

Point-of-care ultrasound in Inflammatory Bowel Disease

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Abstract

Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are chronic, relapsing and destructive inflammatory disorders of the gastrointestinal tract which can lead to organ damage and impair quality of life. A “treat-to-target” strategy based on activity and severity of disease and response to treatment with close monitoring of intestinal inflammation is recommended. Ileocolonoscopy (CS) is considered the first line procedure for the assessment of IBD, and magnetic resonance enterography (MRE) is the current standard for assessing the small bowel and complications in CD, and has been proposed as an alternative procedure to CS in the evaluation of both ileo-colonic CD and ulcerative colitis. Considering that both CS and MRE are invasive and expensive procedures and unappealing to patients, they are unfeasible as frequent and repetitive tools for the monitoring of disease activity.

Bowel ultrasound (US) represents a well-tolerated, non-invasive and cost-effective modality to manage IBD patients in clinical practice. Compared to CS and MRE, bowel US has shown to have the same level of accuracy in assessing and monitoring disease activity and severity of both CD and UC. It can be performed at the point-of-care and therefore allow for real-time clinical decision-making.

Point-of-care ultrasound (POCUS) is suggested as the stethoscope of the future and is gaining interest and diffusion in the medical field because it can be used for the bedside examination of patients.

The aim of this review is to discuss point-of-care bowel ultrasound (POCBUS) in the management of patients with IBD.

Keywords: Inflammatory bowel disease, bowel US, point-of-care ultrasound

Introduction

Inflammatory bowel diseases (IBD), such as Crohn's disease (CD) and ulcerative colitis (UC), are chronic, relapsing and destructive inflammatory disorders of the gastrointestinal tract which can lead to organ damage and impair quality of life^{1, 2}. Ileocolonoscopy (CS) is the first line procedure for the assessment of IBD^{3,4}. However, CS has several drawbacks that must be taken into account: it is not capable of reaching the ileum in up to 15% of patients⁵, with an increased risk of complications and surgery⁶; it is an invasive procedure with a risk of bowel perforation⁷; it causes discomfort and repeated colonoscopies are not well accepted by patients^{8,9}. Furthermore, CD is a progressive, destructive transmural disease leading to extra-visceral lesions (fistulas, strictures, abscesses, mesenteric fat involvement, nodes enlargement) which are not visible on CS¹⁰. Magnetic resonance enterography (MRE) is the current standard for assessing the small bowel disease activity and complications in CD⁴, and recently has been proposed as an alternative procedure to CS in the evaluation of both ileo-colonic CD and UC patients^{11,12}. Nevertheless, MRE is an invasive, time-consuming technique, poorly tolerated by patients, along with limitations to its access.

A “treat-to-target” strategy based on activity and severity of disease and response to treatment with close monitoring of intestinal inflammation is recommended in IBD¹³. However, the invasiveness and poor tolerability of CS and MRE render both techniques unfeasible as tools for the frequent and repetitive monitoring of disease activity.

Bowel ultrasound (US) is a non-invasive technique which does not require specific preparation and contrast media, it is well-tolerated and much cheaper than MRE or CS, and it has shown to be accurate and useful for the management of IBD patients^{9,14,15}. An additional value is its ability to be performed in real time. Point-of-care ultrasound (POCUS) is suggested as the stethoscope of the future¹⁶ and is gaining growing interest and diffusion in the medical field for its use by clinicians for bedside

examination of patients ¹⁷. The concept is that POCUS may lead to early and improved diagnosis ¹⁸.

Accordingly, POCUS has been included in the training program in several medical schools ¹⁹.

The aim of this review is to discuss point-of-care bowel ultrasound (POCBUS) in the management of patients with IBD.

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Methods

We performed a comprehensive review of the literature available on this topic. The literature search terms included “Crohn’s disease” OR “inflammatory bowel disease” OR “IBD” OR “colitis” OR “ulcerative colitis” combined with “ultrasound” OR “bowel ultrasound” OR “point-of-care ultrasound” OR “imaging” OR “non-invasive” OR “ultrasonography” OR “sonography”. We also searched ClinicalTrials.gov and bibliographies of relevant review articles. All relevant papers in English from EMBASE, Ovid, PubMed, Scopus databases were also reviewed.

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Results

Bowel ultrasound: technical aspects

Bowel US does not usually require a specific oral preparation or oral/intravenous contrast. The entire abdomen is systematically scanned through the use of different-frequency probes. Convex probes, at low frequency (5-1 MHz), provide a panoramic view; linear or microconvex probes, with higher frequency (4-8 MHz), produce a high-resolution image and allow for a detailed bowel wall visualization, showing the five-layer pattern. The bowel wall layers are, from the bowel lumen: the interface between the mucosa and the bowel lumen (hyperechoic layer), the deep mucosa (hypoechoic layer), the submucosa (hyperechoic layer), the muscularis propria (hypoechoic layer) and the serosa (hyperechoic layer). Several parameters are evaluated during bowel ultrasound examination^{9,17,20}

- bowel wall thickening (BWT), represented by the distance between the interface mucosa-lumen (hyperechoic layer) and the interface serosa-muscle layer (hyperechoic layer);
- bowel wall pattern (BWP), normally multilayered, in case of intestinal disease it can be focally disrupted, extensively disrupted or lost;
- bowel wall flow (BWF), defined by the presence of vascular signals detected by color or power Doppler with special presets for slow flow. The Limberg score is a semi-quantitative score frequently used for grading the BWF²¹: grade 1 is defined by a thickened bowel wall without vascular signals; grade 2 by the presence of short stretches of vascularity; grade 3 by the presence of longer stretches of vascularity; grade 4 by vascular signals extending into the surrounding mesentery;
- ulcers, represented by depressions in the mucosal layer;
- strictures, represented by a wall thickening with a narrowed lumen, with or without dilatation of the proximal loop;

- fistula, represented by an hypoechoic tract with or without hyperechoic content;
- abscess, represented by an anechoic lesion with an irregular wall, without vascular signals at color Doppler;
- inflammatory mass, represented by an irregular hypoechoogenic lesion, with vascular signals at color Doppler;
- loss of colonic hastration;
- loss of intestinal motility;
- presence of free fluid in the peritoneal cavity;
- enlarged mesenteric lymph nodes;
- mesenteric hypertrophy, represented by the presence of a hyperechoic area surrounding the pathologic intestinal tract.

The measurement of BWT is the most important parameter to assess the presence of CD. Using a BWT cut-off of 3 mm, sensitivity and specificity are 88 and 93%, with a cut-off level of 4 mm, sensitivity and specificity are 75 and 97% respectively²². The use of contrast media, intravenous (contrast-enhanced US: CEUS) or oral, in general 200–500 mL of a hyperosmolar luminal polyethylene-glycol solution (small intestine contrast US: SICUS), have been proposed to increase the accuracy of bowel US in CD^{23, 24, 25}. However, the routine use of contrast media can increase the duration, the invasiveness and the complexity of the procedure and limit its application in everyday clinical practice.

POCUS: lessons from non-inflammatory bowel disease conditions

POCUS is a safe and rapidly evolving diagnostic technique currently used by health care professionals from nearly all specialties. Technological advancements have led to the development of increasingly mobile and miniaturized equipment which allow for ultrasound imaging at the bedside with real-time diagnoses and guidance for clinical-decision making^{18 26}. Considered as the future stethoscope (steth=

chest, scope= to look in), POCUS is able to create high-quality images reflecting the structure and function of organs^{16, 18}. The poor diagnostic accuracy of traditional bedside physical examination tools has reduced their clinical relevance within internal medicine for several years. Many cardiopulmonary abnormalities, such as pericardial fluid, left ventricular systolic dysfunction, pleural effusion, can be missed by physical examination. On the contrary, POCUS is capable of detecting such abnormalities with a sensitivity and specificity of up to 90%¹⁸. Adding POCUS to clinical history and physical examination helps to narrow down differential diagnosis and to plan work-up and treatment²⁷. Clinical management driven from the early use of POCUS increases physician diagnostic accuracy and improves health care resource utilization²⁸. In addition, from a patient point of view, POCUS is very well tolerated and patients prefer to be assessed with POCUS rather than with endoscopic procedures or other more invasive imaging techniques²⁹. Some POCUS protocols based on an algorithmic approach are utilized: BLUE (Bedside Lung Ultrasound in Emergency) for acute respiratory failure; FAST (Focused Assessment with Sonography in Trauma) for peritoneal free fluid; RUSH (Rapid Ultrasound for Shock and Hypotension); CLUE (Cardiovascular Limited Ultrasound Examination) for heart failure¹⁸. POCUS is a strategic tool that in skilled hands can guide clinical decision-making in real time.

Point-of-care bowel ultrasound in the management of Crohn's disease

Bowel ultrasound for assessing activity and complications in CD patients

Five systematic reviews compared diagnostic accuracy of different imaging techniques for assessment of CD^{23,30-33}. Bowel US demonstrated comparable accuracy to CTE and MRE. In particular, sensitivity and specificity of bowel US for assessment of activity was 85 and 91% (vs 81 and 88% for CTE and 80 and 82% for MRE) and for the assessment of complications, all three imaging techniques showed a

sensitivity and specificity of more than 80%³¹. Bowel US was compared to MRE for the assessment of bowel damage (with the use of Lémann index). A high concordance between the two techniques ($r=0.9$, $p < 0.001$) was found³⁴.

A recent meta-analysis showed that bowel US is also accurate for the detection of post-surgical recurrence, sensitivity 0.94 (95% CI 0.86-0.97), specificity 0.84 (95% CI 0.62-0.94), and identified a BWT value ≥ 5.5 mm as a predictor of severe post-surgical recurrence (defined by a Rutgeerts score ≥ 3) with a sensitivity of 84% and a specificity of 98%³⁵.

Most of the included studies in the systematic reviews and in the meta-analysis are single-centre, have a small sample size and only in a few prospective studies were there direct comparisons between different imaging techniques, using high-quality reference standards³⁶⁻⁴⁰.

The METRIC study, a prospective UK multicenter trial enrolling 284 CD patients, showed that both bowel US and MRE had an accuracy $> 90\%$ for detecting small bowel CD. Sensitivity and specificity were significantly greater for MRE, with a 10% and 14% difference for extent ($p=0.02$; $p=0.03$), and a 5 and 12% difference for presence ($p=0.02$; $p=0.05$)⁴¹, however the practitioners were not gastroenterologists with expertise and skills on the use of bowel US in IBD^{14, 42}.

Finally, a recent study compared bowel US accuracy in assessing disease activity and complications in CD patients to MRE + CS together. The sensitivity and the specificity of bowel US for the localization of CD were 88% and 96% and the sensitivity and specificity for disease activity (defined by the presence of ulcers at the CS) were 92% and 100%. In addition, a good concordance of management of CD patients (continuing or changing/optimizing therapy) based on bowel US alone, compared to the clinician's decision (based on clinical parameters, biomarker values, CS and MRE findings), was found ($k 0.768$, $p < 0.001$)⁴³, showing the advantage of bowel US in driving clinical decision-making in real time.

Bowel US can therefore be a good alternative to more invasive and expansive imaging techniques, of which it has similar accuracy. Besides being quick and readily available, bowel US provides answers in real-time and allows for early clinical decision-making in routine IBD care⁴².

Bowel ultrasound for monitoring CD patients

POCBUS is a cost-effective, non-invasive and easily accessible imaging modality. The routine use of POCBUS has led to modifications in the management strategy in up to 60% of patients with CD⁴².

Fig. 1. shows POCBUS of a CD patient treated with biological therapy who developed an enteromesenteric fistula.

Bowel US + CEUS showed an accuracy of 86% in predicting MH with an AUROC (area under the Receiver Operating Characteristic) curve of 0.87. BWT < 3 mm was the best predictor of MH (96%)⁴⁴.

A prospective multicenter study enrolling 51 patients with active CD starting anti-TNF therapy, demonstrated that an ultrasonographic response at 12 weeks (at least 2 mm-decrease of BWT, 1-grade decrease of BWF, 20%-decrease of the mural enhancement after contrast injection and/or disappearance of extramural complications) predicted an ultrasonographic response at 52 weeks ($p < 0.0001$). Patients who did not display ultrasonographic improvement at one year had a worse outcome (change of treatment or surgery) in the following year (13/20 (65%) versus 3/28 (11%), $p = 0.0001$)⁴⁵.

Recently, Ripollés et al., found that BWF > 1 and CEUS (percentage of increase of parietal enhancement after contrast injection $\geq 47\%$) had the same predictive positive value (PPV) for detecting ulcers at colonoscopy (97% vs 100%)⁴⁶, suggesting that CEUS should be used only in very selected cases.

Thirty-six out of 80 CD patients (51%) treated with anti-TNF therapy for at least one year, and considered responders at SICUS (defined by improvement of all individual lesions found at baseline

SICUS), were at lower risk of surgery, hospitalization and need for steroids ($p < 0.0001$, $p = 0.003$ and $p = 0.0001$, respectively) compared to SICUS-non responders after a median time of 18 months⁴⁷.

Considering the transmural nature of CD, recently it has been suggested that transmural healing (TH), defined as the normalization of BWT, could be a goal of treatment which is more accurate than MH alone^{48, 49, 50 51}. CD patients (31% out of 218) with TH (BWT ≤ 3 mm at bowel US) (plus MH) after two years of biologic therapy, were at lower risk of clinical relapse (hazard ratio (HZ) 0.87, $p = 0.01$), hospitalisation (HR 0.88, $p = 0.002$) and surgery (HR 0.94, $p = 0.008$) in the following year, compared to patients with mucosal healing alone (27% out of 218)⁵¹.

The utility of bowel US for monitoring disease activity and response to treatment was further demonstrated by the TRUST study, a 12-month multicenter (47 IBD centers) study, enrolling 234 CD active patients (Harvey-Bradshaw index score ≥ 7). Bowel US was performed at the beginning of treatment and at fixed time intervals (3, 6 and 12 months). Ultrasonographic parameters, including BWT, BWP, BWF, presence of mesenteric lymph nodes, mesenteric hypertrophy and strictures, improved significantly at all time intervals versus baseline ($p < 0.005$). The most substantial changes were at 3 months. Pre-stenotic dilatation, fistulae and ascites improved significantly at 12 months ($p < 0.05$). There was a significant correlation between improvement in BWT and drop in C-reactive protein (CRP) levels at 3 months ($p \leq 0.001$)⁵².

A study assessing the early changes in bowel US parameters in CD patients treated with ustekinumab and exploring the correlation of bowel US response and remission with endoscopic and clinical outcomes during 48 weeks of treatment is ongoing (ultrasound sub-study of CNT01275CRD3005) (<https://clinicaltrials.gov/ct2/show/NCT03107793?term=CNT01275CRD3005&cond=Crohn+Disease&rank=1>). Week 16 results were presented at ECCO 2020. BWT improved significantly already at week 4 ($p = 0.0002$). Moderate-substantial agreement was found between bowel US response ($> 25\%$ reduction in BWT versus baseline) at week 4 and clinical remission, improvement of biomarkers (CRP

and fecal calprotectin) and SES-CD scores at week 16 ([https://doi.org/10.1016/S0016-5085\(20\)30833-7](https://doi.org/10.1016/S0016-5085(20)30833-7)).

To assess ultrasonographic disease activity, several ultrasonographic activity scores have been proposed, but methodology used in most of these studies was sub-optimal⁵³. Novak et al., retrospectively reviewed bowel US and colonoscopy data of 160 patients with CD. They found a significant correlation between both BWT and BWF with disease activity ($p<0.0001$ and $p=0.0292$, respectively). These weighted variables were used to devise an ultrasonographic score which was subsequently validated in a prospective cohort⁵⁴. However, there are some methodological issues to take into account: due to retrospective nature of the study, the procedures were not performed in a blinded fashion, the choice of SES-CD cut-off value for distinguishing active from inactive disease was arbitrary ($\text{SEC-CD} > 5$), and 7 UC patients were included. Studies aiming to develop a reliable and reproducible bowel US activity index, using CS+MRE as reference standards are imperative.

Point-of-care bowel ultrasound in the management of ulcerative colitis

Sensitivity and specificity of bowel US in assessing colonic inflammation were 90% and 96% per-patient analysis, and 74% and 93% per-segment analysis, respectively³⁰. Maconi et al., in a small study suggested that bowel US could be a valuable tool for monitoring the response to treatment. BWT correlated significantly with disease activity and decreased significantly in patients who improved after two months of treatment (7.3 ± 1.9 mm versus 5.0 ± 1.2 mm, $p < 0.001$), while it did not change in patients who did not improve or worsen (7.0 ± 1.9 mm versus 7.7 ± 1.1 mm)⁵⁵. A retrospective study confirmed the correlation of BWT with CRP values and Mayo endoscopic sub-score ($p= 0.0001$; $p < 0.0001$)⁵⁶. Parente et al., showed that a severe score of bowel US (defined by a BWT > 6 mm and presence of BWF) at three months from the beginning of therapy in 74 moderate-to-severe UC patients, was predictor of severe endoscopic activity at 15 months (according to Baron score) (odds ratio, OR

9.1, 95% CI 2.5-33.5)⁵⁷. Recently, non-invasive quantitative criteria (Humanitas ultrasound criteria (HUC) of disease activity based on bowel US findings were developed. Fifty-three UC patients performed bowel US and CS in a blinded way, within one week, irrespective of disease activity. 22 patients were in endoscopic remission (defined as Mayo endoscopic sub-score 0-1), 31 were in endoscopic activity (defined as Mayo endoscopic sub-score 2-3). Colonic wall thickness (BWT), colonic wall flow (BWF), hypoechogenic colonic wall pattern (BWP) and the presence of lymph nodes, all correlated significantly with endoscopic activity ($p < 0.05$). At multivariable analysis, only BWT (per 1-mm increase, OR: 4.05, 95% CI: 1.37-11.9, $p = 0.01$) and BWF (OR: 7.99, 95% CI: 0.67-94.4, $p = 0.09$) were independent predictors for endoscopic activity. The coefficients of BWT and BWF were used to develop quantitative ultrasound-based criteria to identify patients with endoscopic activity. The HUC developed were: (i) the presence of a BWF, and BWT > 3 mm, or (ii) the absence of a BWF, and BWT > 4.43 mm. These criteria showed high accuracy for the detection of endoscopic activity (sensitivity 0.71, specificity 1.00, AUROC 0.891 (95% CI 0.775 to 0.959)⁹. External validation of HUC is ongoing. A longitudinal, multicenter, prospective study in 224 UC patients starting therapy for a flare (Short Clinical Colitis Activity (SCCAI) > 5 points) was performed in order to evaluate the usefulness of bowel US in monitoring response to treatment. Both BWT and BWF decreased significantly already at two weeks from the start of the treatment ($p < 0.001$). Normalization of BWT (< 4 mm for sigmoid colon, < 3 mm for the other colonic segments) correlated significantly with clinical response (decrease in SCCAI by > 3 points versus baseline) at week 12 ($p < 0.001$)⁵⁸. **Fig. 2.** shows bowel US of a UC patient with a partial response to biological therapy.

In summary bowel US can be used for assessing and monitoring disease activity and response to treatment in UC. HUC are easy and practical in detecting endoscopic activity. Larger studies aiming at validating and evaluating the response to treatment of bowel US scores are needed.

Discussion

Bowel US is strategic in the management of IBD (**Table 1**). It is a non-invasive, cost-effective, and readily available tool which can be repeatedly performed in real-time at the bedside. (**Fig. 3.**). In the era of “treat-to-target” with the need of providing close monitoring to patients, it can be a valuable alternative to CS+MRE, by providing a non-invasive, objective assessment of inflammation in real time. Bowel US has shown to be accurate in assessing both disease activity and complications in IBD^{4,9,20,30,59}, and to have a significant impact on driving clinical decision-making in routine IBD care^{42,43}. The HUC are easy and practical criteria with a specificity of 100% for disease activity in UC⁹.

Bowel US at the point of care is an effective tool to optimize and expedite management of IBD patients with minimal additional time, costs or patient inconvenience⁶⁰ (**Table 2**). POCBUS has been shown to have a sensitivity of 80%-90% and a specificity of 94%-98% in properly discriminating inflammatory from non-inflammatory diseases in patients with abdominal symptoms⁶¹. In addition, it has led to the modification of treatment strategies in more than 60% of the patients with a known diagnosis of CD⁴². The current goal of treatment in IBD is endoscopic MH¹³. However, MH is only a surrogate marker for intestinal healing, which does not take into account the layers under the mucosa. Both histological remission and TH may be more accurate treatment targets rather than MH alone^{49,62, 51}. A nationwide survey of patients with IBD showed that CS had the lowest acceptability among the IBD monitoring tools, on the contrary bowel US was the most acceptable tool (visual analog scale (VAS)= 4.4 (1.2-7.3) vs 9.3 (8.7-9.7), p < 0.0001). MRE was more acceptable than CS (VAS= 8.0 (5.0-9.2), p < 0.0001) but less than bowel US⁸. Acceptability of bowel US is high not only because it is a fast, non-invasive procedure which does not require any preparation, but also for the doctor-patient relationship that occurs during the examination⁴³.

