248.
50. Ripollés T, Martínez-Pérez MJ, Paredes JM, Vizuete J, García-Martínez E, Jiménez-Restrepo DH. Contrast-enhanced ultrasound in the differentiation between phlegmon and abscess in Crohn's disease and other abdominal conditions. *Eur J Radiol.* 2013;82(10):e525-e531.
51. Calabrese E, La Seta F, Buccellato A, et al. Crohn's disease: a comparative prospective study of transabdominal ultrasonography, small intestine contrast ultrasonography, and small bowel enema. *Inflamm Bowel Dis.* 2005;11:139-145.
52. Calabrese E, Maaser C, Zorzi F, et al. Bowel ultrasonography in the management of Crohn's disease. A review with recommendations of an international panel of experts. *Inflamm Bowel Dis.* 2016;22(5):1168-1183.
53. Parente F, Greco S, Molteni M, et al. Oral contrast enhanced bowel ultrasonography in the assessment of small intestine Crohn's disease. A prospective comparison with conventional ultrasound, x ray studies, and ileocolonoscopy. *Gut*. 2004;53(11):1652-1657.
54. Calabrese E, Petruzziello C, Onali S, et al. Severity of postoperative recurrence in Crohn's disease: correlation between endoscopic and sonographic findings. *Inflamm Bowel Dis.* 2009;15(11):1635-1642.
55. Maaser C, Sturm A, Vavricka SR, et al; European Crohn's and Colitis Organisation [ECCO] and the European Society of Gastrointestinal and Abdominal Radiology [ESGAR]. ECCO-ESGAR Guideline for Diagnostic Assessment in IBD Part 1: initial diagnosis, monitoring of known IBD, detection of complications. *J Crohns Colitis.* 2019;13(2):144-164.
56. Horsthuis K, Bipat S, Bennink RJ, Stoker J. Inflammatory bowel disease diagnosed with US, MR, scintigraphy, and CT: meta-analysis of prospective studies. *Radiology*. 2008;247(1):64-79.
57. Dong J, Wang H, Zhao J, et al. Ultrasound as a diagnostic tool in detecting active Crohn's disease: a meta-analysis of prospective studies. *Eur Radiol*. 2014;24(1):26-33.
58. Liu W, Liu J, Xiao W, Luo G. A diagnostic accuracy meta-analysis of CT and MRI for the evaluation of small bowel Crohn disease. *Acad Radiol*. 2017;24(10):1216-1225.
59. Greenup AJ, Bressler B, Rosenfeld G. Medical imaging in small bowel Crohn's disease-computer tomography enterography, magnetic resonance enterography, and ultrasound: "Which one is the best for what?". *Inflamm Bowel Dis.* 2016;22(5):1246-1261.
60. Rieder F, Zimmermann EM, Remzi FH, Sandborn WJ. Crohn's disease complicated by strictures: a systematic review. *Gut*. 2013;62(7):1072-1084.
61. Chen YJ, Mao R, Li XH, et al. Real-time shear wave ultrasound elastography differentiates fibrotic from inflammatory strictures in patients with Crohn's disease. *Inflamm Bowel Dis.* 2018;24(10):2183-2190.
62. Bhatnagar G, Rodriguez-Justo M, Higginson A, et al. Inflammation and fibrosis in Crohn's disease: location-matched histological correlation of small bowel ultrasound features. *Abdom Radiol (NY)*. 2021;46(1):144-155.
63. Allocca M, Fiorino G, Bonifacio C, Peyrin-Biroulet L, Danese S. Noninvasive multimodal methods to differentiate inflamed vs fibrotic strictures in patients with Crohn's disease. *Clin Gastroenterol Hepatol.* 2019;17(12):2397-2415.
64. Lu C, Gui X, Chen W, Fung T, Novak K, Wilson SR. Ultrasound shear wave elastography and contrast enhancement: effective biomarkers in Crohn's disease strictures. *Inflamm Bowel Dis.* 2017;23(3):421-430.
65. Săftoiu A, Gilja OH, Sidhu PS, et al. The EFSUMB guidelines and recommendations for the clinical practice of elastography in non-hepatic applications: update 2018. *Ultraschall Med.* 2019;40(4):425-453.
66. Dillman JR, Stidham RW, Higgins PD, et al. Ultrasound shear wave elastography helps discriminate low-grade from high-grade bowel wall fibrosis in ex vivo human intestinal specimens. *J Ultrasound Med*. 2014;33(12):2115-2123.
67. Stidham RW, Xu J, Johnson LA, et al. Ultrasound elasticity imaging for detecting intestinal fibrosis and inflammation in rats and humans with Crohn's disease. *Gastroenterology.* 2011;141(3):819-826.e1.