Beside the established role of ultrasound-based techniques in assessing disease activity, severity, and complications in IBD patients, bowel US is still not widely used as expected. This is probably due to

the following reasons: first, in several countries, US is still part of the radiologist expertise, but it is not yet integrated in the training program of gastroenterologists in medical schools. To overcome this limitation, some international groups such as the International Bowel Ultrasound Group (IBUS) has proposed the first internationally recognized curriculum for learning bowel US (www.ibus-group.org). Second: the common perception of the medical community is that US is highly operator-dependent^{31,59,63}. Actually, some studies on inter-observer variability found a fairly-good agreement for most bowel US parameters^{64,65,66}, not higher than variability found for other diagnostic procedures. The use of standardized protocols, international performance and training standards in bowel US may overcome these limitation⁶⁷. Third: the variety of healthcare reimbursement policies can strengthen or weaken the role of US in the management of IBD. In those countries where public healthcare systems are strong enough, the use of US is encouraged because significantly cheaper than other cross-sectional imaging, whereas in those countries where reimbursement comes from private insurance companies, the use of US is still limited. Therefore, more data on cost-benefit ratio of bowel US are needed to encourage the use of US in these systems.

In conclusion, bowel US is a valuable, easy tool, which allows better management of IBD patients in clinical practice. It can be performed at the point of care to expedite clinical decision-making and to optimize management of patients with IBD. **Fig. 4.** shows a proposed flow-chart for the use of bowel US in the monitoring of IBD. Finally, to facilitate integration of bowel US in clinical practice, a coordinated approach both at the national and international level is required incorporating identifiable international performance and training standards in bowel US.

Conflict of Interest

MA received consulting fees from Nikkiso Europe and lecture fees from Janssen, Abbvie and Pfizer; FF received consulting fees form Amgen, Abbvie and lecture fees from Janssen and Pfizer; GF as a consultant and a member of Advisory Boards for MSD, Takeda Pharmaceuticals, AbbVie, Pfizer, Celltrion, Amgen, Sandoz, Samsung, and Janssen Pharmaceuticals LP-B reports personal fees from Merck, Abbvie, Janssen, Genentech, Mitsubishi, Ferring, Norgine, Tillots, Vifor, Hospira/Pfizer, Celltrion, Takeda, Biogaran, Boehringer-Ingelheim, Lilly, HAC-Pharma, Index Pharmaceuticals, Amgen, Sandoz, Forward Pharma GmbH, Celgene, Biogen, Lycera, and Samsung Biosepsis; SD reports personal fees from Abbvie, Ferring, Hospira, Johnson & Johnson, Merck, Millennium Takeda, Mundipharma, Pfizer, Tigenix, UCB Pharma, and Vifor.

Author contributions

Mariangela Allocca conceived and designed the study; Mariangela Allocca, Gionata Fiorino and Federica Furfaro drafted the manuscript; Laurent Peyrin-Biroulet and Silvio Danese critically revised the manuscript; all Authors approved the final version of the manuscript.

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Figure legends

Fig. 1. Patient with colonic Crohn's disease in therapy with infliximab+azathioprine for three months.

Point-of-care bowel ultrasound (POCBUS) led to the interruption of therapy and the planning of a multidisciplinary team with surgeons in real time. (A) Descending colon with bowel wall thickening (5.5 mm) and focal disruption of echostratification. The arrow indicates ulcer. (B) Transverse colon with bowel wall thickening (6.5 mm) and loss of normal bowel wall pattern. The double arrow indicates stenotic lumen. (C-D) Transverse colon with stenosis and pre-stenotic dilatation. (E-F) Transverse colon with fistula.

Fig. 2. Patient with left-sided ulcerative colitis in therapy with vedolizumab for three months. Point-of-care bowel ultrasound (POCBUS) led to optimization of vedolizumab. (A) Sigmoid colon with normal bowel wall thickness and normal echopattern. (B-C-D) Descending colon with bowel wall thickening (4.5 mm) and focal disruption of echostratification. The arrow indicates the passage from normal to pathological colonic tract.

Fig. 3. Unique properties of bowel US which render it a strategic tool in the management of inflammatory bowel disease.

Fig.4. Flow-chart for use of scheduled bowel ultrasound / point-of-care bowel US (POCBUS) in the monitoring of IBD.

* C-reactive protein (CRP), fecal calprotectin

Table 1. Bowel ultrasound (US) for the management of inflammatory bowel disease

| Bowel US in Crohn's disease | Bowel US in ulcerative colitis |
|--|---|
| <ul style="list-style-type: none"> Assessing disease activity and severity Assessing extent in small bowel disease Assessing complications (strictures, fistulae, abscesses, lymph nodes, mesenteric hypertrophy) Evaluating bowel damage (Léman index) Detecting post-surgical recurrence Monitoring therapeutic response Assessing transmural healing (TH) Predicting outcomes | <ul style="list-style-type: none"> Assessing disease activity and severity (HUC, Humanitas Ultrasound Criteria) Assessing colonic extent Assessing complications (strictures, lymph nodes, mesenteric hypertrophy) Monitoring therapeutic response Predicting outcomes |

Table 2. Point-of-care bowel ultrasound (POCBUS): role and utility in inflammatory bowel disease.

| | |
|---|---|
| Performed in real-time in in- and out-patients | <ul style="list-style-type: none"> • → to narrow the differential diagnosis • → to set the further work-up and treatment • → to improve health care resource utilization |
| Discerning in real-time inflammatory from non-inflammatory diseases | <ul style="list-style-type: none"> • → to speed up diagnosis • → to improve allocation of resources • → to allow early beginning of treatment |
| Real-time detecting of flare/recurrence of disease and complications | <ul style="list-style-type: none"> • → to speed up clinical decision-making • → to expedite further investigations and management |
| Monitoring therapeutic response | <ul style="list-style-type: none"> • → to drive real-time clinic decision-making • → to allow early optimization/change therapy |

Figure 1

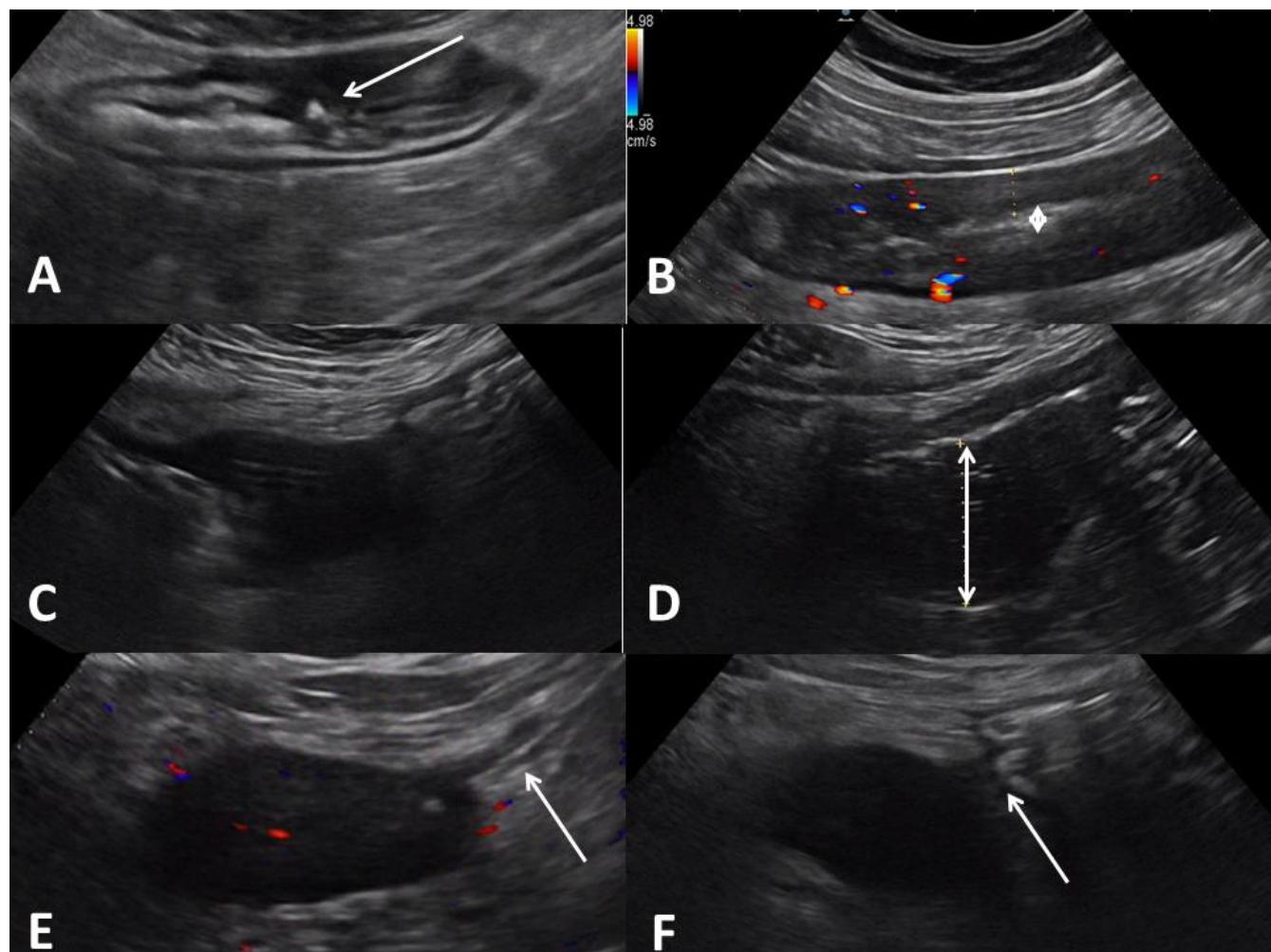
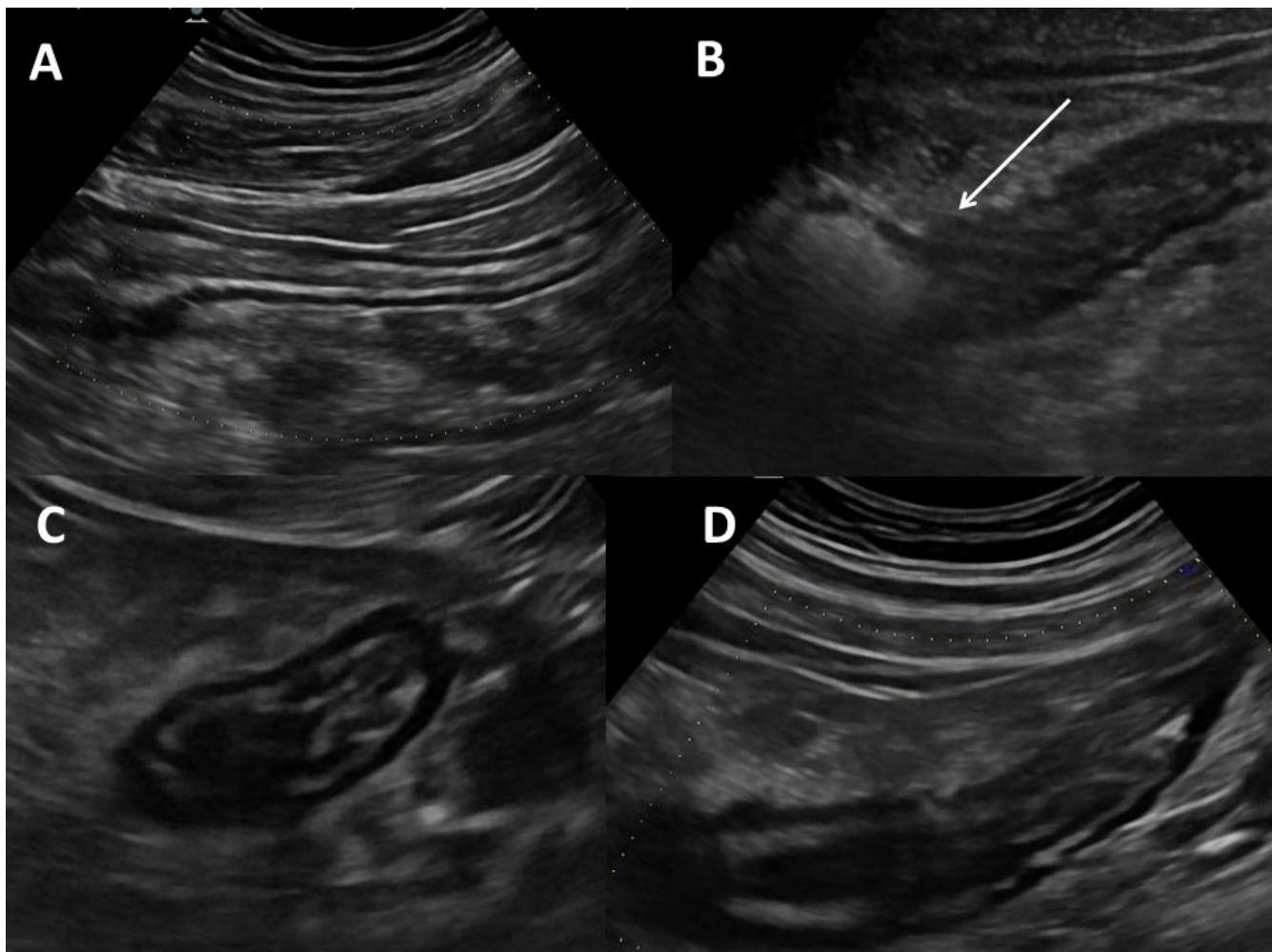


Figure 2



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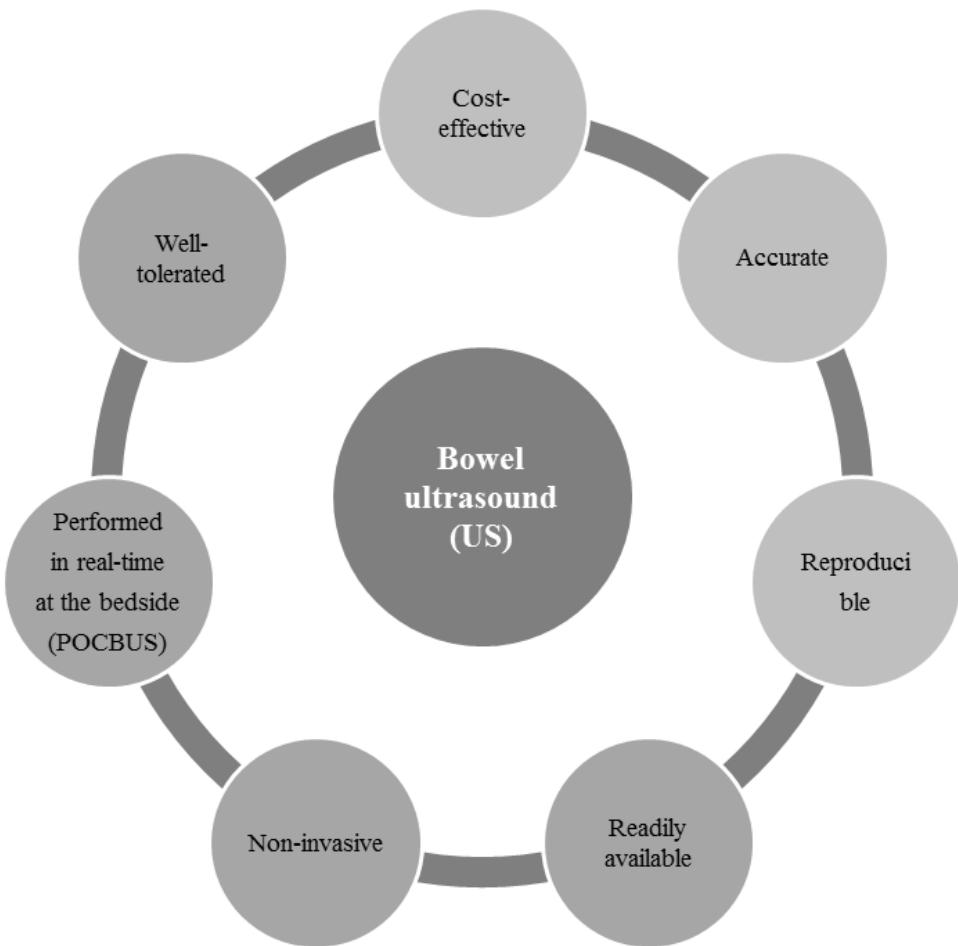
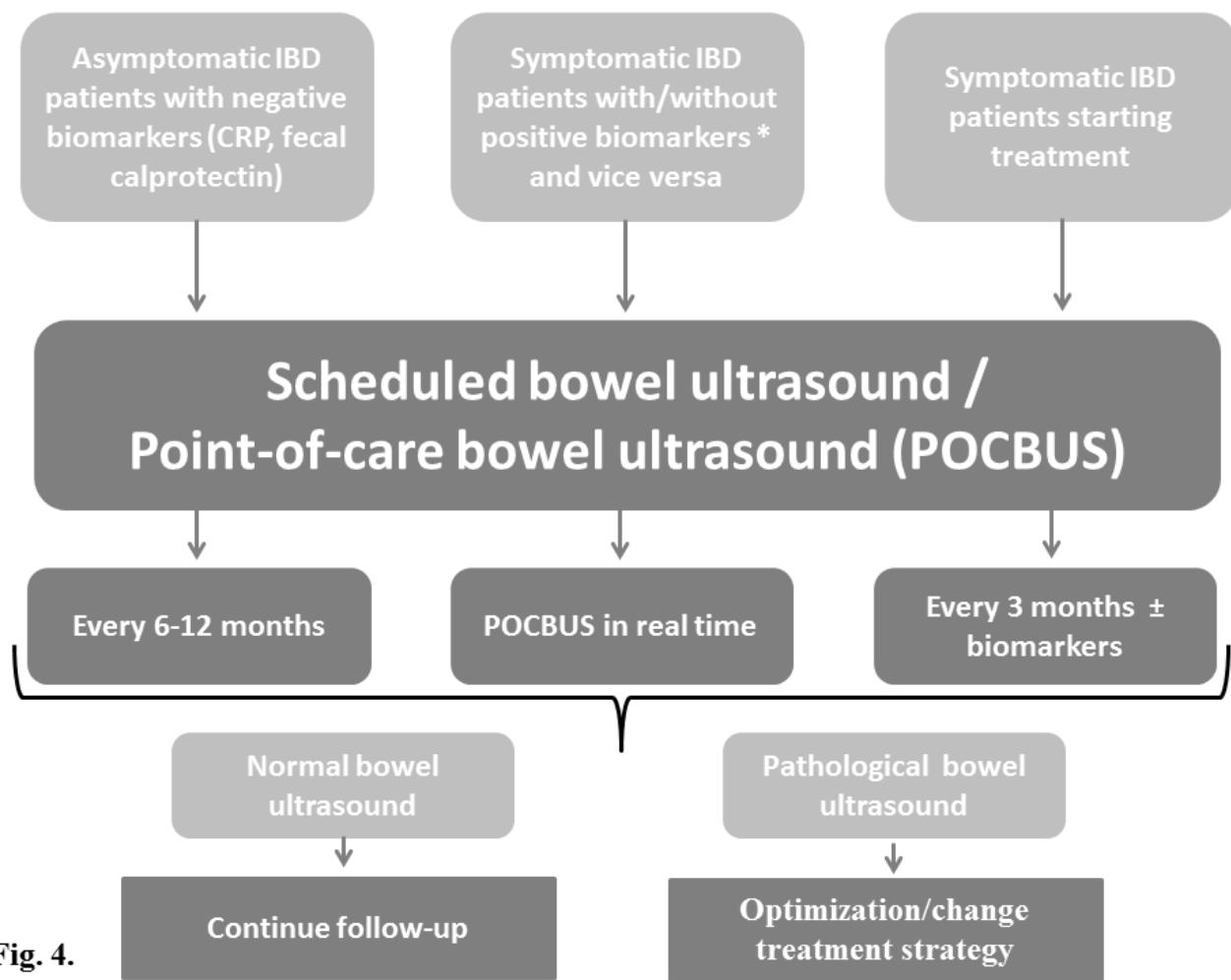


Fig. 3.

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**Fig. 4.**

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Review

Bowel Ultrasound in Inflammatory Bowel Disease: How Far in the Grayscale?

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Abstract: Bowel ultrasound (BUS) is a non-invasive and accurate technique for assessing activity, extension of disease, and complications in inflammatory bowel diseases. The main advantages of BUS are its safety, reproducibility, and low costs. Ancillary technologies of BUS (i.e., color Doppler and wave elastography) could broaden the diagnostic power of BUS, allowing one to distinguish between inflammation and fibrosis. Considering the costs and invasiveness of colonoscopy and magnetic resonance, BUS appears as a fast, safe, and accurate technique. The objective measures of disease allow one to make clinical decisions, such as optimization, switch, or swap of therapy. Previous studies reported a sensitivity and a specificity of more than 90% compared to endoscopy and magnetic resonance. Lastly, transperineal ultrasound (TPUS) is a promising approach for the evaluation of perianal disease in Crohn's disease (CD) and disease activity in patients with ulcerative proctitis or pouchitis. Bowel ultrasound is being incorporated in the algorithm of managing inflammatory bowel diseases. Transmural healing evaluated through ultrasonography is emerging as a complementary target for disease treatment. In this review, we aimed to summarize and discuss the current evidence on BUS in the management of inflammatory bowel diseases and to address the challenges of a full validation of this technique.

Keywords: bowel ultrasound; inflammatory bowel disease; transperineal ultrasound; bowel thickness



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1. Introduction

Inflammatory bowel diseases (IBD) are chronic, progressive, and disabling conditions, characterized by a relapsing and remitting behavior and long-term complications (i.e., colo-rectal cancer and demolitive surgery) [1,2]. Dedicated physicians are becoming confident with the “treat-to-target” strategy in the management of IBD, aiming to prevent end-organ dysfunction [3,4]. For years, symptom control has been the primary therapeutic goal of IBD patients. However, clinical remission is not a reliable outcome for the optimal management of IBD. Indeed, one out of four patients who are clinically asymptomatic can have an endoscopically active disease. Conversely, even in the presence of endoscopic remission, symptoms continue to be reported [5,6]. In the need for objective and measurable endpoints, bowel ultrasound (BUS) has gained increasing relevance. Traditionally, ultrasound was not considered a valid method for the assessment of the small bowel and colon [7]. It has taken a long time since the first studies in the 1970s on the effectiveness of this technique for bowel examination and its recent scientific acknowledgement [7]. According to the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE-II), transmural healing (TH), assessed by imaging techniques including bowel ultrasound (BUS), is considered a treatment target neither in Crohn's disease (CD) nor in ulcerative

colitis (UC) [4]. Nevertheless, especially in CD, transmural healing is an adjunctive outcome to endoscopic remission and might represent a state of deeper healing [4]. Current recommendations recognize BUS as a valid method for the assessment of the small bowel in newly diagnosed CD and, generally, for the monitoring of IBD [8]; however, a standardization of the intestinal and extraintestinal features of active disease is still needed. The main advantages of BUS are its non-invasiveness and low costs compared to computed tomography (CT) or magnetic resonance imaging (MRI) [9]. It has been recently demonstrated that when performed by a skilled operator, BUS has a comparable sensitivity and specificity to second-level techniques for assessing disease activity and complications of IBD [9–11]. Moreover, BUS is readily available and can be performed bedside by the dedicated gastroenterologist upon need (i.e., point-of-care BUS (POCBUS)) [12]. The monitoring through BUS of the bowel wall thickness (BWT) predicts the outcomes of IBD patients, particularly in CD for its transmural features [9–11]. In this review, we aim to examine and summarize the technical aspects and the current evidence on BUS in the management of IBD, focusing on the detection of disease activity, complications, and the newly emerging transperineal approach.

2. Technique and Features of Normality

Since the intestine is located superficially in the abdomen, the most detailed visualization of the bowel wall is acquired through a mid-frequency range transducer (5–10 MHz) micro-convex array [13], whereas the regular abdominal probes and the linear probes are low-frequency (1–6 MHz) and high-frequency transducers (10–18 MHz), respectively. The operator will assess the following main features of the intestinal tracts: wall thickness, wall border, echo pattern, vascularity, and motility. Several extraintestinal features belong additionally to the complete abdominal evaluation (i.e., lymph nodes, mesenteric fat, free abdominal fluid) [13,14].

According to the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) guidelines, the examination can be systematically performed with the aim of evaluating the whole intestine, starting from the hypogastrium, or left iliac fossa, firstly assessing the sigmoid colon, and then continuing along the colon to the terminal ileum, appendix, small bowel, and up to the stomach [13,14]. A fasting of 4–6 h is advisable, but not essential, in order to reduce the luminal content, the blood flow, and the peristaltic activity [13,14]. The iliopsoas muscle and the common iliac vessels can be used as landmarks to identify the sigmoid or the terminal ileum in the left or right iliac fossa, respectively. The normal bowel is stratified with five concentric layers that can be distinguished for their echogenicity (Figure 1): the most inner layer identifies the hyperechoic mucosa/lumen interface, while the most outer layer is an echogenic interface between the serosa and the confining organs or structures [15,16]. The BWT is the only fully quantitative ultrasound parameter that is measured from the external hyperechoic layer of the serosa to the internal hyperechoic interface between the lumen content and the mucosa [15,16]. To date, a bowel thickness of 2 mm was established by the EFSUMB guidelines as a threshold for the definition of normality [13]. In contrast, most studies and meta-analyses indicate a cut-off between 3 and 4 mm as a threshold of disease activity, especially for IBD patients [17,18]. In addition, a semi-quantitative grading of intestinal wall vascularity through the *Limberg score* has been described in the literature and is routinely used in clinical practice (Table 1) [18,19]. The evaluation of the rectum deserves to be discussed separately: the sensitivity of BUS in detecting a rectal location of IBD is approximately 15% [17,18]. Some recent evidence suggested a cut-off of 4 mm of BWT for the rectum, measured transperineally [20].

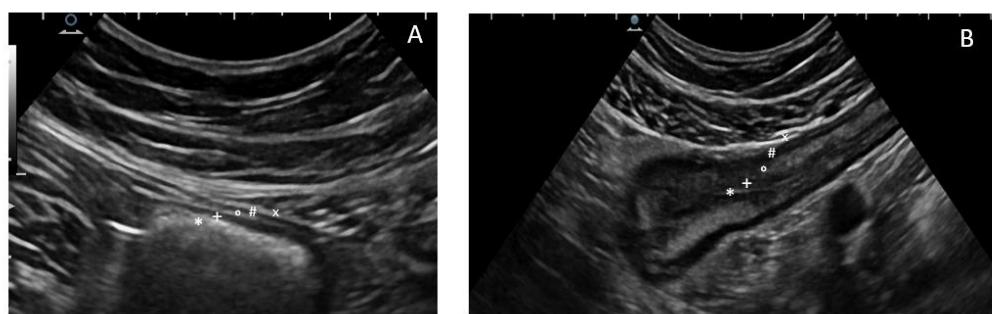


Figure 1. The five concentric layers of a normal (A) and thickened (B) bowel wall at ultrasonography. The most inner layer identifies the hyperechoic mucosa/lumen interface (*), then the hypoechoic mucosa (+), the hyperechoic sub-mucosa (°), and the hypoechoic muscularis propria (#), while the most outer layer is an echogenic interface between the serosa and the confining organs or structures (x).

Table 1. Semi-quantitative assessment of vascularity through Limberg score (19).

| Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|--|---|---|--|
| No vascularization signal at color Doppler | Mild: minimal signal, short stretches of vascularity in spots | Moderate: longer stretches of vascularity, blood vessels located only intra-mural | Severe: long continuous intra- and extra-mural blood vessels, extending into the mesentery |

Regarding the evaluation of the bowel diameter, it can considerably vary (i.e., recent meals or fluid intake), but when the small bowel dilated segment becomes larger than 25 mm it is generally considered as abnormal, especially if a reduction in motility is observed, and a large bowel of more than 5 cm is also considered abnormal [14]. With respect to motility, the operator should assess any loss of elasticity and peristaltic movements [13,14]. Finally, among the evaluable extraintestinal features there are mesenteric fat, mesenteric lymph nodes, and abdominal free fluid [13,14]. An example of normal findings at bowel ultrasound of the sigmoid colon is shown in Figure 2.

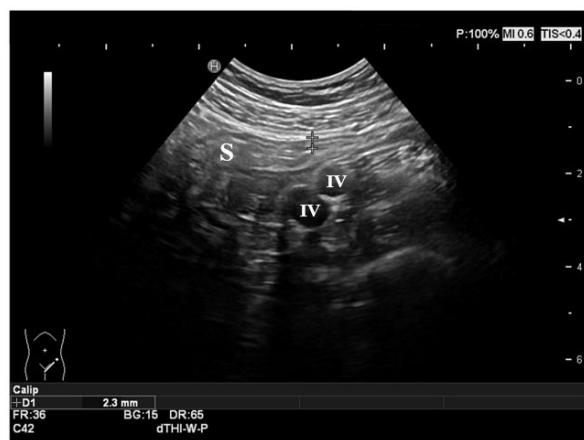


Figure 2. Normal ultrasonographic features of the gut. The sigmoid colon is shown in the figure, with normal thickness and stratification of the layers. The iliac vessels represent the anatomic landmark in the left iliac fossa. S: sigmoid colon; IV: iliac vessels.

3. Crohn's Disease in Bowel Ultrasound

Crohn's disease (CD) is a chronic, progressive disease that may affect any site of the gastro-intestinal tract, with a typical segmental/skip and transmural involvement [2]. The diagnosis and the monitoring of CD is based on the combination of clinical, laboratory, and endoscopic findings; histopathological reports; and imaging studies. There are known advantages in terms of detection of BUS over endoscopy in several cases, such as an incomplete colonoscopy, proximal locations of disease (i.e., distant from the ileo-cecal valve), and complications (i.e., fistulas, abscesses, and strictures) [9–12]. The indications to perform BUS in CD patients are summarized in Table 2.

Table 2. Indications to perform BUS in Crohn's disease.

Indications to Perform BUS in Crohn's Disease

- Initial work-up in suspected CD (i.e., differential diagnosis)
- Baseline evaluation of disease activity and extension before therapy
- Suspected complications (i.e., fistulas, abscesses, strictures)
- Monitoring after/during the treatment course (response vs. worsening)

The accuracy of BUS in CD assessment has been extensively demonstrated [17,19,21,22]. Several meta-analyses assessed the pooled sensitivity and specificity of BUS in CD by 88–89% and 93–97%, respectively [17,22], thus demonstrating that the detection of active disease in CD patients is precise and reliable, particularly for locations of disease in the small bowel [17,22]. Therefore, the ultrasonographic examination can be used to monitor disease activity and response to medical treatments [17,22].

3.1. Ultrasound Features of CD

A cut-off of bowel thickness greater than 3 mm is commonly adopted to predict disease activity with a sensitivity of 88–89% and a specificity of 93–96% [17,18,22]. Interestingly, a cut-off of 4 mm has a lower sensitivity (75%) despite a higher specificity (97–98%) [17]. When assessing the BWT of the colon, it is the most precisely determined when avoiding the haustrations [14–16]. Moreover, the longitudinal extent of disease has to be measured [14–16]. A lack of compressibility by the transducer and the loosening of the normal wall stratification can be observed in active CD [14–16]. In subjects with acute CD, the bowel wall appears hypoechoic, reflecting the corresponding oedema of the tissue infiltrate; in case of severely active diseases, it is possible to visualize the presence of deep mural ulcers that can additionally disrupt the stratification of the bowel wall [14–16]. With this regard, several studies proved that the loss of mural stratification is associated with

clinical and biochemical activity, as well as with histological activity, and with an increased risk of surgery in CD [19,23,24].

As mentioned above, a semi-quantitative assessment of bowel wall vascularity using color Doppler imaging gives a complementary estimation of disease activity: the vascular patterns correlate with clinical and endoscopic activity [25,26]. In detail, the *Limberg score* (Table 1) is associated with the clinical activity, estimated through the Crohn's disease activity index (CDAI), with a sensitivity of 82% ($p = 0.01$) [25]. The same study revealed a statistically significant association between the histological activity and the vascularity assessed at BUS ($p = 0.03$) [25]. Concerning endoscopy, considerable correlation (correlation coefficient $r = 0.70$, $p < 0.001$) was detected between the *Limberg score* and the simple endoscopic score for Crohn's disease (SES-CD) at colonoscopy of 108 CD patients [26].

Furthermore, BUS allows the evaluation of several extraintestinal, indirect features of disease. In detail, enlarged loco-regional mesenteric lymph nodes are commonly encountered at BUS [15,16]. Inflammatory lymph nodes related to active CD have an oval shape and appear hypoechoic, with a diameter less than 5 mm and a short axis less than half of their longitudinal diameter [13,14]. This finding is less specific than BWT, echo pattern, and vascularity in terms of prediction of disease activity, and it could be linked to young age, early disease, and with the presence of abscesses or fistulae [27]. Mesenteric fat hypertrophy or creeping fat is an additional parameter of inflammation: the typical aspect is hyperechoic, almost "solid" [13,14,28]. Mesenteric fat hypertrophy has been less extensively investigated compared to all other sonographic findings, and it is known to be correlated with the clinical biochemical activity of CD [28]. Extraintestinal BUS findings are shown in Figure 3. Free fluid is a further common and reproducible BUS finding, generally found close to the inflamed bowel tract. It seems to be rather unspecific since it is commonly encountered in several non-IBD conditions [14].

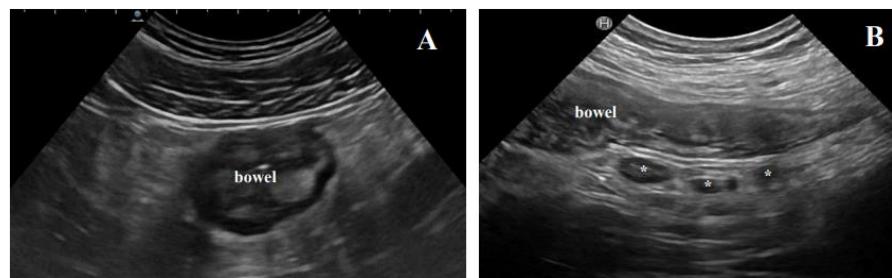


Figure 3. Extraintestinal findings of active disease at BUS. (A) The typical hyperechoic, almost "solid" appearance of mesenteric fat hypertrophy; (B) inflammatory lymph nodes (*) in a Crohn's disease patient with active disease.

Lastly, it has been extensively demonstrated in retrospective studies that BUS is able to detect and predict an early surgical recurrence after ileo-colonic resection [29–31].

3.2. Complications of Crohn's Disease

In the natural history of CD, abdominal complications, such as stenosis, fistulae or abscesses, and, more rarely, free perforation, can occur [2]. In these cases, a prompt diagnosis is desirable since the management often involves surgery [8].

A recent prospective comparative study conducted on a cohort of CD patients demonstrated that BUS has a sensibility and a specificity in detecting strictures, fistulas, and abscesses located in the terminal ileum of 88–100% and 90–98%, respectively [32]. A lower sensitivity of this technique was observed with respect to colonic segments (76%) [32]. At US examination, a bowel stenosis is characterized by thickened walls with associated narrowed lumen (less than 10 mm) and dilatation of the proximal loop of 25–30 mm [14–16]. Additionally, hyperperistalsis of the pre-stenotic intestinal tract can be observed [14–16]. In general, in our clinical practice, the chronic stenosis has a particular disposition of the material inside the dilated loop: it is solid on the bottom and fluid on the top. A

recent systematic review confirmed BUS as a highly precise technique for the diagnosis of stenosis: the estimated sensitivity ranged from 80 to 100%, and the specificity varied from 63 to 75% [33]. With respect to stenosis, there is an open debate whether BUS is able to distinguish between a predominantly inflammatory and a fibrotic stricture. The relevance of this issue consists in a substantially different management: patients with evidence of a prominent inflammation might benefit from medical treatment, whereas patients with evidence of a fibrotic stricture would rather be advised for surgery (i.e., strictureplasty, resection) or endoscopic dilation [34]. It has been proven that a purely inflammatory stenosis would appear hypoechoic and highly vascularized, while a preserved stratified echo pattern can indicate fibrosis with no or poor signal at color Doppler [23,34]. Nevertheless, in real clinical practice, the stenosis is rather composed at the same time by an inflammatory and a fibrotic component: this explains the heterogeneity and inconclusiveness of the many studies on this topic, even when the stricture features are assessed through contrast-enhanced ultrasound (CEUS) or elastography [23,35,36].

A penetrating CD can be complicated by fistulas that are visualized as hypoechoic tracts originating from the intestinal wall either with a blind end or rather in continuity with mesenteric structures and confining organs (i.e., entero-mesenteric, entero-enteric, entero-vaginal, entero-vesical). The sensitivity of BUS in detecting a fistulizing disease is lower than for other complications of CD and has been assessed by 67–87% [37].

Conversely, the abscess is a purulent collection; the absence of gaseous material often allows one to distinguish fistulas from abscesses [13,14]. The typical sonographic appearance of an abdominal abscess is a hypo or an-echoic lesion containing gaseous (seen as bubbles) and liquid material, having often irregular margins and a posterior wall enhancement [13,14]. A further distinction must be made between an abscess and an inflammatory mass [38]. The latter is frequently highly vascularized and presents a diffusely increased enhancement at contrast-enhanced ultrasound (CEUS), while an abscess would enhance only in the periphery, with a typical avascular center [38]. BUS has been demonstrated to be similarly accurate as computed tomography (CT) and magnetic resonance (MRI) in diagnosing abdominal abscesses in patients with CD [39]. In more detail, according to a recent systematic review, the sensitivity and specificity with this latter specific indication ranged from 81 to 100% and 92 to 94%, respectively [39]. Notably, the detection of an abdominal abscess in patients treated with biologic agents demands a temporary discontinuation of the therapy and contraindicates an eventual therapy start, highlighting the relevance of the ultrasound monitoring [8].

3.3. Transperineal Ultrasound

Transperineal ultrasound (TPUS) allows one to evaluate the distal rectum, anal canal, and the perianal tissues that are not visualized in the transabdominal examination [38]. Indeed, the sensitivity of BUS in detecting disease activity of the rectum can be as low as 15% [40]. TPUS is easy and noninvasive compared to endo-rectal/anal approaches. The evidence concerning the accuracy of TPUS in IBD is still rare, and its clinical use is only emerging in very recent years. The exam is performed with the patient on the left lateral decubitus and with bent legs [40]. The main indications of TPUS are any known or suspected fistulas or collection in the perianal region in CD patients. In these patients, the use of intravenous contrast can improve the assessment of perianal abscesses, allowing a better differentiation from inflammatory masses and fistulas [41]. Several anatomical landmarks can be identified: the anal canal, internal and external anal sphincters, symphysis pubis, urinary bladder, prostate, and vagina [41].

In detail, the location of the fistula/collection should include the site of the anal canal (i.e., inner third, middle, or outer third), and the site on a clock representation is where 12 o'clock corresponds to the anterior wall of the anus [42]. Fistulae of the perianal region are classified according to Parks classification, which summarizes the anatomical course of the fistula in relation to the sphincters [43]. The Parks classification is reported in Figure 4. Among the available data, Mallouhi et al. firstly reported a sensitivity of 100% and a

specificity of 94–100% of TPUS in detecting perianal fistulas and abscesses in a cohort of 62 IBD patients [44].

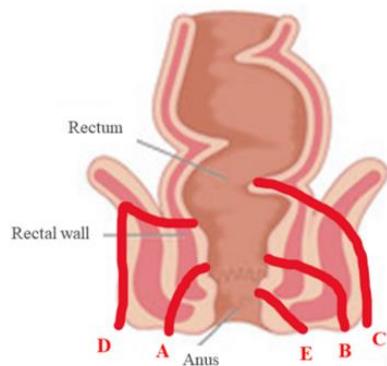


Figure 4. Parks classification of perianal fistulas (40). A: inter-sphincteric; B: trans-sphincteric; C: extra-sphincteric; D: supra-sphincteric; E: superficial perianal fistula.

A recent systematic review with meta-analysis by Maconi et al. showed that TPUS has high sensitivity in detecting and classifying perianal fistulas (98.3 and 92.8%, respectively) [45]. A comparable accuracy was also found for the detection of perianal abscesses (sensitivity of 86.1%) [45]. Perianal abscesses can vary in size and shape and are classified as pelvi-rectal, inter-sphincteric, ischiorectal, and superficial perianal abscesses [45]. Despite the above-mentioned studies, pelvic MRI remains the preferred and recommended radiologic modality for the most detailed imaging of perianal CD [8]. Figure 5 shows examples of TPUS findings. Considering that a pelvic MRI costs on average USD 550 (range 500–1000), these high costs might be overcome by TPUS in the future.

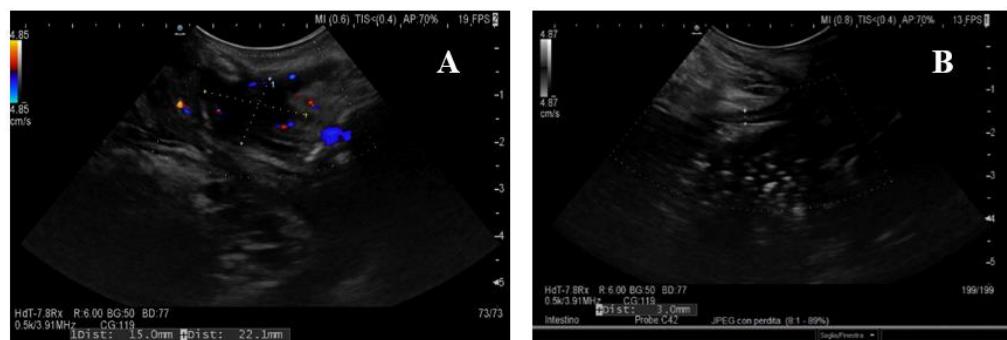


Figure 5. Ultrasonographic findings of transperineal ultrasound (TPUS). (A) A perianal abscess in an operated CD patient with typical peripheral color Doppler signal. (B) The wall of an ileal pouch is measured with the transperineal approach. CD: Crohn's disease.

4. Ulcerative Colitis

Ulcerative colitis (UC) is typically a mucosal disease rather than transmural; the gold standard for the diagnosis and monitoring is endoscopy [3,7]. Despite an initial disbelief due to the nature of inflammatory involvement in UC, BUS is emerging as accurate both in detecting active disease and assessing the extension of active UC [13,14]. Moreover, BUS addresses the disadvantages of endoscopy, such as its invasiveness and costs [13,14].