68. Baumgart DC, Müller HP, Grittner U, et al. US-based real-time elastography for the detection of fibrotic gut tissue in patients with stricturing Crohn disease. *Radiology.* 2015;275(3):889-899.
69. Fraquelli M, Colli A, Casazza G, et al. Role of US in detection of Crohn disease: meta-analysis. *Radiology*. 2005;236(1):95-101.
70. Quaia E, Gennari AG, van Beek EJR. Differentiation of inflammatory from fibrotic ileal strictures among patients with Crohn's disease through analysis of time-intensity curves obtained after microbubble contrast agent injection. *Ultrasound Med Biol*. 2017;43(6):1171-1178.
71. Tandon P, Leung K, Yusuf A, Huang VW. Noninvasive methods for assessing inflammatory bowel disease activity in pregnancy: a systematic review. *J Clin Gastroenterol*. 2019;53(8):574-581.
72. Jha AK, Chaudhary M, Dayal VM, et al. Optimal cut-off value of fecal calprotectin for the evaluation of ulcerative colitis: an unsolved issue? *JGH Open*. 2018;2(5):207-213.
73. Julsgaard M, Hvas CL, Gearry RB, et al. Fecal calprotectin is not affected by pregnancy: clinical implications for the management of pregnant patients with inflammatory bowel disease. *Inflamm Bowel Dis*. 2017;23(7):1240-1246.
74. De Voogd F, Wilkens R, Gecse K, et al. A reliability study: strong inter-observer agreement of an expert panel for intestinal ultrasound in ulcerative colitis. *J Crohns Colitis*. 2021;15(8):1284-1290.
75. De Voogd F, Joshi H, Van Wassenaer E, Bots S, D'Haens G, Gecse K. Intestinal ultrasound to evaluate treatment response during pregnancy in patients with inflammatory bowel disease. *Inflamm Bowel Dis*. 2022;28(7):1045-1052.
76. Leung Y, Shim HH, Wilkens R, et al. The role of bowel ultrasound in detecting subclinical inflammation in pregnant women with Crohn's disease. *J Can Assoc Gastroenterol.* 2019;2(4):153-160.
77. Ryan JM, Rogers AC, O'Toole A, Burke JP. Meta-analysis of histological margin positivity in the prediction of recurrence after Crohn's resection. *Dis Colon*

Rectum. 2019;62(7):882-892.
78. Torres J, Bonovas S, Doherty G, et al. ECCO guidelines on therapeutics in Crohn's disease: medical treatment. *J Crohns Colitis*. 2020;14(1):4-22.
79. Celentano V, Beable R, Ball C, et al. The Portsmouth protocol for intra-operative ultrasound of the small bowel in Crohn's disease. *Colorectal Dis*. 2020;22(3):342-345.
80. Viganò L, Mineccia M, Bertolino F, et al. Intraoperative ultrasonography in patients undergoing surgery for Crohn's disease. Prospective evaluation of an innovative approach to optimize staging and treatment planning. *Updates Surg*. 2019;71(2):305-312.
81. Danese S, Semeraro S, Papa A, et al. Extraintestinal manifestations in inflammatory bowel disease. *World J Gastroenterol*. 2005;11(46):7227-7236.
82. Kristensen SL, Ahlehoff O, Lindhardsen J, et al. Disease activity in inflammatory bowel disease is associated with increased risk of myocardial infarction, stroke and cardiovascular death—a Danish nationwide cohort study. *PLoS One*. 2013;8(2):e56944.
83. Yarur AJ, Czul F, Levy C. Hepatobiliary manifestations of inflammatory bowel disease. *Inflamm Bowel Dis*. 2014;20(9):1655-1667.
84. Broomé U, Bergquist A. Primary sclerosing cholangitis, inflammatory bowel disease, and colon cancer. *Semin Liver Dis.* 2006;26(1):31-41.
85. Madsen GR, Wilkens R, Boysen T, et al. The knowledge and skills needed to perform intestinal ultrasound for inflammatory bowel diseases—an international Delphi consensus survey. *Aliment Pharmacol Ther.* 2022;56(2):263-270.
86. Bezzio C, Furfaro F, Monteleone M, et al. The learning curve of bowel ultrasonography (US) in assessing inflammatory bowel diseases. Preliminary results. *Dig Liver Dis.* 2013;45:S150. Abstract P.08.20.
87. Sheridan MB, Nicholson DA, Martin DF. Transabdominal ultrasonography as the primary investigation in patients with suspected Crohn's disease or recurrence: a prospective study. *Clin Radiol.* 1993;48(6):402-404.
88. Dolinger MT, Cleveland NK, Rubin DT, Dubinsky MC. Guide to intestinal ultrasound credentialing, documentation, and billing for gastroenterologists in the United States [published online May 2, 2023]. *Am J Gastroenterol*. doi:10.14309/ajg.0000000000002253.