As reported by Smith et al. in their systematic review on the topic, BUS appears valuable in the routine assessment and management of patients with UC [46].

Common findings at BUS include the BWT, the loss of haustration and stratification, mesenteric changes, presence of lymphadenopathy, and an irregular mucosal surface due to post-inflammatory polyps and/or deep ulcerations [47].

Data from comparative and prospective studies have shown a strong correlation between wall thickness (>3 and 4 mm) and colonic vascular flow with C-reactive protein

values and the endoscopic score [9,10,41]. These studies have led to the full validation of an ultrasonographic score, the Milan ultrasound criteria, that can be easily calculated ($1.4 \times$ bowel thickness (mm) + $2 \times$ vascular flow) and indicates activity when ≥ 6.3 [10,11]. In contrast with CD, in UC patients, the loss of bowel wall stratification with a hypoechoic pattern is rarely observed; when present, it is associated with a severe disease [45].

Additionally, BUS may also be adopted for assessing response to treatment, in terms of reduction of the wall thickness [48]. A reduction in BWT of ≥ 2.5 mm has been proposed as sonographic response to therapy and is able to predict the clinical remission at a one-year follow-up [49].

Lastly, since the rectum is not always visualized with the transabdominal approach, TPUS has been proposed as a more accurate method with this respect. Indeed, TPUS has been investigated in UC with a good correlation between the rectal bowel wall thickness and *Limberg score* with the rectal Mayo score at endoscopy and histological scores (i.e., Nancy index) [20]. In this last study, a BWT ≥ 4 mm predicted endoscopic activity more accurately when evaluated through transperineal ultrasound compared to transabdominal ultrasound with a sensitivity and specificity of 100 and 45.8%, respectively ($p = 0.0002$) [20].

5. Discussion and Future Perspectives

This review elucidates the technical aspects and the current evidence on BUS in the management of IBD. The STRIDE-II recommendations, though recognizing BUS as a valuable method to assess the degree of inflammation in IBD, do not include TH as a treatment target either in CD or UC and is rather considered as an adjunctive target [4]. The meaning of “adjunctive target” is still under investigation and needs clarification. In our view, an adjunctive value of BUS in the management of IBD finds place, for example, in the decision of optimizing the therapy with biologic agents. Certainly, changing the therapy line exclusively on the basis of BUS findings might lead to a precocious withdrawal of the treatment, which is not advisable in view of the limited available therapy lines. Still, the possibility, offered by BUS, of frequent assessments allows a tempestive and anticipated optimization of the therapy without waiting for the endoscopic assessment, which could be wisely postponed.

To date, a growing body of evidence has been accumulating on the predictive value of TH, evaluated through BUS on the long-term outcomes [50–52]. Indeed, it has been demonstrated that sonographic remission evaluated after one year of anti-TNF therapy was associated with a longer remission without the need for a therapy change and a reduced need for surgery [51,52].

A further advantage of BUS, specifically compared to endoscopy, consists in assessing the entire gastrointestinal tract allowing, when suspected, the prompt recognition of complications (i.e., abscesses, stenoses, and fistulas) of CD and the subsequent prompt referral of the patient to surgeons. Notably, BUS is crucial in accelerating this process; however, it would substitute MRI in the pre-surgical evaluation.

Beyond these indications, the role of BUS has been increasingly broadened in recent years from the evaluation of disease activity and its complications toward the monitoring of disease progression and treatment response both in CD and UC [53,54]. Recent data endorse the adoption of BUS in the tight monitoring of IBD patients due to its accuracy in assessing signs of response and TH [53,54]. Particularly in the management of CD, BUS can be incorporated as a “bridge” examination to colonoscopy, since the reduction of the BWT accurately predicts the endoscopic response [53,54].

BUS is increasingly gaining relevance also in UC, especially considering the high costs of endoscopy. However, even though the role of BUS in UC also comprehends disease monitoring, it is to a lesser extent considering the unsubstituted value of colonoscopy in the diagnosis of cytomegalovirus (CMV) infection and in the surveillance for dysplasia/colon-rectal tumor.

In its route toward standardization, an evidence-based assessment through BUS has latterly been defined by an expert international panel of gastroenterologists and radiol-

ogists [21]: these efforts are going to endorse the use of BUS in future clinical trials as a substitute or alongside of endoscopy. In this survey, among the statements of greatest agreement for a good quality BUS assessment there were the cut-off of 3 mm for BWT both for the colon and small bowel, the use of the semi-quantitative *Limberg score* for vascularity, the need of acquiring an image of the rectum, and the description of the loss of stratification and/or the submucosal prominence [55].

An important matter of debate is the training of dedicated gastroenterologists: indeed, validated training times and acquirable skills are lacking, and there is no consensus on the definition of an “expert” BUS operator.

In the future, the combination of BUS and biomarkers, primarily fecal calprotectin, would largely substitute the more costly monitoring techniques (endoscopy and MRI) for their reliability in decision making.

Despite the gathered evidence, BUS has been widely underemployed in many countries outside of Europe. In particular, in North America (i.e., USA) this was due to a lack of local expertise and to less available training programs [56]. Moreover, there was historically a rooted skepticism on the clinical application of BUS as well as reimbursement matters [56].

As presented in the text, CEUS is an additional helpful tool in the characterization of suspected abscesses and inflammatory phlegmons, as well as in confirming the route of a fistula and quantitatively determining disease activity in IBD. Concerning the distinction between fibrotic and inflammatory strictures in IBD, there is encouraging evidence that CEUS integrated with further ultrasonographic tools would soon be determinant in this distinction.

Finally, the newly emerging TPUS represents a valid technique with possible future applications in the monitoring of operated IBD patients with ileal pouch, who more frequently receive medical treatment in the long term. Whether TPUS might be accurate in the monitoring of therapy response in pouchitis warrants dedicated prospective studies.

As far as we are concerned, despite the emergence of histology as a powerful target for better long-term outcomes, BUS would gain a well-defined place in the management algorithm of IBD due to its non-invasiveness, cost-effectiveness, readily availability, and reproducibility. The future challenges of this diagnostic modality consist of gaining increased accuracy for proximal disease (i.e., duodenum, jejunum, etc.) as well as for colonic segments.

In the upcoming era of more and more rigorous therapeutic targets, such as TH and histological healing, BUS can become the main instrument for a tailored monitoring and management strategy allowing one to anticipate and drive clinical decisions.

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Clinical utility of small bowel ultrasound assessment of Crohn's disease in adults: a systematic scoping review

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ABSTRACT

Background Ultrasound (US) is an alternative to magnetic resonance enterography, and has the potential to significantly reduce waiting times, expedite clinical decision-making and improve patient experience. Point of care US is an advantage of the US imaging modality, where same day scanning, interpretation and treatment decisions can be made.

Aim To systematically scope the literature on point of care US use in small bowel Crohn's disease, generating a comprehensive list of factors relating to the current understanding of clinical utility of this imaging modality.

Methods Searches included MEDLINE, EMBASE, Cochrane Library, Cumulative Index to Nursing and Allied Health Literature, PsycINFO, clinicaltrial.gov, 'TRIP' and Epistemonikos. Reference lists of included studies were hand searched. Search terms were searched for as both keywords and subject headings (MeSH) as appropriate. Searches were performed with the 'suggested search terms' and 'explode' selection, and restricted to 'human', 'adult' and 'English language' publications. No date limits were applied to be as inclusive as possible. Two investigators conducted abstract and full-text review. No formal quality appraisal process was undertaken; however, quality of sources was considered when reporting findings. A narrative synthesis was conducted.

Results The review included 42 sources from the UK, Europe, Japan, Canada and the USA. Small bowel ultrasound (SBUS) has been shown to be as accurate in detecting the presence of small bowel Crohn's disease, is quicker, safer and more acceptable to patients, compared with magnetic resonance enterography. SBUS is used widely in central Europe and Canada but has not been embraced in the UK. Further research considering economic evaluation, clinical

Significance of this study

What is already known on this topic

→ Small bowel ultrasound (SBUS) has been shown to have a relatively comparable accuracy to magnetic resonance enterography in detecting the presence of small bowel Crohn's disease. SBUS and point of care ultrasound (POCUS) are used widely in central Europe, Canada and some parts of the USA, but have not been embraced in the UK and other parts of the world.

What this study adds

→ This study consolidates and comprehensively presents what is known regarding the clinical utility of SBUSs and POCUS for use in Crohn's disease. This study gives an insight into the future directions of research in this field.

How might it impact on clinical practice in the foreseeable future

→ This study is the first step in a programme of work to investigate barriers and enablers to implementation of a SBUS, point of care, service for Crohn's disease in the National Health Service. Through this work, we have been able to better direct our research to investigate stakeholder perceptions of barriers to implementation, clinical decision-making behaviours and cost-effectiveness studies.

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decision-making and exploration of perceived barriers to future implementation of SBUSs is required.

INTRODUCTION

The UK prevalence of Crohn's disease (CD) is one of the highest worldwide.¹ The mean cost per patient-year during

follow-up has been reported as €3542 (median €717 (214–3512)) for patients with CD, with an overall annual cost to the National Health Service (NHS) of up to £470 million.²

Assessing treatment response with more objective measures and a wider array of biological therapies has significantly increased the projected inflammatory bowel disease (IBD) healthcare burden for the next decade.^{3 4} To ensure cost-effective IBD practice, complex and expensive pharmacological interventions should be targeted at patients most likely to benefit.⁵

Cross-sectional imaging is used to diagnose and monitor disease activity in small bowel CD (SBCD).⁶ Magnetic resonance enterography (MRE), with oral preparation and intravenous contrast is a standard of care modality in the UK for assessment and monitoring of SBCD.⁶ However, waiting times for an NHS MRE may be up to 4 weeks or in some instances longer, with reporting is then undertaken at a later date. Additionally, the use of gadolinium as contrast agent has a risk of allergy, is expensive and has been implicated with long-term brain deposition in exposed patients.⁷ The European Crohn's and Colitis Organisation (ECCO) and the European Society of Gastrointestinal and Abdominal Radiology (ECCO-ESGAR) guidelines have already negated some of the risks posed by the use of gadolinium, by stating that gadolinium should be used on a case-by-case basis.⁸ Some centres are moving away from its use and have shown no significant decrease in accuracy.⁹ However, there is still a clinical need to find quicker, more tolerable and cheaper alternatives for monitoring patients with IBD.

Abdominal ultrasound (US) is an alternative to MRE, with the potential to reduce waiting times, speed up clinical decision-making and improve patient experiences and outcomes.¹⁰ Point of care (abdominal) US (POCUS) is an advantage of the US imaging modality, where same day scanning and interpretation can be undertaken.

This review is undertaken as the first step in investigating the use of POCUS for assessment of disease activity in SBCD. Due to the vastness of the existing evidence and the objective of this review, it was decided that a scoping review, rather than a systematic literature review, was more appropriate.¹¹ The objective was to systematically scope the literature on POCUS use in SBCD, identify specific characteristics and expand the current understanding of the clinical utility of POCUS for patients with SBCD.

Multidimensional model of clinical utility

Clinical utility can be described as a multidimensional judgement about the usefulness, benefits and drawbacks of an intervention. The model of dimensions of clinical utility presented by Smart¹² (figure 1) provides a frame work for assessing the clinical utility of a new technology or technique, asking whether the innovation is appropriate, accessible, practicable and

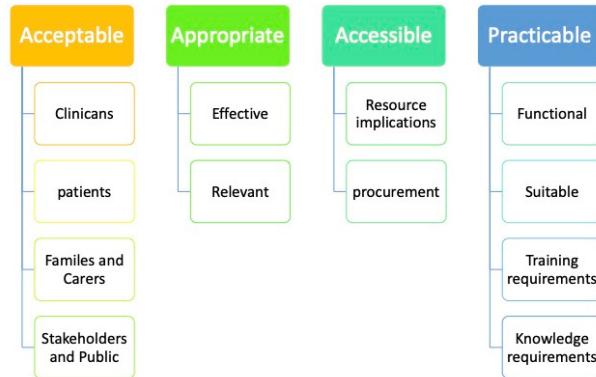


Figure 1 Factors of Clinical utility from Smart.²⁷ The model of dimensions of clinical utility presented by Smart¹² encompasses elements of work practice alongside other factors such as economic considerations, stakeholder acceptability and future planning for interventions and services. Assessing the clinical utility of a new technology or technique involves asking whether the innovation is appropriate, accessible, practicable and acceptable for the purposes of the task intended.^{12 58 59}

acceptable for the purposes of the task intended. In this scoping review, factors were identified and grouped into themes in relation to the factors of clinical utility.

METHODS

Preliminary searches of MEDLINE, Cochrane Database of Systematic Reviews and JBI Evidence Synthesis were conducted, no current systematic reviews or scoping reviews on the same topic were identified. Methods for this study were developed based on established scoping review methodology.^{13 14} The research question was ‘What evidence is currently available on the clinical utility of POCUS for the diagnosis and management of SBCD?’.

Inclusion criteria

Searches of electronic databases of published literature included MEDLINE, EMBASE, the Cochrane Library, Cumulative Index to Nursing and Allied Health Literature and PsycINFO. Searches were also conducted of clinicaltrial.gov for current clinical trials, ‘TRIP’ and Epistemonikos. Reference lists of included studies, grey literature and non-indexed sources were hand searched to identify additional sources of relevance.

Search terms were searched as keywords in title and/or abstract and subject headings (MeSH) as appropriate. Search terms (table 1) were determined through consideration of previously reviewed literature and preliminary searches of Google Scholar. The Boolean operator ‘OR’ was used within each facet to maximise searches, with the operator ‘AND’ used between facets to combine terms, truncation of terms was used to be as inclusive as possible. Searches were performed with ‘suggested search terms’ and ‘explode’ selection, included any type of study design, and restricted to ‘human’, ‘adult’ and ‘English language’ publications.

Table 1 Key search terms

| Crohn's disease (MeSH) | Small bowel | Ultrasound (MeSH) |
|----------------------------|-------------|--------------------------|
| Crohn's disease | Ileal | Ultrasound |
| Crohn's | Ileum | US |
| CD | Ileitis | Sonography |
| Crohn* | | Echography |
| Inflammatory bowel disease | | Point of care ultrasound |
| IBD | | POCUS |
| | | Ultrasonography |

CD, Crohn's disease; IBD, inflammatory bowel disease; POCUS, point of care ultrasound; US, ultrasound.

No date limits were applied to be as inclusive as possible.

Two investigators (SJR and GM) independently screened the title and abstract of all retrieved citations for inclusion against inclusion criteria. Each author reviewed each title and abstract, if both agreed to include the full text for review it was included, if both chose to exclude it was excluded. There were no disagreements which led to the need for a third author deliberation. No formal quality appraisal process was

undertaken; however, quality of sources was considered when reporting findings.

The two investigators (SJR and GM) then each independently assessed all full-text articles to determine if they met inclusion criteria. There were no disagreements about study eligibility at the full-text review stage that required discussion with a third investigator. Reasons for exclusion of full-text sources were recorded and reported in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses¹⁵ flow diagram (figure 2). A narrative synthesis was conducted to explore relationships within and across the included sources.

RESULTS

The review included 42 sources (online supplemental table 1). A common view across 24 of the included sources was that US is non-invasive test that is acceptable to and well-tolerated by patients, is safe and is inexpensive.^{8 10 16-37}

Only four sources directly mention the use of POCUS,^{10 30 36 38} the remainder discuss the use of SBUS. For the purposes of this review, we consider the use of SBUS without contrast agents, minimal or no

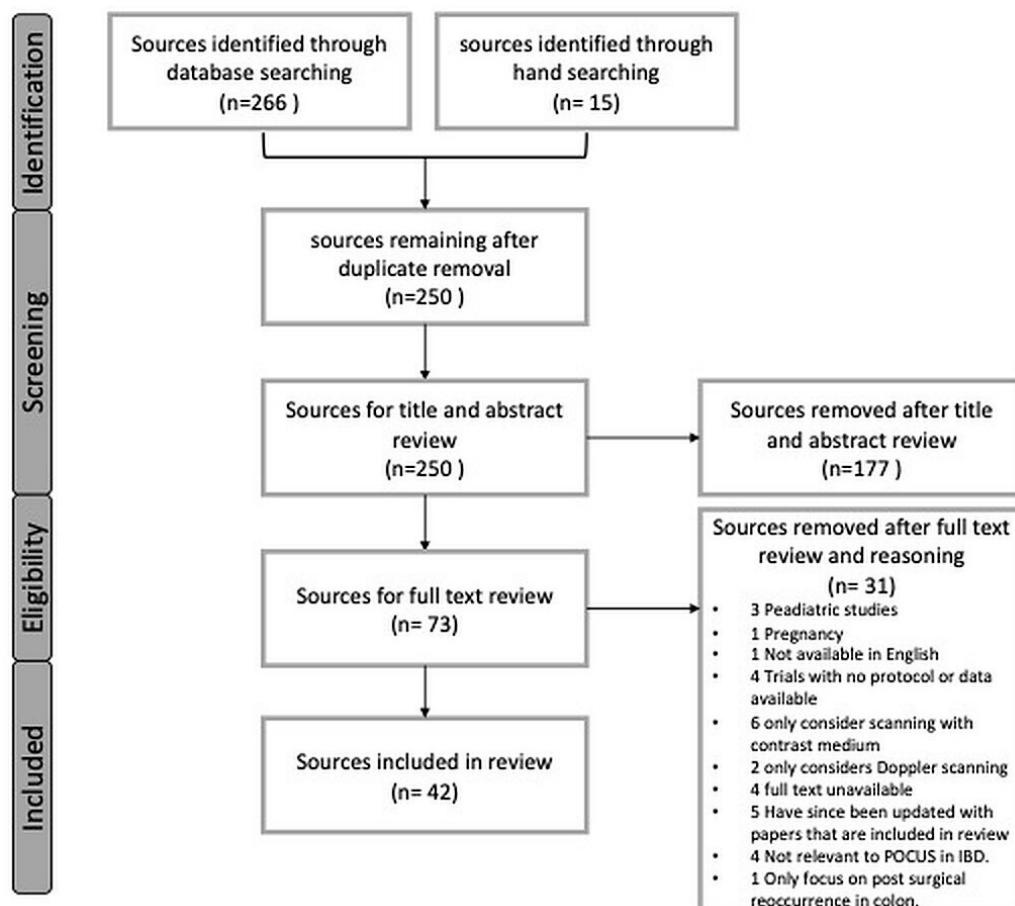


Figure 2 PRISMA flow diagram—supplemental material. The flow diagram depicts the flow of sources through the different phases of screening for inclusion and exclusion. We included 42 sources in our scoping review. Reasons for full-test exclusion are detailed in the PRISMA flow diagram. IBD, inflammatory bowel disease; POCUS, point of care ultrasound; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

bowel preparation and not the use of specialised tests such as Doppler or elastography scanning.

In central Europe and Canada, SBUS is widely used, often performed by gastroenterologists. This allows gastroenterologists to have a whole view of patient management, reducing waiting times for clinical decision-making.^{34 36}

The METRIC study showed that both SBUS and MRE had a diagnostic accuracy above 90% for detecting SBCD. Sensitivity of SBUS for small bowel disease presence and extent were 92% and 70%, respectively.³⁹ Sensitivity and specificity were significantly greater for MRE, with a 10% and 14% difference for extent and a 5% and 12% difference for presence.³⁹ It was also found that there was substantial sonographic agreement for the presence of SBCD, both in newly diagnosed and relapsed disease.⁴⁰ Agreement for SBCD extent was inferior to that of presence alone; this is in contrast to previous work by Parente *et al*,⁴¹ who reported near perfect agreement for segmental localisation.

The most prominent parameter for detection of inflammation throughout the reviewed sources was bowel wall thickness (BWT), which correlates well with clinical disease activity markers.^{8 10 17-22 24 25 27-29 32 34 35 37 38 42-46} The most common cut-off value was BWT exceeding 3 mm being considered pathological and a BWT of 2 mm or less considered normal.^{31 32 42}

A number of SBUS scores have been developed, most lack validation, were developed from small sample sizes or are limited to quantification of ‘damage’ or the risk of surgery.^{25 47} Novak *et al*²⁵ have developed a promising, simple US score for identifying CD activity comparing BWT to endoscopic activity, however the results reported have not yet been externally validated.²⁵

Fraquelli *et al*³⁴ notes that the use of SBUS in different clinical settings may impact on the utility of SBUS. In specialist centres where the pretest probability of IBD is elevated, US would be used to ‘rule in’ the disease. Alternatively, in primary care SBUS would be a useful tool to ‘rule out’ the disease.⁴⁸

Paredes *et al*⁴⁹ used SBUS for assessing changes induced with an antitumour necrosis factor (TNF) therapy in CD. The study reported a significant reduction in BWT in patients receiving anti-TNF therapy, however, ‘resolution’ of inflammation visible on SBUS was only achieved in 29% of subjects.³⁴ Results from Ripolles *et al*⁴⁵ showed that SBUS may be able to predict the 1-year response to anti-TNF therapy after 12 weeks of treatment with 85% (22/26) of patients showing a sonographic response at 12 and 52 weeks. Moreover, in the majority of patients (96%), clinical and biological response corresponded to sonographic response. Multiple authors suggest that SBUS may have a role in supporting MRE as a useful examination for monitoring the response to treatment in CD patients.^{23 29 34 38 50}

The METRIC³⁹ study found no major difference between MRE and SBUS on therapeutic decision-making. Both tests agreed with a final therapeutic decision based on all tests in >75% of cases. Very little further investigation into the impact of the use of SBUS on the clinical decision-making behaviours of clinicians has been undertaken, nor exploration of the confidence of clinical decisions made using each imaging modality.

Multiple sources refer to SBUS being inexpensive, however there is little empirical evidence within the included sources to support this claim.^{20-23 26 39 51} The METRIC³⁹ study presents data on a cost-utility analysis of MRE versus SBUS indicating a trend towards SBUS over MRE. However, given the small non-significant differences in costs and QALYs between the two options, it was not possible to endorse US or MRE on cost-effectiveness grounds.

The benefits of POCUS being performed by a member of the clinical IBD team include increased capacity for real-time interpretation of findings, expediting decisions concerning disease management and strengthening the rapport between healthcare professionals (HCPs) and patients.^{35 36 38} Many centres have standalone IBD US lists. These lists may be advantageous in expanding capacity to perform SBUS, particularly in centres where gastroenterologists are not trained in SBUS. This may also maximise healthcare resource allocation via predictable patient bookings.³⁶

Over the last few years, outside of the UK, the widespread availability of US technology and the increasing expertise of practitioners has boosted the uptake and role of US in assessing patients with IBD.^{31 34 39 43} Throughout the included sources, results reported were from SBUS being performed by individuals with extensive experiences of SBUS.^{16 17 19-21 26 28-30 37 44 45 48} For example, Taylor *et al*³⁹ report that the team involved in the METRIC study had an average of 8 years (4–11) experience of interpreting US. Despite SBUS typically being performed using standard devices and techniques, the uptake is not widespread or universal. Multiple authors have speculated this is due to lack of training availability and the substantial training and experience requirements of those performing the test.^{34 52} However, interobserver agreement between sonographers with variable experience in SBUS has been reported in preliminary studies showing satisfactory results.^{10 16 17 34 36 37 40 42 48} With appropriate training, transabdominal US can be performed by specialist gastroenterologists in clinic as part of routine care.³⁰ Gastroenterologist-performed SBUS is yet to establish universal acceptance.⁵³ The benefit of SBUS being performed within a radiology department by a dedicated sonographer or radiologist is the potential for increased diagnostic accuracy in detecting pathology.³⁶

SBUS and MRE are the most preferred imaging modalities by patients with CD.³⁹ SBUS is well

tolerated by patients with IBD.^{8 26} MRE recovery time has been shown to be significantly longer than US, with 15 participants out of 149 (10%) reporting immediate recovery following MRE compared with 102/147 (69%) for US.⁵⁴ The proportion of participants willing to repeat MRE was 127/147 (91%). This was lower than for US where 133/135 (99%) were happy to repeat the test.⁵⁴ Overall 128/145 patients rated MRE as very or fairly acceptable, while 144/146 (99%) participants rated US as very or fairly acceptable. Issues reported by patients concerning MRE mainly reflected ingesting contrast, repeated breath holds and the after-effects of contrast such as diarrhoea and bloating. Perceived scan burden was significantly higher for MRE than SBUS. One important finding is that patients rated diagnostic accuracy as the most important attribute and more important than the challenges related to discomfort of undergoing scans.⁵⁵ None of the included sources presented findings related to preferences of HCPs or patients as to where and when SBUS should be delivered.

DISCUSSION

Mucosal healing, defined by the absence of ulcerations, is recommended as the therapeutic goal in clinical practice. MRE is the current standard for assessing SBCD, however. It is expensive, time consuming and poorly tolerated by patients.^{7 30}

Meta-analyses suggest that MRE and SBUS have similar accuracy for diagnosing and staging SBCD.⁵⁶ SBUS could be a good alternative to more invasive and expensive imaging techniques. Besides being quick, well-tolerated and readily available, SBUS is reported and interpreted at the time of scanning and allows for expedited clinical decision-making.¹⁰

POCUS is reported as having impact on clinical decision-making in routine IBD care by expediting clinical decision-making.^{10 30 36} However, there is no current evidence on the impact that SBUS has on the nature of clinical decision-making behaviours, or confidence of HCPs making those clinical decisions.

Multiple sources referred to SBUS as inexpensive. However, none of the included sources presented clear data relating to cost or cost effectiveness of SBUS or POCUS. More data on the cost effectiveness of SBUS are needed to encourage the implementation of SBUS in IBD services.¹⁰ SBUS involves the use of standard US equipment that is readily available in most hospitals, however increasing scanning capacity also involves increased resources such as staffing and training. SBUS is often seen as having limited clinical utility due to operator dependence.³⁶ However, this criticism is perhaps more reflective of a previous lack of identifiable international performance and training standards.³⁶ NHS radiology workforce is short staffed by 33%, and is already at a deficit before considering the backlog following COVID-19.⁵⁷ ECCO-ESGAR guidelines describe

the dedicated training in bowel US process, and that SBUS should be performed following training in general abdominal US.⁸

Although various SBUS activity scores are available, the methodology for development was insufficient in most studies. There are several scoring systems for disease activity assessment using SBUS in CD, however until recently none had been completely validated.

There is no current work to investigate patient or HCPs preferences or service delivery. There are also questions relating to HCP perceptions of acceptability related to the diagnostic accuracy and confidence in basing clinical decisions on SBUS. It would seem prudent to investigate broader stakeholder perceptions of the use of POCUS in order to better understand perceived barriers and enablers to POCUS implementation in world-wide healthcare systems and recognise and manage preferences for future service delivery.

Limitations

Scoping reviews do not formally evaluate the quality of evidence gathering information from a wide range of study designs and methods, providing a descriptive account of available information leading to broad overview of the available literature. The outcomes represent an accurate response to the research question. Continuous conversations between authors occurred throughout to ensure a unanimous decision regarding article searches, thus limiting any potential bias. The scope of background information collected, disease activity levels, depth of data relating to the use of SBUS/POCUS vary vastly between sources.

CONCLUSIONS

SBUS has been shown have a relatively comparable accuracy to MRE in detecting presence of SBCD. SBUS and POCUS are used widely in central Europe, Canada and some parts of the USA, but has not been embraced in the UK and other parts of the world. The resources required in terms of equipment are readily available in most hospitals. Resource implications for future implementation include training of gastroenterologists and staffing of supporting radiology departments.

Multiple sources reported SBUS as an inexpensive test, however there is scant literature to support this. Further research in this area would better inform decision-makers regarding future intervention implementation.

SBUS is reported as being a useful tool to expedite clinical decision-making, but there is no evidence relating to the impact on the nature of clinical decision-making by HCPs. Further research in this area would help us to better understand the impact of POCUS on clinical practice, leading to better

understanding of practicable and acceptable aspects of clinical utility.

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Original Article

Defining Transabdominal Intestinal Ultrasound Treatment Response and Remission in Inflammatory Bowel Disease: Systematic Review and Expert Consensus Statement



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Abstract

Background and Aims: No consensus exists on defining intestinal ultrasound response, transmural healing, or transmural remission in inflammatory bowel disease, nor clear guidance for optimal

timing of assessment during treatment. This systematic review and expert consensus study aimed to define such recommendations, along with key parameters included in response reporting.

Methods: Electronic databases were searched from inception to July 26, 2021, using pre-defined terms. Studies were eligible if at least two intestinal ultrasound [IUS] assessments at different time points during treatment were reported, along with an appropriate reference standard. The QUADAS-2 tool was used to examine study-level risk of bias. An international panel of experts [$n = 18$] rated an initial 196 statements [RAND/UCLA process, scale 1–9]. Two videoconferences were conducted, resulting in additional ratings of 149 and 13 statements, respectively.

Results: Out of 5826 records, 31 full-text articles, 16 abstracts, and one research letter were included; 83% [40/48] of included studies showed a low concern of applicability, and 96% [46/48] had a high risk of bias. A consensus was reached on 41 statements, with clear definitions of IUS treatment response, transmural healing, transmural remission, timing of assessment, and general considerations when using intestinal ultrasound in inflammatory bowel disease.

Conclusions: Response criteria and time points of response assessment varied between studies, complicating direct comparison of parameter changes and their relation to treatment outcomes. To ensure a unified approach in routine care and clinical trials, we provide recommendations and definitions for key parameters for intestinal ultrasound response, to incorporate into future prospective studies.

Key Words: Intestinal ultrasound; inflammatory bowel disease; treatment response; transmural remission; transmural healing

1. Introduction

Transabdominal intestinal ultrasound [IUS] is gaining acceptance as a point-of-care test to objectively assess disease activity in inflammatory bowel disease [IBD].¹ IUS has several advantages over conventional cross-sectional imaging modalities: it is non-invasive, patient-friendly, easily repeated while being preparation and radiation free. Thus, the clinician can directly assess inflammatory activity in real time, helping patients understand their disease while facilitating clinical decisions without delay.^{2,3}

IUS's ability to assess colonic and small bowel inflammation has been compared with clinical scores, biologic markers, endoscopy, and radiological modalities at diagnosis and during disease flare, with good accuracy in ulcerative colitis [UC]⁴ and Crohn's disease [CD].⁵ However, the role of IUS as a monitoring tool after treatment initiation has not been standardised.^{2,4,6,7} Currently, no consensus definition exists for IUS response or transmural remission/healing [TR], nor clear guidance for optimal assessment intervals during follow-up.^{8,9} These standards are vital for the consistent application of IUS as a modality to assess treatment outcomes and establish therapeutic targets, to ensure comparability between future studies.

We aimed to provide expert recommendations for IUS assessment of treatment response in IBD and define IUS key parameters to include in response reporting. We therefore conducted a systematic review of the literature, followed by a RAND/UCLA [University of California at Los Angeles] expert panel appropriateness process.¹⁰

2. Materials And Methods

2.1. Information sources and searches

The systematic review was conducted in accordance with the PRISMA recommendations [PROSPERO-ID CRD42019136983]. A systematic search of Embase [Ovid, 1984], Medline [Ovid, 1946], and Cochrane Central from database inception to February 27, 2020, laid the foundation for the expert consensus process. After the consensus process, an additional systematic search on Embase [Ovid, 1984], Medline [Ovid, 1946], and Cochrane Central from

February 27, 2020, to July 26, 2021, was performed. The detailed search strategies and the outcomes of interest, eligibility, and exclusion criteria are outlined in [Supplementary Material 1, available as Supplementary data at ECCO-JCC online](#). In the tables and figures, updated search articles are identified by a light grey background.

2.2. Study selection and data extraction

All studies were uploaded to the Covidence systematic review software, with automatic removal of duplicates.¹¹ Using a priori defined eligibility criteria, two researchers screened all uploaded titles and abstracts independently. Studies were eligible for inclusion if patients were diagnosed with IBD, in all disease stages, receiving any pharmacological treatment. Patients should undergo at least two IUS assessments during the study period and disease activity should be assessed by either clinical scores, biochemistry, faecal calprotectin [FC], endoscopy, other cross-sectional imaging, or a combination of the above. When published in peer-reviewed journals/presented at conferences, prospective and retrospective full-text articles and abstracts of international conferences were included. Titles and abstracts that met the eligibility criteria and studies with uncertain eligibility were included for full-text screening. The same two researchers independently reviewed these full-text studies to verify the in- and exclusion criteria. Reference lists from reviews and scoring studies were screened for eligibility before exclusion. Articles reporting on the performance of IUS scores were excluded since the performance of these scores has been evaluated elsewhere.^{7,12} In case of disagreement of eligibility, a third researcher was consulted, and consensus through discussion was obtained. During the inclusion process, researchers were not blinded to journal titles, study authors, or institutions. If missing or incomplete data were crucial for the eligibility assessments, study authors were contacted [maximum one email attempt]. All included studies were extracted in accordance with the study protocol. A meta-analysis was not planned, given the expected heterogeneity among studies. The data underlying this article will be shared at reasonable request to the corresponding author.

2.3. Quality assessment

All included studies were independently assessed for risk of bias by at least two researchers, according to the QUADAS-2 tool.¹³ Risk of bias was evaluated across four domains: patient selection, index test, reference standard, and flow and timing. Applicability concerns were evaluated across three domains: patient selection, index test, and reference standard. Any disagreements were first handled between two researchers. A third researcher was consulted if a consensus could not be reached.

2.4. RAND/UCLA process

An expert panel consisting of 18 international IUS experts, all active researchers within IBD and IUS, participated in the modified RAND/UCLA process.¹⁰ Experts were selected from the International Bowel Ultrasound [IBUS] group's executive or scientific committees or close collaborators and active researchers within the topic of this review. There were 195 statements generated based on the evidence from the systematic review, along with additional general statements not covered by the literature search. The expert panellists were asked to individually score the appropriateness of each statement on a Likert scale from 1 [highly inappropriate] to 9 [highly appropriate]. An agreement was met when four or more panellists rated outside the 3-point region containing the median [1–3, 4–6, and 7–9] using the survey tool in REDCap.^{14,15} Dependent on the area of expertise, experts did not vote on all statements [total vote count ranging from 14 to 18, see [Supplementary Material 2, available as Supplementary data at ECCO-JCC online](#)]. In particular, some statements on ulcerative colitis [UC] received fewer votes, which reflects the individual panel members' unwillingness to make a statement based on the low number and quality of published UC articles. Based on the first voting round, the panel met in June 2020 to discuss the voting results via an online videoconference, which led to rephrasing and adding statements for clarification, followed by the second round of individual online rating of 149 statements. A final online videoconference was held to clarify the remaining uncertainties and contradictions in November 2020. A closing voting round with 13 statements followed shortly thereafter.

3. Results

3.1. Systematic review

The first part of the systematic review [database inception to February 27, 2020] resulted in 5419 identified records; 25 articles, 13 abstracts, and one research letter passed the eligibility criteria [[Figure 1](#), white background]. Corresponding authors for three additional articles and five abstracts were contacted for vital data; none rendered any response, and these articles/abstracts were consequently excluded. Only three Crohn's disease [CD] studies and one UC study report sample sizes over 100 patients. Six CD and three UC studies report sample sizes between 50 and 100, and 24 CD and five UC studies report sample sizes between 11 and 48 and 7 and 26, respectively [[Tables 1 and 2](#); and [Supplementary Tables 2 and 3, available as Supplementary data at ECCO-JCC online](#)] [three studies examine both CD and UC]. The selected studies applied to the study questions. However, most studies had high risk of bias in at least one domain. The majority used an inaccurate reference standard, like clinical scores or biochemistry [[Figure 2](#)]. Endoscopy or radiological reference standards exhibited low risk of bias. There were 31/39 failing to report the time between IUS and reference standard. The index test [IUS] risk of bias was evenly distributed

between the low [12], high [11], or unclear [16] categories. A large proportion of unclear assessments came from the included abstracts, 48% [12/25] [[Supplementary Figure 1, available as Supplementary data at ECCO-JCC online](#)].

After the RAND/UCLA process, the additional search resulted in 407 new records, with six articles and three abstracts meeting eligibility criteria [[Supplementary Figure 1](#)]. Despite a high risk of bias, all studies applied to the study question [[Supplementary Figure 2, available as Supplementary data at ECCO-JCC online](#), with a light grey background, and [Supplementary Figure 3, available as Supplementary data at ECCO-JCC online](#)]. Total study populations ranged from 13 to 244. The new data provide a more complete and updated systematic review with more accurate comments on consensus results.

3.2. Rand/UCLA process

The results from the RAND/UCLA process [[Table 3](#)] are presented together with the results from the systematic review, most recent published data, and expert opinion. The RAND/UCLA statements during all three votes can be viewed in [Supplementary Material 2](#). Under inappropriate [InA], uncertain [Unc], and appropriate [App], the number of panellists voting as either 1–3, 4–6, or 7–9 is presented.

3.3. Statements for both Crohn's disease and ulcerative colitis

3.3.1. Machine recommendations.

- 3.3.1.1. Treatment response can be assessed by intestinal ultrasound. [InA. 0, Unc. 0, App. 17]
- 3.3.1.2. Response should be assessed with:
- 3.3.1.2.1. the same type of probe [high frequency vs abdominal probe]; [InA. 0, Unc. 2, App. 15]
- 3.3.1.2.2. constant machine settings [Doppler scale, presets, etc.]. [InA. 1, Unc. 1, App. 15]

A mid- to high-frequency ultrasound probe, >5 MHz, gives higher resolution when imaging the intestine and should therefore be used when assessing inflammation, treatment response, and remission.⁴⁹ An abdominal probe may be useful to map out deeper pelvic structures or complications, but lower-frequency probes do not exhibit sufficient resolution for assessing mural inflammation.⁵⁰ Consistent machine settings using the same type of probe during all IUS examinations reduce confounding factors, ensuring that changes in IUS are attributable to alteration in pathophysiology rather than equipment/acquisition settings. Although consensus was not achieved, using the same machine during follow-up might be preferable, certainly when assessing colour Doppler signals [CDS] [[Supplementary Material 2; second round voting results, 1.2](#)].⁵¹

3.3.2. Response rate.

- 3.3.2.1. Response rate detected by intestinal ultrasound is comparable with:
- 3.3.2.1.1. rate of improvement in luminal inflammation, assessed by endoscopy; [InA. 0, Unc. 3, App. 14]
- 3.3.2.1.2. rate of magnetic resonance enterography improvement. [InA. 0, Unc. 0, App. 17]

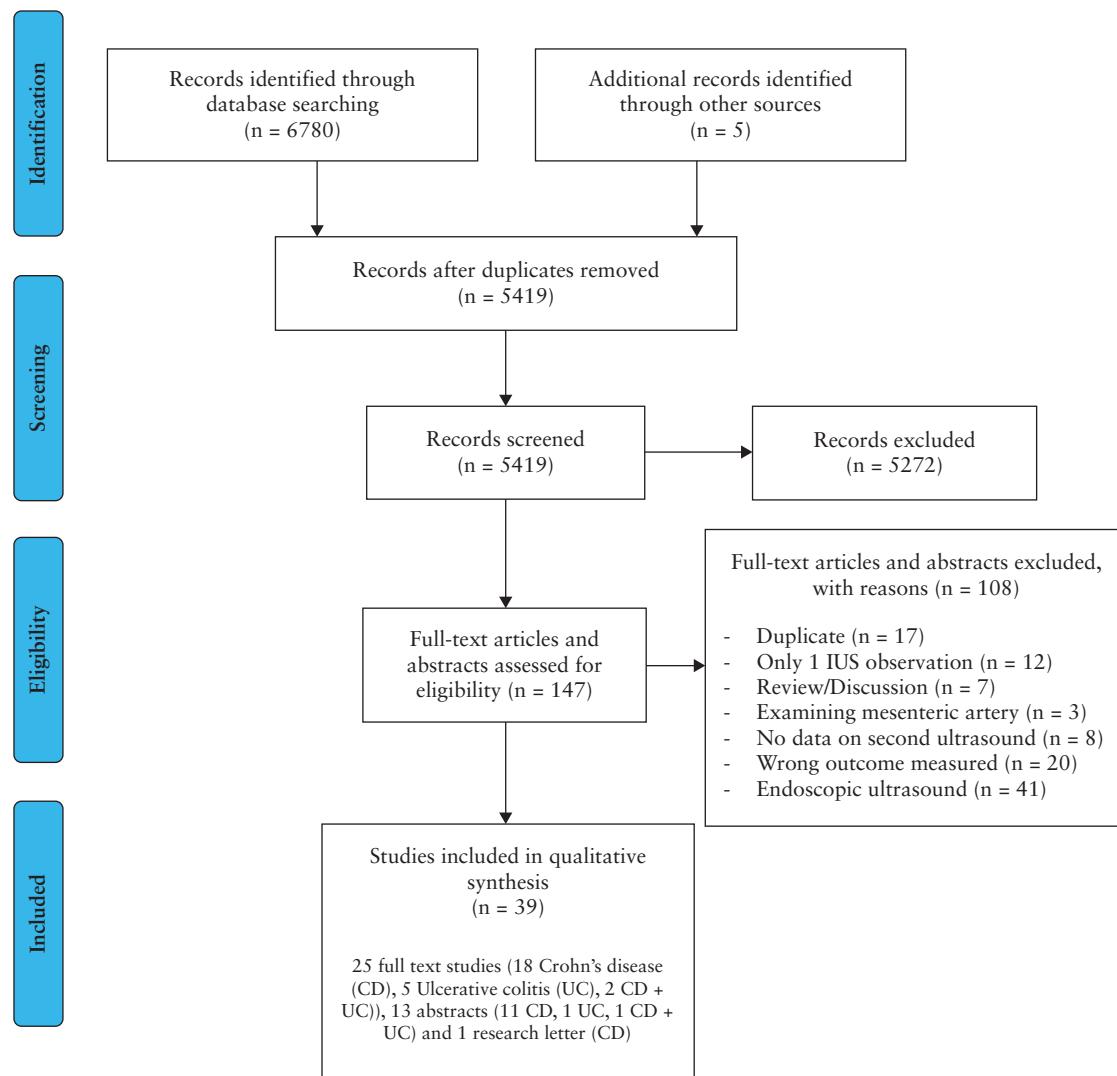


Figure 1. PRISMA flow diagram, summarising the study selection process and results, stop date February 27, 2020.

Therapeutic response rates in IBD are at least in part influenced by the individual therapeutic mechanisms of action, compared with placebo response and the severity and chronicity of disease. Response rates also vary depending on the measure, whether clinical, endoscopic, or a radiological modality. These factors make inter-modality comparisons challenging. Nevertheless, published data support IUS findings demonstrating response rates comparable to those seen on endoscopy and magnetic resonance enterography [MRE]. The largest CD IUS trial by Kucharzik *et al.* [n = 234] showed that 75% of patients exhibited increased bowel wall thickness [BWT] in the terminal ileum and 47% in the sigmoid colon at baseline. After 12 months of therapy, the rates were reduced to 36% and 23%, respectively [n = 134].²⁰ In UC, Maaser *et al.* [n = 224] showed that 89% exhibited increased BWT in the sigmoid colon at baseline, followed by 38% at Week 12 [n = 178].⁴⁰ Similar rates of improvement are reported for endoscopy by Bouguen *et al.*⁵² and Vasudevan *et al.*⁵³ and for MRE by Ordás *et al.*⁵⁴ and Castiglione *et al.*¹⁹

- 3.3.2.2. Response rate in intestinal ultrasound is dependent on:
 - 3.3.2.2.1. class of drug (5-aminosalicylate [5-ASA] vs. steroids vs. immunosuppressants vs. Biologics); [InA. 1, Unc. 3, App. 13]
 - 3.3.2.2.2. disease duration [new-onset vs. long-term established disease]; [InA. 0, Unc. 2, App. 15]
 - 3.3.2.2.3. histological composition of a pathological segment [active inflammation only vs. fibrotic only vs. combined].

Regardless of the reference standard, response rates in IBD are drug dependent.⁹ IUS accurately reflects this during follow-up. No study specifically reports data on 5-ASA-treated patients, IUS demonstrates a rapid response to steroids. In CD patients, early changes are seen after 3–8 days, with an increasing likelihood of observed change after 4 weeks.²² In UC, IUS response can be detected after

Table 1. Crohn's disease—full-text articles—adults.

| Author | No. of patients | Treatment | Time point of assessment | Reference standard | IUS response/remission definition | BWT decrease or no. of patients with/without increased BWT | CDS decrease or no. of patients with/without increased CDS | IUS remission | IUS response/mission association with reference standard |
|--------------------------------|-----------------|----------------------|-----------------------------------|--------------------|--|---|---|---|---|
| Paredes 2019 ¹⁶ | 33 | Anti-TNF | Baseline, 12 weeks, 1 year | CDAI | Response: decrease in BWT >2 mm and CDS decrease by 1 grade. Remission: BWT ≤3 mm and CDS grade 0 or 1 | Week 12: Median decrease 1.5 mm [24%] | Baseline: CDS 2 or 3: 28 [85%] Week 12: 11 [42%] [33%], $p <0.001$ | Week 12: 7 [21%]. 1 year: 14 [42%] | N/A |
| Paredes 2010 ¹⁷ | 24 | Anti-TNF | Baseline, 2 weeks after induction | CDAI | Response: BWT decrease >0.5 mm and CDS decrease by 1 grade. Remission: BWT ≤3 mm, CDS grade 0, no intraabdominal complications | Decrease in 11 [46%] patients. Responders [mean ± SD]: 1.2 ± 1.6 mm [19%]. Non-responders: 0.1 ± 0.2 mm, $p = 0.01$ | Baseline: CDS 2 or 3: 17 [71%] 2 weeks after induction: 11 [46%] $p <0.02$. CDS decreased in 10 [42%] | BWT normalisation: 29%. CDS normalisation: 33%. Transmural complications: 50% | No decrease of BWT or CDS in patients without treatment response, $p <0.05$ |
| Castiglione 2013 ¹⁸ | 133 | Anti-TNF or AZA/6-MP | Baseline, 2 years | CDAI, SES-CD, CRP | Response: N/A. Remission: BWT <3 mm | Mean decrease anti-TNF: 2.0 mm [33%], AZA/6-MP: 0.4 mm [6%] | N/A | Anti-TNF: 17/66 [25%]. AZA/6-MP: 3/67 [5%] | TR with ER: $\kappa = 063$, $p = 001$. 2 TR cases were without ER. |
| Castiglione 2017 ¹⁹ | 40 | Anti-TNF | Baseline, 2 years | CDAI, SES-CD, MRE | Response: N/A. Remission: BWT ≤3 mm | Mean decrease IUS: 2.2 mm [36%]. MRE: 2.7 mm [N/A] | N/A | 10 [25%]: Type of anti-TNF did not determine a significant difference in TR outcome | TR with CDAD: $\kappa = 027$, $p <0.01$. TR with CRP: $\kappa = 079$, $p = 0.02$. IUS remission and ER $\kappa = 063$, $p <0.01$. IUS remission and MRE remission $\kappa = 090$; $p <0.01$. CRP and TR $\kappa = 027$, $p = <0.01$. TR and CRP $\kappa = 079$, $p = 0.02$ |

Table 1. Continued

| Author | No. of patients | Treatment | Time point of assessment | Reference standard | IUS response/relief definition | BWT decrease or no. of patients with/without increased BWT | CDS decrease or no. of patients with/without increased CDS | IUS remission | IUS response/relief association with reference standard |
|---------------------------------|-----------------|---------------------------------|---|--------------------|---|--|---|---------------|--|
| Kucharzik 2017 ²⁰ | 234 | CS, anti-TNF, AZA/MTX, 5-ASA | Baseline, 3 months, 6 months, and 12 months | HBI | Abnormal BWT TI: >2 mm. Colon: >3 mm. Response: N/A. Remission: N/A | Sub-group 1 [all scans, N = 134]: abnormal BWT at baseline, 3, 6, and 12 months: TI: 75%, 57%, 44%, and 36%. Sigmoid: 47%, 22%, 27%, 23%. All with p-values <0.05. Sub-group 2 [baseline, 3 months, N = 182] TI normalisation: 107 [59%]. A 10% or 25% BWT reduction was found in 95% and 80% of patients, respectively | Sub-group 1: CDS 3 + 4. Baseline, 3, 6, 44%, 18%, 14%, and 10%, p <0.001 | N/A | Sub-group 2: BWT reduction = HBI reduction in 86%. CDS change [3 + 4 = >1 + 2] correlated with CRP at Months 3 and 12 in both sub-groups. Sub-group 2: correlation between CRP and BWT [TI], Spearman = 0.46 and BWT and HBI [transverse colon], Spearman 0.42 |
| Ripolles 2016 ²¹ | 51 | Anti-TNF. Anti-TNF + AZA/MTX | Baseline, 12 weeks, 1 year, 2 years [clinical] | HBI, CRP | Response: decrease in BWT [≥ 2 mm], CDS [≥ 1], CEUS—mural enhancement [$\geq 20\%$] and/or absence of complications. Remission: BWT ≤ 3 mm, CDS = 0, no complications | 12 weeks mean decrease: 1.2 mm [18%], p <0.05. 52 weeks: 1.5 mm [24%], p = NS | Baseline CDS 3–4: 43 [84%]. 12 weeks: 19 [37%] p = NS. 26 [51%] improved with normalisation in 7 | N/A | No correlation between clinical and sonographic changes between baseline, 2nd and 3rd examination |
| Ripolles 2008 ²² | 28 | 5-ASA or CS \pm AZA | Baseline, 3–8 days, 4 weeks | CDAI, CRP | BWT ≥ 3 mm abnormal. Response: decrease in CDS [$3 = >2$ or $2 = >0/1$, not from 1 = >0] and BWT [$\geq 25\%$ decrease]. Sonographic active disease: CDS ≥ 2 or BWT >5 mm | 4 weeks mean decrease 0.8 mm [12%], p = NS | Baseline: grade 2–3 vascularity: 18/22 [82%]. CDAI >150 and 4/6 [67%]. CDAI <150 2nd examination: improvement | N/A | No correlation between clinical and sonographic changes between baseline, 2nd and 3rd examination |

Table 1. Continued

| Author | No. of patients | Treatment | Time point of assessment | Reference standard | IUS response/relief definition | BWT decrease or no. of patients with/without increased BWT | CDS decrease or no. of patients with/without increased CDS | IUS remission | IUS response/relief association with reference standard |
|--------------------------------------|-----------------|---------------------|---|------------------------------|---|--|--|--|--|
| Dubbins 1984 ²³ | 19 | AZA/MTX | Baseline, 2–4 months | N/A | N/A | Mean decrease 6 mm [60%] | Mean decrease 6 mm [60%] | N/A | in 5/22 [23%]. 3rd examination: 15/22 [68%] with increased vascular |
| Onali 2010 ²⁴ | 25 | 5-ASA ± CS | 1 year, 2 years, 3 years | CDAI, Rutgeerts' score, SBFT | CD recurrence: 1) BWT >3 mm, 2) stiff loop = increased BWT, not distended by oral contrast, 3) small bowel dilation, diameter >2.5 cm | 1-year recurrence: 2.5/25 [100%]. BWT median [range] 5 mm [3.5–10], 3.5 mm in one patient with Rutgeerts' io 10–2 years: 21/21 [100%]. 3 years: 15/15 [100%]. 3.5 mm in one patient with Rutgeerts' io | N/A | N/A | N/A |
| Moreno 2014 ²⁵ | 30 | Anti-TNF ± AZA/6-MP | Baseline, 14 months [range: 13–25 months] | CDEIS | Remission: BWT ≤3 mm, CDS = 0–1, and CEUS peak enhancement <46% | Mean decrease 3 mm [40%], $p = <0.05$ | Baseline CDS 3–4:27 [90%]. After treatment: 6 [20%], $p \leq 0.001$ | Segmental assessment: 37/59 [64%]. Overall assessment: 15/30 [50%] | Segmental assessment: 37/59 [64%]. Overall assessment: 15/30 [50%] [93%]. Overall: TR vs. ER: $\kappa = 0.73$, $p < 0.001$. BWT ≤3 mm predicts ER |
| Orlando 2018 ²⁶ | 30 | Anti-TNF | Baseline, 14 weeks, 52 weeks | Surgery is outcome | Remission: BWT ≤3 mm | Mean SD decrease 0.74 ± 1.2 mm [1.25 ± 1.95%], $p \leq 0.05$, ADA vs. IFX = NS | BWT variations and TR were not influenced by CDS or BWS [$p = \text{NS}$] | Week 14: 8 [27%]. Week 52: 9 [30%] | N/A |
| Socaciuc 2015 ²⁷ Δ | 13 | N/A | Baseline, 12 weeks | CDAI | N/A | 12 weeks decrease: 1.7 mm [25%] | N/A | Wilcoxon [$z = 213$, $p = 0.033$]. Spearman: [$rho = 0.65$, $p = 0.015$] | |

Table 1. Continued

| Author | No. of patients | Treatment | Time point of assessment | Reference standard | IUS response/relief definition | BWT decrease or no. of patients with/without increased BWT | CDS decrease or no. of patients with/without increased CDS | IUS remission | IUS response/remission association with reference standard |
|----------------------------|-----------------|----------------|---|--------------------|--|---|---|---------------|--|
| Goertz 2018 ³⁸ | 11 | VED | Baseline, 2 weeks, 6 weeks, 14 weeks | HBI | N/A | 5 responders: baseline: 5.3 ± 0.8 mm. Week 14: 5.3 ± 1.8 mm. 6 non-responders: baseline: 6.6 ± 0.6 mm. 14 weeks 6.1 ± 1.2mm | 5 responders: baseline: 2.4 ± 0.9. Week 14: 1.2 ± 0.8. 6 non-responders: baseline: 6.6 ± 0.6 mm. 14 weeks 2.0 ± 0.6, 14 weeks 1.5 ± 0.8 | N/A | N/A |
| Quaia 2019 ³⁹ | 115 | Anti-TNF ± CS | Baseline, 6 to 18 weeks | CDAI, CD-EIS | N/A | 12 weeks decrease: response group: 3.0 mm [43%]. Non-response group: 1.0 mm [14%] | N/A | N/A | N/A |
| Saevik 2014 ³⁰ | 14 | CS or anti-TNF | Baseline, 1 month, 3 months, 12 months | CDAI | BWT > 2 mm abnormal if lumen >0.5 cm or abnormal if BWT > 3 mm + lumen <0.5 cm | 1-month decrease: 0.3 mm [5%]. 12 weeks: 0.01 mm [0.2%]. 1 year: 1.6 mm [34%] | N/A | N/A | N/A |
| Chen 2018 ³¹ | 29 | AZA + EEN | Baseline and when clinical parameters became normal | CDAI, SES-CD | Remission: ≤3 mm and normalization of IUS parameters. ^b CDS 3/4: positive | Decrease 4.4 mm [47%], $p < 0.05$ | Positive baseline: 90%. During follow-up: 17%, $p < 0.05$ | 5 [17%] | N/A |
| Hoffman 2019 ³² | 57 | UST | Baseline, 24 ± 6 weeks, 24–48 ± 6 weeks | HBI | Response: ≤3 mm | Baseline abnormal BWT: 19/22 [79%], 24 ± 6 weeks, 8/13 steroid free | N/A | N/A | |
| | | | | | | clinical remission/non-response, 6/13 [46%] had BWT >3 mm, $p = 0.43$. Weeks 24–48 ± 6: 6/13 in response /remission with improvement or no inflammation vs. 5/13 non-response, $p = \text{NS}$ | | | |

Table 1. Continued

| Author | No. of patients | Treatment | Time point of assessment | Reference standard | IUS response/remission definition | BWT decrease or no. of patients with/without increased BWT | CDS decrease or no. of patients with/without increased CDS | IUS remission | IUS response/remission association with reference standard |
|------------------------------|-----------------|--------------------|---|--------------------|--|---|---|---|--|
| Zorzi 2019 ³³ | 80 | Anti-TNF | Baseline, 18 months [median] | ER | BWT: >3 mm, abnormal. Improved lesions: [a] BWT improvement [≥ 1 mm] or normalisation TI <3 mm; colon <4 mm; [b] decreased length; [c] no worsening of other IUS parameters ^c | 41 [51%] were classified as responders, 27 [34%] as partial responders, and 12 [15%] as non-responders. There was a significant relationship between ultrasonographic response and clinical outcomes considered | N/A | N/A | N/A |
| Calabrese 2021 ³⁴ | 188 | ADA, IFX, UST, VED | Baseline, 3 months, 6 months, 12 months | HBI, CRP, FCP | Remission: ileum BWT \leq 3 mm, colon BWT \leq 4 mm and normalisation of other parameters ^d | Ileum: median 0.5 mm [8%]. 6 months: 1 mm [17%]. 12 months: 1 mm [17%], $p < 0.05$. Colon: 3 months: 0.85 mm [14%]. 6 months: 1.45 mm [23%]. 12 months: 2.35 mm [37%], $p < 0.05$ | Ileum: baseline: 125/158 [79%] with increased CDS, 3 months: 89/158 [56%]. Colon: 3 months: 67/156 [43%]. 12 months: 52/133 [39%], $p < 0.05$. Colon: baseline: 22/30 [73%]. | 3 months: 125/158 [79%]. 6 months: 31/188 [16%]. | |
| Hoffman 2020 ³⁵ | 23 | UST | Baseline, 8 weeks | CDAI, CRP | Response: decrease of BWT ≥ 1.0 mm | 10/23 [43%] responded | [39%], $p < 0.05$ | 3 months: 14/30 [47%]. 6 months: 10/25 [40%]. 12 months: 9/23 | |
| | | | | | | Baseline: 9 patients with Limberg 2, 8 weeks: 4 | Baseline: 9 patients with Limberg 2, 8 weeks: 4 | Responders: substantial decrease in CDAI ≥ 70 points and CRP ≥ 0.5 mg/dl in 9/10 and 8/10, respectively | |

Table 1. Continued

| Author | No. of patients | Treatment | Time point of assessment | Reference standard | IUS response/remission definition | BWT decrease or no. of patients with/without increased BWT | CDS decrease or no. of patients with/without increased CDS | IUS remission | IUS response/remission association with reference standard |
|--|-----------------|--|--------------------------------------|-----------------------------|---|--|---|--|--|
| Li Ma 2021 ³⁶ | 77 | AZA/MTX ± Anti-TNF, 5-ASA | Baseline, 6 months | CDAI, CRP, SES-CD, CTE, MRE | Remission: BWT ≤ 3 mm and normalisation of other parameters ^e | N/A | N/A | 6 months: 25/77 [32%] | TR and ER poorly correlated, $k = 0.387, p < 0.05$ |
| Helwig 2021 ³⁷ ^f | 180 | AZA/MTX ± anti-TNF, anti-integrin, systemic CS | Baseline, 12 ± 4 weeks, 52 ± 4 weeks | HBI | Response: BWT reduction ≥ 25% or a normalisation of BWT/Remission: three different definitions. 1] Normalisation of BWT [ileum ≤ 2 mm, sigmoid ≤ 4 mm, rest of colon ≤ 3 mm] and normalised CDS, 2] normalised BWT and CDS, restored BWS and no I-fat [minus one factor that could not be assessed]. 3] All factors normalised | 12 weeks: No. of patients with response: 77/118 [65%] | N/A | 12 weeks: Definition: 1: 58/180 [32%] 2: 67/180 [37%] 3: 43/180 [24%] | 12 weeks: Definition: 1: 58/180 [32%] 2: 67/180 [37%] 3: 43/180 [24%] |
| Jessen 2020 ³⁸ ^g | 21 | IFX | Baseline, Week 6 | HBI, partial Mayo score | N/A | N/A | Data not stratified by disease. | N/A | N/A |
| | | CD, 20 UC | | | | | Responders: median 1 CDS point decrease Non-responders: median 0 CDS points decrease | | |

⁵-ASA, mesalazine; ADA, adalimumab; anti-TNF, infliximab and adalimumab; AZA, azathioprine; AZA/6-MP, azathioprine/mercaptopurine; CDAI, Crohn's Disease Activity Index; CDS, colour Doppler signal; CRP, C-reactive protein; CS, corticosteroids; CTE, computer tomography enterography; EEN, Total Protein Enteral Nutritional Powder; ER, endoscopic remission; FCP, faecal calprotectin; HBI, Harvey-Bradshaw Index; IEX, infliximab; IUS, intestinal ultrasound; MRE, magnetic resonance enterography; N/A, not available; NS, not significant; UST, ustekinumab; SBT, small bowel follow-through; SD, standard deviation; SES-CD, Simple Endoscopic Score—Crohn's Disease; TI, terminal ileum; TR, transmural remission; UC, ulcerative colitis; VED, vedolizumab; CEUS, contrast-enhanced ultrasound.

^aNo colour Doppler signal, normal five-layer bowel wall stratification, no lymph node enlargement, or presence of strictures or pre-stenotic dilation.

^bNo colour Doppler signal, normal bowel wall stratification, strictures, fistulae, inflammatory fat, lymph nodes, stenosis, pre-stenotic dilation, abscesses, fissures, and fistulae.

^cOr fistulising disease.

^dColour Doppler signals, length of disease, bowel wall stratification, inflammatory mesenteric fat, lymph nodes, stenosis, pre-stenotic dilation, abscesses, fissures, and fistulae.

^eColour Doppler signals, bowel wall stratification, inflammatory mesenteric fat, abscesses, and fistulae=.

^fReport data on both Crohn's disease and ulcerative colitis, stratified by disease.

^gReport data on both Crohn's disease and ulcerative colitis, not stratified by disease.

Table 2. Ulcerative colitis.

| Author | Total no. patients | Treatment | Time of assessment | Reference standard | IUS response/remission definition | BWT decrease or no. of patients with/without increased BWT | CDS decrease or number of patients with/without increased CDS | IUS remission | IUS response/ remission association with reference standard |
|-----------------------------|--------------------|--|---|---|---|--|--|---------------|--|
| Socaciu 2015 ^{27b} | 25 | N/A | Baseline, 3 months | Truelove-Wirts | N/A | Median decrease 0.15 mm [3%] | N/A | N/A | Wilcoxon [Z = 0.85, $p = \text{NS}$], Spearman: [$\rho = 0.28$ $p = \text{NS}$] N/A |
| Goertz 2018 ^{28b} | 7 | VEDO | Baseline, 2 weeks, 6 weeks, 14 weeks | Mayo score | N/A | Responders: N = 4, 10 mm [17%]. Non-responders: N = 3, NS | N/A | N/A | |
| Parente 2010 ³⁹ | 74 | CS | Baseline, 3 months, 9 months, 15 months | Baron endoscopic score | US severity [0–3] Grade 0 = BWT <4 mm, CDS 0–1 Grade 1 = BWT 4–6 mm, CDS 1 = BWT 4–6 mm, CDS 2 = Grade 2 = BWT 6–8 mm, CDS 2 = Grade 3 = BWT >8 mm, CDS 2 = 2 | Normal colon = sigmoid colon ≤4.0 mm, descending, transverse and ascending colon ≤3.0 mm | US decrease or no. of patients with/without increased BWT | N/A | 3 months: $\kappa = 0.76$ 9 months: $\kappa = 0.88$ 15 months: $\kappa = 0.9$ |
| Maaßer 2019 ⁴⁰ | 224 | CS, AZA/ κ -MP, Anti-TNF, Anti-integrin | Baseline, 2 weeks, 6 weeks, 12 weeks | SCCAI | Increased BWT: sigmoid colon at baseline, 2, 6, and 12 weeks 89%, 39%, 35%, and 32%Descending colon at baseline, 2, 6, and 12 weeks 83%, 43%, 43%, and 38% | Increased BWT: sigmoid colon at baseline, 2, 6, and 12 weeks 23%, 16%, and 13%. Descending colon at baseline, 2, 6, and 12 weeks 15%, 7%, 5%, and 7% | Improvements in CDS; sigmoid colon at baseline, 2, 6, and 12 weeks 23%, 16%, and 13%. Descending colon at baseline, 2, 6, and 12 weeks 15%, 7%, 5%, and 7% | N/A | |
| Maconi 1999 ⁴¹ | 30 | CS ± 5-ASA ± salazopyrine | Baseline, 2 months | Truelove-Wirts X-ray double-contrast barium enema | Abnormal BWT ≥4 mm of 2.3 mm [31%]. 14 [47%] did not improve | 2 months: 16 [53%] improved. Decrease of 2.3 mm [31%]. 14 [47%] did not improve | N/A | N/A | 1-year relapse: 1 in EUR group, 9 in non-EUR group N/A |
| Yoshida 2011 ⁴² | 26 | Cyatheresis ± CS + 5-ASA | Baseline, 2–3 weeks | UC-DAI score, at baseline and 12 months | Early ultrasonic response [EUR]: decrease in BWT by >2.5 mm | +0.7 mm, $p = \text{NS}$ | N/A | N/A | |
| Hearn 2019 ^{43a} | 9 | N/A | Baseline + 11 months | N/A | N/A | BWT improvement: onographic remission 1.6 mm, $p = 0.04$. No sonographic remission 0.1 mm, $p = \text{NS}$ | 2 [22%] | N/A | |

Table 2. Continued

| Author | Total no. patients | Treatment | Time of assessment | Reference standard | IUS response/definition | BWT decrease or no. of patients with/without increased BWT | CDS decrease or number of patients with/without increased CDS | IUS remission | IUS remission association with reference standard |
|---------------------------------|--------------------------------|---------------------|--------------------------------------|--|--|---|--|--|---|
| Maser 2019 ^{4a} | [29%] from study nr 4 | Anti-TNF | Baseline, 2 weeks, 6 weeks, 12 weeks | SCCAI, CRP, FCP | Abnormal BWT sigmoid colon,>4 mm, descending colon>3 mm | Week 6: 44 received anti-TNF21 [48%] normalised.15 [34%] decrease in BWT | Increased CDS at Weeks 6 and 12 had higher SCCAI than no CDS [$p < 0.001$] | N/A | N/A |
| Arienti 1996 ⁴⁵ | 57 | High doses of IV CS | Baseline, 10 days | Truelove-Witts | Normal BWT <3mm “ultrasonic activity index” = the sum of maximum BWT in all four segments [in mm] | IUS activity in the severe group All: before treatment: 1.89 mm, after treatment 1.89 mm, $p = 0.001$ | In the 8/41 [19.5%] patients that underwent surgery 3 months later, none had an improvement in IUS parameters, some worsening 5/41 [12%] | N/A | In the 8/41 [19.5%] |
| De Voogd 2021 ^{46a} | 29 | TOF | Baseline, 8 weeks | Endoscopic Mayo score, Robarts Histology Index | N/A | Endoscopic remission group: BWT sigmoid mean reduction, 2.59 ± 1.44 mm, descending colon, 1.82 ± 1.01 mm, $p = <0.05$. Endoscopic remission showed a cut-off value for BWT in sigmoid ≤ 2.87 mm [AUROC: 0.91 [0.83–0.99], sensitivity 83% and specificity 100%] and for descending, ≤ 2.80 mm [AUROC: 0.98 [0.94–1.00], sensitivity 91% and specificity 92%] | N/A | BWT and endoscopic Mayo score showed high correlation [$\rho = 0.68$ sigmoid colon, $\rho = 0.75$ descending colon, $p < 0.05$]. BWT and Robarts Histology Index moderate correlation [$\rho = 0.49$, $p < 0.05$] | |

Table 2. Continued

| Author | Total no. patients | Treatment | Time of assessment | Reference standard | IUS response/definition | BWT decrease or no. of patients with/without increased BWT | CDS decrease or number of patients with/without increased CDS | IUS remission | IUS response/remission association with reference standard |
|-----------------------------------|--------------------|--|-----------------------|-------------------------|--|--|--|---|--|
| Helwig 2021 ^{37b} | 171 | AZA/MTX ± Anti-TNF, Anti-integrin; systemic CS | Baseline,12 ± 4 weeks | SCCA1 | Response: BWT reduction >25% or a normalisation of BWT;Remission: three different definitions. 1] Normalisation of BWT [ileum ≤2 mm, sigmoid ≤4 mm, rest of colon ≤3 mm] and normalised CDS. 2] Normalised BWT and CDS, restored BWS and no I-fat [minus one factor that could not be assessed]. 3] All factors normalised | 12 weeks: no. of patients with response: 100/131 [76%] | N/A | 12 weeks: Definition1] 90/171 [53%][2] 105/171 [61%][3] 77/171 [45%] | N/A |
| Jessen 2020 ^{38c} | 21 CD, 20 UC | IFX | Baseline, Week 6 | HBI, partial Mayo score | N/A | Data not stratified by disease. Responders: median 1 CDS point decrease. Non-responders: median 0 CDS points decrease | N/A | N/A | N/A |
| Kucharczik 2020 ^{47,48c} | 21 CD, 29 UC | Biologics, JAK2 inhibitor | Baseline, Week 12 | HBI, SCCAI | Abnormal BWT: sigmoid colon >4 mm, rest of colon and ileum >3 mm | Data not stratified by disease. Pathological segments baseline: 121 [54.8%]. Week 12: 53 [24%], $p < 0.05$ | Data not stratified by disease. Baseline: 25 [50%] patients with increased CDS. Week 12: 7 [14%], $p < 0.05$ | N/A | N/A |

Table 2. Continued

| Author | Total no. patients | Treatment | Time of assessment | Reference standard | IUS response/remission definition | BWT decrease or no. of patients with/without increased BWT | CDS decrease or no. of patients with/without increased CDS | IUS remission association with reference standard |
|----------------------------|--------------------|-----------|--------------------|-------------------------------------|-----------------------------------|--|--|---|
| Maaser 2020 ^{a,b} | 244 | N/A | Baseline, Week 12 | Stool frequency and rectal bleeding | Abnormal BWT: sigmoid colon >4 mm | N/A | N/A | Rectal bleeding correlation with abnormal BWT: $r = 0.417$. Stool frequency correlation with abnormal BWT: $r = 0.483$. The two combined: $r = 0.518$ |

Anti-TNF, infliximab, adalimumab, or golimumab; AZA/6-M, azathioprine/mercaptopurine; AZA/MTX, azathioprine/methotrexate; biologics, no data on which biologics; BWT, bowel wall thickness; CDS, colour Doppler signal; CRP, C-reactive protein; CS, corticosteroids; FCP, faecal calprotectin; IFX, infliximab; N/A, not available; SCCAI, Simple Clinical Colitis Activity Index; TOF, tofacitinib; UC, ulcerative colitis; UC-DAI, Ulcerative Colitis Disease Activity Index; VEDO, vedolizumab; IUS, intestinal ultrasound; IV, intravenous; CD, Crohn's disease; HBI, Harvey-Bradshaw Index; AUROC, area under receiver operating characteristic curve.

^aAbstract.

^bReport data on both Crohn's disease and ulcerative colitis, stratified by disease.

^cReport data on both Crohn's disease and ulcerative colitis, not stratified by disease.

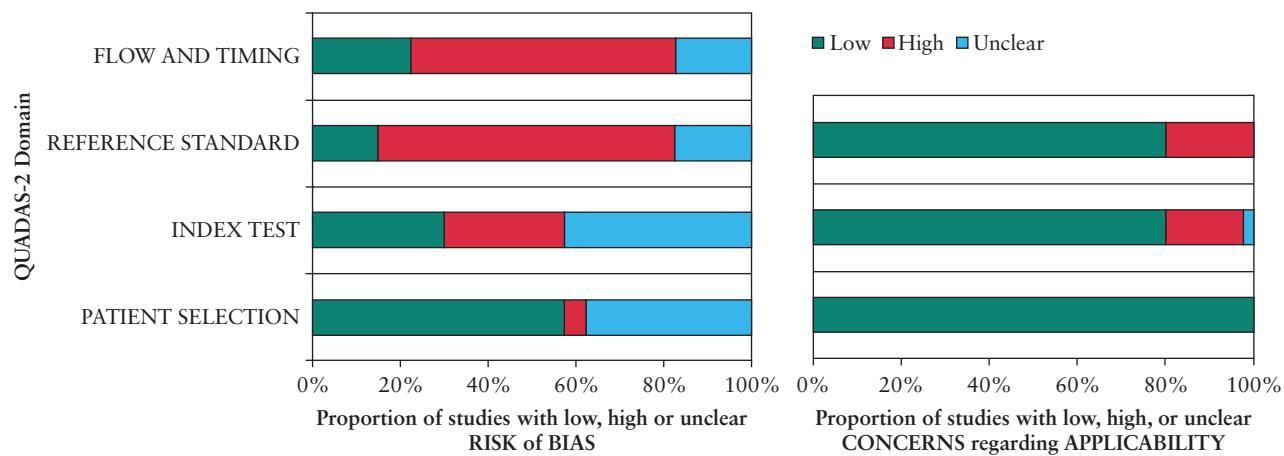


Figure 2. Risk of bias and applicability—studies from the systematic review, stop date February 27, 2020.

10–14 days,^{40,45} possibly even earlier.⁵⁵ Such rapid rates of improvement have not been reported for biologics or immunomodulators. Two years after treatment initiation with either anti-tumour necrosis factor [TNF] or azathioprine, Castiglione *et al.* showed a significant difference in transmural remission [TR] rates by 25% [17/66] vs. 4% [3/67], respectively.¹⁸ In addition, a pediatric [$n = 28$]⁵⁶ and an adult study [$n = 234$],²⁰ showed no difference in changes of IUS parameters between patients treated with anti-TNF as monotherapy or in combination with azathioprine, 6 and 12 months after treatment initiation, respectively.

In CD patients, a shorter disease duration [11 ± 8 vs. 19 ± 9 months, $p = 0.01$] is associated with better IUS and endoscopic responses after 2 years of maintenance treatment with biologics or thiopurines.¹⁸ After 3 months of variable treatment, a divergence of treatment effect can be seen; 41% [$n = 16$] with disease duration <2 years exhibited improvement, compared with 20% [$n = 10$] with a disease duration >5 years, $p < 0.001$.²⁰ After 12 months [$n = 188$], the only predictor for higher risk of unchanged/worsened disease was a longer disease duration, $p = 0.02$ (odds ratio [OR] 3.0, [1.2–7.9]).³⁴

Strictures and/or fistulae prognosticate inadequate treatment response, with reported data showing inconsistent results. After 12 weeks of anti-TNF treatment, 33% [3/9] with baseline stenosis or fistulae responded to treatment.¹⁶ After 2 years, 17% [1/6] with stenosis responded.¹⁹ Other studies found no response after 12 and 14 months, respectively [0/5,²¹ 0/3²⁵]. The presence of stenosis before biologic treatment was associated with worse IUS response after 12 weeks, $p < 0.001$.²¹ These rates are much lower than uncomplicated luminal inflammation. Taken together, differences in IUS responses are more likely explained by patient phenotype, disease course, and treatment efficacy than by IUS-specific factors.

- 3.3.2.3. Response time is generally shorter in ulcerative colitis compared with Crohn's disease. [InA. 0, Unc. 1, App. 16]
- 3.3.2.4. In responders, colonic disease tends to respond faster with respect to reduced bowel wall thickness than small bowel disease. [InA. 0, Unc. 2, App. 15]

Most studies report cross-sectional data on disease location and distribution at baseline but do not report stratified measures during

follow-up. Thus, our statements are based on limited evidence. Kucharzik *et al.* [$n = 234$, variable treatment] showed normalisation of BWT in the colon within 3 months, with only minor improvement thereafter. For terminal ileum, the proportion of patients with normalisation of BWT increased steadily throughout the 12-month follow-up period.²⁰ These findings were similar to the STARDUST sub-study [$n = 76$, ustekinumab], with IUS response for colon and terminal ileum at 40% and 30%, respectively, at Week 16,⁵⁷ with a continued difference at Week 48, 63% vs. 40%.⁵⁸ A significant reduction of BWT was already observed at Week 4.⁵⁷ Early initial response was also documented in a paediatric population with a significant reduction of BWT, CDS, and length of disease 2 weeks after initiation with infliximab [IFX].⁵⁶ In adults with UC, a significant and clinically relevant proportion of patients showed normalisation of BWT after only 2 weeks of treatment.⁴⁰ Given the anatomical location of disease and the fact that CD is a transmural disease whereas UC is not, response may occur faster in UC than in CD. This claim is further supported by many of the co-authors' clinical observations.

- 3.3.2.5. Response rate, in general, is different for:
 - 3.3.2.5.1. strictures than luminal disease; [InA. 0, Unc. 2, App. 15]
 - 3.3.2.5.2. phlegmons than luminal disease; [InA. 0, Unc. 3, App. 14]
 - 3.3.2.5.3. abscesses than luminal disease. [InA. 0, Unc. 2, App. 15]

Treatment responsiveness is related to the reversibility of the disease process. In a mixed cohort of patients with inflammatory and stricturing CD, treated with anti-TNF as monotherapy or in combination with azathioprine for 12 weeks, all 33 patients with inflammatory disease responded as determined by reducing BWT, compared with only 6/9 with stricturing disease.¹⁶ After 2 years of treatment, only 17% [1/6] with stricturing disease achieved TR, compared with 23% [9/40] with inflammatory luminal disease.¹⁹ Similarly, Ripollés *et al.* report an IUS response/remission for 56% [29/51] after 1 year, with no improvement documented in the six patients with stricturing disease. Stricturing behaviour was the only sonographic feature associated with a negative predictive value for response [$p = 0.0001$].²¹ The same tendency was reported by Moreno *et al.*, with three colonic strictures at baseline turning into four after a median duration of 14 months, whereas a significant luminal improvement in other

Table 3. RAND/UCLA process results.

| | | InA | Unc | App | Total |
|--|--|-----|-----|-----|-------|
| 3.3.3. Statements for both Crohn's disease and ulcerative colitis | | 0 | 0 | 17 | 17 |
| 3.3.3.1. Machine recommendations | | 0 | 0 | 17 | 17 |
| 3.3.3.1.1. Treatment response can be assessed by intestinal ultrasound | | 0 | 0 | 17 | 17 |
| 3.3.3.1.2. Response should be assessed with: | | 0 | 0 | 17 | 17 |
| 3.3.3.1.2.1. - the same type of probe [high-frequency vs. abdominal probe] | | 0 | 2 | 15 | 17 |
| 3.3.3.1.2.2. - constant machine settings [Doppler scale, preset, etc.] | | 1 | 1 | 15 | 17 |
| 3.3.3.2. Response rate | | | | | |
| 3.3.3.2.1. Response rate detected by intestinal ultrasound is comparable with: | | 0 | 3 | 14 | 17 |
| 3.3.3.2.1.1. - rate of improvement in luminal inflammation, assessed by endoscopy | | 0 | 0 | 17 | 17 |
| 3.3.3.2.1.2. - rate of magnetic resonance enterography improvement | | 0 | 0 | 17 | 17 |
| 3.3.3.2.2. Response rate in intestinal ultrasound is depending on: | | 1 | 3 | 13 | 17 |
| 3.3.3.2.2.1. - class of drug [mesalazine vs. steroids vs. immunosuppressants vs. biologics] | | 0 | 2 | 15 | 17 |
| 3.3.3.2.2.2. - disease duration [new onset vs. long-term established disease] | | 0 | 1 | 16 | 17 |
| 3.3.3.2.2.3. - histological composition of pathological segment [active inflammation only vs. fibrotic only vs. combined] | | 0 | 1 | 16 | 17 |
| 3.3.3.2.3. Response time is generally shorter in ulcerative colitis compared with Crohn's disease | | 0 | 1 | 16 | 17 |
| 3.3.3.2.4. In responders, colonic disease tends to respond faster with respect to bowel wall thickness than small bowel disease | | 0 | 2 | 15 | 17 |
| 3.3.3.2.5. Response rate in general is different for: | | 0 | 2 | 15 | 17 |
| 3.3.3.2.5.1. - strictures than luminal disease | | 0 | 3 | 14 | 17 |
| 3.3.3.2.5.2. - phlegmons than luminal disease | | 0 | 2 | 15 | 17 |
| 3.3.3.2.5.3. - abscesses than luminal disease | | 0 | 2 | 15 | 17 |
| 3.3.3.3. Length of disease | | | | | |
| 3.3.3.3.1. Length in both Crohn's disease and ulcerative colitis should be reported using involved colonic segment[s] [sigmoid colon, descending colon, transverse colon, ascending colon, caecum] | | 0 | 0 | 18 | 18 |
| 3.3.3.3.2. For terminal ileum, length should be reported as distance in cm and distance from ileocaecal valve [if possible] or as proximal small bowel | | 0 | 0 | 18 | 18 |
| 3.3.3.4. Measuring bowel wall thickness | | | | | |
| 3.3.3.4.1. Response depends on baseline thickness and should be reported in: | | 2 | 1 | 14 | 17 |
| 3.3.3.4.2. - absolute [mm] and relative [%] change from baseline | | 0 | 1 | 15 | 16 |
| 3.3.3.4.3. - continuous measurements and is preferred over categories | | 0 | 1 | 16 | 17 |
| 3.3.3.4.4. - continuous measurements and should be measured with one decimal for increased precision | | 1 | 1 | 15 | 17 |
| 3.3.3.4.5. - continuous measurements, as a mean of two measures in cross-section and two measures in longitudinal orientation | | | | | |
| 3.3.3.5. Defining the worst segment | | | | | |
| 3.3.3.5.1. The worst segment in both Crohn's disease and ulcerative colitis is defined by the most pathological bowel wall thickness; however, if two segments have the same bowel wall thickness, the order of secondary parameters for defining the worst segment should be the grading of colour Doppler signals, bowel wall stratification, and then inflammatory mesenteric fat, respectively | | 0 | 1 | 17 | 18 |
| 3.3.3.6. Disease activity indices | | | | | |
| 3.3.3.6.1. If a score is used, the score should summarise measures of all individual segments | | 0 | 3 | 14 | 17 |
| 3.3.3.6.2. Treatment response could be a combined change in one or more activity parameters, specified as a point-reduction from an activity score [present or in the future], bowel wall thickness [continuous, and/or colour Doppler signals [ordinal], and/or bowel wall stratification [ordinal], and/or inflammatory mesenteric fat [ordinal]] [IBUS-SAS] | | 0 | 3 | 14 | 17 |

Table 3. Continued

| | |
|--|--------------------------|
| 3.4. Crohn's disease | |
| 3.4.1. Response definition and timing of assessment in Crohn's disease | |
| 3.4.1.1. Treatment response is identified by reduction of bowel wall thickness [continuous measurements] [$>25\%$ or >2.0 mm or [>1.0 mm and one colour Doppler signal reduction] | 0 3 15 18 |
| Intestinal ultrasound complications that should be assessed for response: | |
| 3.4.1.2. - strictures | 0 2 15 17 |
| 3.4.1.2.1. - phlegmons | 0 3 14 17 |
| 3.4.1.2.2. - abscesses | 1 3 13 17 |
| 3.4.1.2.3. - abscesses | 0 0 0 17 |
| 3.4.1.3. Response should initially be assessed in the small and large bowel after treatment initiation [regardless of treatment] at 14 ± 2 weeks. However, in a subset of patients, response after steroids or biologics may occur already after 4 weeks. Early intestinal ultrasound assessment may in certain situations be beneficial between Weeks 4 and 8 | 0 |
| 3.4.1.4. Ideal assessment of intestinal ultrasound response within first year of treatment initiation/escalation/change is at baseline, Week 14 ± 2 , and between Weeks 26 and 52 + IUS depending on elevated faecal calprotectin or symptoms or clinical suspicion of flare | 1 1 15 17 |
| 3.4.2. Transmural remission, definition and timing of assessment in Crohn's disease | |
| 3.4.2.1. Transmural remission of terminal ileum, small and large bowel is defined by bowel wall thickness ≤ 3 mm and normal/no colour Doppler signal | 0 1 17 18 |
| In some patients, sigmoid colon may contain an enlarged muscularis propria [outer hypoechoic layer—typical in diverticular disease], allowing for bowel wall thickness up to 4 mm without resembling active inflammation | 3 1 13 17 |
| 3.4.2.2. Transmural remission should be assessed after treatment initiation [regardless of treatment] between 26 and 52 weeks. | 0 3 14 17 |
| 3.4.2.3. Transmural remission may occur already at Week 12 but with increasing likelihood up to 1 [maybe 2] years | 0 0 17 17 |
| 3.5 Ulcerative colitis | |
| 3.5.1. Response definition and timing of assessment in ulcerative colitis | |
| 3.5.1.1. Treatment response in ulcerative colitis is identified by reduction of bowel wall thickness [continuous measurements] [$>25\%$ or >2.0 mm or >1.0 mm and one colour Doppler signal reduction] | 0 3 15 18 |
| Ideal assessment of intestinal ultrasound response within first year of treatment initiation/escalation/change is at baseline, Week 14 ± 2 , and between Weeks 26 and 52 + intestinal ultrasound depending on elevated faecal calprotectin or symptoms or clinical suspicion of flare | 0 2 14 16 |
| 3.5.1.2. After treatment initiation, response should be measured in all segments that were affected at baseline | 0 0 14 14 |
| 3.5.2. Transmural remission, definition, and timing of assessment in ulcerative colitis | |
| 3.5.2.1. Transmural remission in ulcerative colitis of the large bowel is defined by bowel wall thickness ≤ 3 mm and normal/no colour Doppler signal | 0 1 17 18 |
| In some patients, sigmoid colon may contain an enlarged muscularis propria [outer hypoechoic layer—typical in diverticular disease], allowing for bowel wall thickness up to 4 mm without resembling active inflammation | 3 1 13 17 |
| 3.5.2.2. Transmural remission in ulcerative colitis should be assessed after treatment initiation [regardless of treatment] at Week 14 ± 2 . | 0 2 16 18 |
| 3.5.2.3. Transmural remission in ulcerative colitis may occur already at Week 4 but with increasing likelihood up to Week 12 [potentially 1 year] | 1 3 14 18 |
| 3.6. Adults vs. paediatric population | |
| 3.6.1. The remission/response statements for Crohn's disease, may be used in both adult and paediatric populations | 2 1 14 17 |
| 3.6.2. The remission/response statements for ulcerative colitis, may be used in both adult and paediatric populations | 2 2 12 16 |
| Under inappropriate [InA], uncertain [Unc], and appropriate [App], the number of panelists voting as either 1–3, 4–6, or 7–9 is presented. | |

IBUS-SAS, International Bowel Ultrasound Segmental Activity Score; IUS, intestinal ultrasound.

segments/patients was observed.²⁵ In a paediatric study by Civitelli *et al.*, 4/32 had stricture disease at baseline with no significant improvement after 9–12 months.⁵⁹ In the large TRUST CD trial [$n = 134$], the presence of strictures at baseline was 25%, followed by 12% [$p = 0.03$], 10% [$p = 0.001$], and 9% [$p \leq 0.001$], at 3, 6, and 12 months respectively. The presence was 5% for abscesses, followed by 2%, 1.5%, and 0.7%, respectively, non-significant [NS]. Both BWT and CDS had higher improvement rates compared with these complications.²⁰ No study report data on phlegmons. In the RAND/UCLA process, only one study specifically reported on fistula healing response with a transabdominal approach.³¹ Consequently, statements regarding fistulae were not included in the RAND/UCLA process. Moreno *et al.* [$n = 46$, entero-mesenteric in 70%] recently published a retrospective study, showing that a complete closure of fistulae was achieved in 24/46 [52%] after immunosuppressive treatment, suggesting that IUS could be efficient in monitoring fistulae.⁶⁰ However, high-quality studies focusing on strictures, fistulae, phlegmons, and abscesses are warranted.

3.3.3. Length of disease

- 3.3.3.1. Length in both Crohn's disease and ulcerative colitis should be reported using involved colonic segment[s] [sigmoid colon, descending colon, transverse colon, ascending colon, cecum]. [InA. 0, Unc. 0, App. 18]
- 3.3.3.2. For the terminal ileum, the length should be reported as distance in cm and distance from the ileocaecal valve [if possible] or as proximal small bowel. [InA. 0, Unc. 0, App. 18]

Length of disease is rarely reported in prospective observational trials and almost never included in their IUS response/remission definition. If reported, studies use the extension of disease in centimetres and/or affected bowel segment.³⁰ Castiglione *et al.* [$n = 40$ CD patients] showed that small bowel length decreased from 35 ± 18 cm at baseline to 20 ± 11 cm after 2 years of treatment with anti-TNF, $p \leq 0.01$. Corresponding data for MRE were 45 ± 15 cm to 18 ± 12 cm, $p < 0.001$.¹⁹ Calabrese *et al.* [$n = 188$ CD patients] showed a decrease of median length [range] of ileal disease from 15 [4–60] cm at baseline, to 10 [0–60] cm after 3 months, 10 [0–60] cm after 6 months, and 10 [0–50] cm after 12 months of treatment with biologics, $p < 0.05$. Corresponding values for colonic disease were 40 [20–100] cm, 30 [0–100] cm, 20 [0–100] cm, and 10 [0–100] cm, respectively, $p < 0.05$.³⁴ Three pediatric CD studies used similar ways of reporting extension. After treatment with anti-TNF ± immunomodulators, IUS length decreased from 13 ± 5 cm to 8 ± 6 cm after 9–12 months [$n = 32$]⁵⁹ and from 12 ± 5 cm to 9 ± 5 cm [2 weeks], 8 ± 7 cm [4 weeks], 4 ± 4 cm [13 weeks], and 5 ± 6 cm [26 weeks], $p < 0.0001$ [$n = 28$].⁶¹ Only in patients with endoscopic response did the extension decrease significantly.⁵⁹ Similar data were reproduced in an abstract [$n = 13$ children, CD] exhibiting a decrease from 11.3 ± 1.4 cm to 6.8 ± 3.8 cm, 14 weeks after treatment initiation.⁶¹ Another way of reporting the extent of disease is the number of affected segments before and after treatment. In CD patients, 59 segments containing ulcers were evaluated with IUS and endoscopy after a mean treatment period of 14 months with anti-TNF and or immunomodulators. Endoscopy showed remission in 42 segments and IUS showed remission

in 37, $\kappa = 0.76$, $p = 0.001$. Endoscopy identified 77 affected segments at baseline, and IUS identified 75. During follow-up, the numbers were reduced to 43 and 29, respectively, $p < 0.001$.²⁵ In UC, using X-ray double-contrast barium enema as the reference standard, IUS correctly defined the extension of UC in 74% of patients, 9/11 with left-sided, 4/7 with subtotal, and 7/9 with pancolitis.⁴¹ Further, the two largest studies on UC and CD report their data based on segmental involvement, which gives a good overview of the treatment response and/or remission for different segments and thereby the burden of disease over time.^{20,40}

3.3.4. Measuring bowel wall thickness

- 3.3.4.1. Response depends on baseline thickness and should be reported in:
absolute [mm] and relative [%] change from baseline; [InA. 2, Unc. 1, App. 14]
- 3.3.4.1.2. continuous measurements, preferred over categories; [InA. 0, Unc. 1, App. 15]
- 3.3.4.1.3. continuous measurements within 1 decimal for increased precision; [InA. 0, Unc. 1, App. 16]
- 3.3.4.1.4. continuous measurements, as a mean of two measures in cross-section and two measures in longitudinal orientation. [InA. 1, Unc. 1, App. 15]

The exact method for measuring BWT, number of measures, and values are rarely described in observational studies. A standard mode of measurement has recently been suggested by European Federation of Societies for Ultrasound in Medicine and Biology [EFSUMB] and IUS experts.⁶² The latter suggest using continuous numbers with one decimal and a mean of two measures in cross-section and two in longitudinal to avoid any limitation of measuring in one scan plane. This allows for high reliability with an intraclass correlation coefficient [ICC] of 0.96 by 12 readers.⁶² Further, a reduction as low as >0.5 mm has been reported for 11/17 with a partial clinical response or remission (based on Crohn's Disease Activity Index [CDAI] without BWT decline in non-responders, $p = 0.001$).¹⁷ Uncertainty between 0.5 and 1.0 mm may be allowed, and accuracy of mean measurements down to 0.1 mm can be important when assessing minor changes over time. When using BWT to assess treatment response/remission over time, both an absolute and a relative change from baseline should be reported. If only one of the latter is used, different conclusions might be drawn. Categorisation of BWT has been used in several scores and may be combined with other IUS variables.^{63,64} Categorising BWT as a standalone into grades of severity is not sufficient to categorise disease activity and is not recommended. For example, if BWT severity class is defined as 3–5 mm, a reduction of 1 mm might result in different activity category, depending on a baseline value of 4.5 mm or 5.5 mm.

3.3.5. Defining the worst segment

- 3.3.5.1. The worst segment in both Crohn's disease and ulcerative colitis is defined by the most pathological bowel wall thickness; however, if two segments have the same bowel wall thickness, the order of secondary parameters for defining the worst segment should be the grading of colour Doppler signals, bowel wall stratification, and then inflammatory mesenteric fat, respectively. [InA. 0, Unc. 1, App. 17]

BWT is the most widely used, reported, and reliable IUS parameter [ICC = 0.96] in clinical observational trials, closely followed by CDS [$\kappa = 0.6$].^{7,12} Increased BWT alone or combined with increased CDS suggests more severe disease.^{12,22} Although less reliable,⁶² loss of bowel wall stratification [BWS] is associated with ulcers,⁶⁵ and inflammatory fat [I-fat] has been shown to be present in endoscopically active disease only.⁶⁶ Combined with our clinical experience, we suggest that BWS and I-fat can be used as contributory parameters when assessing the worst segment.^{7,12} However, since the interrater reliability of IUS parameters assessed by 12 IUS experts in CD patients was low to moderate for BWS and I-fat, $\kappa = 0.39$ and $\kappa = 0.51$, respectively, assessment of these parameters should be carefully considered in combination with more reliable parameters.⁶² In UC, the interrater reliability between two experts was 0.92 for BWT and 0.60–0.79 for CDS [depending on disease location]. No data are reported for I-fat or BWS.⁶⁷ In addition, De Voogd *et al.* showed 30 cine-loop cases to six IUS experts, resulting in an ICC of 0.96 for BWT, $\kappa = 0.63$ for CDS, $\kappa = 0.36$ for I-fat, and $\kappa = 0.24$ for BWS,⁶⁸ further confirming the high interrater variability between I-fat and BWS.

3.3.6. Disease activity indices

- 3.3.6.1. If a score is used, the score should summarise measures of all individual segments. [InA. 0, Unc. 3, App. 14]
- 3.3.6.2. Treatment response could be a combined change in one or more activity parameters, specified as a point reduction from an activity score [present or in the future], bowel wall thickness [continuous] and/or colour Doppler signals [ordinal], and/or bowel wall stratification [ordinal] and/or inflammatory mesenteric fat [ordinal]. [InA. 0, Unc. 3, App. 14]

Empirically, IUS response and remission rates for both CD and UC are prone to considerable variation between patients and can occur segmentally. We therefore recommend measurements from all segments to be included in a future responsive score for the assessment of treatment response. Further, a future validated score should focus on responsiveness and define levels for response and remission, like the validated Maria and simple Maria scores for MRE.^{54,69} Most of the current scores that use BWT, CDS, BWS, and I-fat generally correlate well with their respective reference standard. However, two recent systematic reviews both conclude that no current published score is validated.^{7,12} After the RAND/UCLA process, several new scores have been published, using different combinations of BWT, CDS, BWS, I-fat, clinical symptoms, contrast IUS, and elastography.^{62,64,66,67,70–75} Interestingly, Saevik *et al.* used only BWT and CDS in their score, excluding BWS and I-fat due to poor interobserver agreement.⁶⁴ In our opinion, no score using continuous measures of BWT is sufficiently validated for responsiveness, and future extensive validation studies are warranted before any specific score can be recommended.

3.4. Crohn's disease

3.4.1. Response definition and timing of assessment in Crohn's disease

- 3.4.1.1. Treatment response is identified by reduction of bowel wall thickness [continuous measurements] [>25%] or [>2.0 mm] or [>1.0 mm and one colour Doppler signal reduction]. [InA. 0, Unc. 3, App. 15]
- 3.4.1.2. Intestinal ultrasound complications that should be assessed for response:
 - 3.4.1.2.1. strictures; [InA. 0, Unc. 2, App. 15]
 - 3.4.1.2.2. phlegmons; [InA. 0, Unc. 3, App. 14]
 - 3.4.1.2.3. Abscesses. [InA. 1, Unc. 3, App. 13]
- 3.4.1.3. Response should initially be assessed in the small and large bowel after treatment initiation [regardless of treatment] at 14 ± 2 weeks. However, in a subset of patients, response after steroids or biologics may occur already after 4 weeks. Early intestinal ultrasound assessment may, in certain situations, be beneficial between weeks 4 and 8. [InA. 0, Unc. 0, App. 17]
- 3.4.1.4. Ideal assessment of intestinal ultrasound response within the first year of treatment initiation/escalation/change is at baseline, week 14 ± 2 , AND between week 26–52 + IUS depending on elevated f-Calprotectin OR symptoms OR clinical suspicion of flare. [InA. 1, Unc. 1, App. 15].

Different prospective definitions of IUS treatment response have been proposed in the literature, primarily using BWT alone or in combination with CDS [Table 2, Supplementary Table 2 and 3].^{16,17,20–22,32} Few of these definitions are correlated with clinical outcomes.^{21,22,34,37} Although not part of the response definition, both strictures, phlegmons, and abscesses should be reported when assessing response, especially if interested in disease prognosis. These complications are identified utilizing the recommendations from the EFSUMB group.⁶

3.4.1.5. Bowel wall thickness

After 2 weeks of variable treatment, absolute and relative reductions in BWT of 0.6–0.9 mm [11–16%] have been reported.^{56,61} After 4 weeks the BWT was reduced to 0.3–1.3 mm, [5–23%],^{22,30,56} after 12 weeks to 0.01–3.0 mm [0.2–43%],^{16,17,21,27,29,30,34,56,76} after 6 months to 1.0–1.9 mm [17–34%],^{34,56,76} after 1 year to 1.4–2.35 mm [22–34%],^{21,30,34,77} and after 2 years to 2.0–2.2 mm [33–36%].^{18,19} Only one study investigated azathioprine monotherapy and found a non-significant reduction of 0.4 mm [6%] after 2 years.¹⁸ Unfortunately, in most of these studies, responders and non-responders were reported together. Consequently, a group treatment effect is seen rather than an isolated effect reflecting endoscopic response. Data heterogeneity may indeed reflect diversity in reporting and patient populations among studies. Both absolute and relative reductions were increased when only focusing on treatment responders [defined by clinical scores].

After 4 weeks of any treatment, BWT decreased by 2.2 mm as opposed to 0.9 mm in the non-response group, $p < 0.05$.⁷⁸ After 6–18 weeks, BWT decreased by 3.0 mm [43%] as opposed to 1.0 mm [14%], $p = \text{not available}$ [N/A].²⁹ After 12 weeks, BWT decreased by 1.5 mm [24%]¹⁶ and 1.2 mm [19%] as opposed to 0.1 mm, $p = 0.01$, in the non-response group.¹⁷ A median reduction of 1.7 mm in 13 patients after 3 months of treatment, compared with a reduction in Simple Endoscopic Score in CD [SES-CD], showed $\rho = 0.65$, $p = 0.015$.²⁷

3.4.1.6. Colour Doppler signal

Most studies apply the original or a modified version of the ordinal Limberg score [0–4]⁷⁹ and report the number of patients with stable or declined CDS at each time point. CDS response is usually accompanied by a reduction of BWT between 0.5 to 2.0 mm or by 25% in prospective response definitions [see Tables 1 and 2; and Supplementary Tables 2 and 3]. It is therefore difficult to assess the impact of a CDS reduction alone on clinical outcomes. Only two studies investigated this specifically. Ropollas *et al.* showed that 17/28 treated with 5-ASA, or with corticosteroids as monotherapy or combined with azathioprine, experienced relapse or needed surgery during follow-up. At Week 4, 76% had an increased CDS compared with 18% in the non-relapse group, $p < 0.01$.²² A mean reduction of 2.7 CDS points was reported in those achieving long-term remission [1-year follow-up] compared with 1.2 points in non-responders, $p = 0.014$.⁸⁰ Therefore, a sole reduction of one CDS point without subsequent reduction in BWT is likely insufficient to predict good long-term outcomes. Increased CDS is not always detected at baseline, even with an increase in BWT. In general, one can expect that between 39% and 80% have an elevated baseline CDS [Limberg ≥ 2].^{16,17,20,22,25,59,81,82} Ropollas *et al.* found an early improvement in CDS after 3–8 days of treatment in 23%, followed by 32% with normalised CDS after 4 weeks.²²

In conclusion, based on this evidence, a reduction in BWT of $>25\%$ or >2.0 mm or [>1.0 mm with one CDS grade reduction] seems to be accurate when defining treatment response.

3.4.1.7. Timing of response assessment

Kucharzik *et al.* [$n = 182$] observed a 10% or 25% reduction of BWT in 95% and 80% of patients after 3 months, respectively. Like BWT, a reduction of CDS mainly occurs within the first 3 months. However, continuous improvement is seen for ileal disease as previously outlined.²⁰ Ropollas *et al.* showed that 22/26 patients with a prospectively defined sonographic improvement [BWT normalisation or decrease of ≥ 2 mm with a decrease of one CDS grade] after 12 weeks continued with further improvement at 52 weeks; data were not stratified for type of segment. Further, the response at 12 weeks seems to predict response at 52 weeks with a sensitivity of 76% and a specificity of 82%, odds ratio of 14.²¹ Dillman *et al.* [$n = 28$, paediatrics] performed a regression analysis and found that a mean daily reduction in BWT after infliximab [IFX] treatment was 0.004 mm after adjustment for covariates. It took 2 weeks for BWT and CDS to reach a significant reduction, which was maintained at follow-up visits after 1, 3, and 6 months.⁵⁶

3.4.2. Transmural remission, definition, and timing of assessment in Crohn's disease

- 3.4.2.1. Transmural remission of the small and large bowel is defined by bowel wall thickness ≤ 3 mm with normal/0 colour Doppler signal. [InA. 0, Unc. 1, App. 17]
- 3.4.2.2. In some patients, sigmoid colon may contain an enlarged muscularis propria [outer hypoechoic layer typical in diverticular disease], allowing for bowel wall thickness up to 4 mm without resembling active inflammation. [InA. 3, Unc. 1, App. 13]
- 3.4.2.3. Transmural remission should be assessed after treatment initiation [regardless of treatment] between 26 and 52 weeks. [InA. 0, Unc. 3, App. 14]
- 3.4.2.4. Transmural remission may occur already at Week 12 but with increasing likelihood up to 1 year [maybe 2 years]. [InA. 0, Unc. 0, App. 17]

No expert consensus on the definition of TR has previously existed.⁸ We recognise that a BWT ≤ 4 mm of the sigmoid can be normal for some patients, especially if diverticula are present. However, based on the studies from Castiglione *et al.*^{18,19,83} and Moreno *et al.*²⁵ combined with our own expert opinion, a majority of the panel recommend defining TR as BWT ≤ 3 mm with normal CDS for both small and large bowel. This definition is consistent with the definition previously suggested in the article by Geyl *et al.*⁸⁴ and with the recommendation from Goodsall *et al.* for clinical trials.⁸⁵ Based on cross-sectional studies, a BWT cut-off value of 3 mm gives a sensitivity of 89% and a specificity of 96% in detecting inflammation.⁵ Further, a recent systematic review and meta-analysis, based on both CD and UC, concluded that a colorectal segment <3 mm is highly likely to be present in segments achieving endoscopic remission [ER] [negative predictive value 92.7%].⁸⁶ With this definition, one can expect that between 20% and 30% will achieve TR after 12 weeks,^{16,17} with 30–50% achieving TR after 1 year on biologics.^{16,25}

3.4.2.5. BWT and its association with transmural remission

The most used definition of IUS TR in prospective observational trials is BWT ≤ 3 mm alone or in combination with other IUS parameters [Table 1; Supplementary Tables 2 and 3].^{8,84} BWT ≤ 3 mm alone has a substantial association with endoscopic remission [ER] [defined as the absence of ulcerations, SES-CD <2 , $\kappa = 0.63$, $p = 0.01$]^{18,19} and an almost perfect agreement with TR assessed by MRE [defined as BWT ≤ 3 mm without signs of hypervascularisation], $\kappa = 0.9$, $p \leq 0.01$.¹⁹ As expected,⁹ BWT ≤ 3 mm alone has a fair association with clinical remission [CDAI <150], $\kappa = 0.27$, $p \leq 0.01$, and a substantial association with C-reactive protein [CRP], $\kappa = 0.79$, $p = 0.02$.^{18,19} These data are derived from two studies which, combined, focused on TR rates in 173 patients 2 years after treatment with anti-TNF. The same research group compared 1-year clinical outcomes with three different groups: TR combined with ER [$n = 68$], ER alone [$n = 60$], and without objective evidence of remission [$n = 90$]. TR

Table 4. Crohn's disease—proportion of patients achieving transmural remission at each assessment.

| Transmural remission definition | Treatment | Week 4 | Week 8 | Week 8 - 12 | Weeks 12-16 | 6 months | 9-12 months | 14-18 months | 2 years | 3 years |
|--|--|--------|------------------|-------------------------------------|-------------------|--|-------------------------------------|--|-------------------|---------|
| BWT ≤3 mm | Anti-TNF/aza/6-MP | | | | | 27% ²⁶ 30% ²⁷ | 30% ²⁶ | 25% ¹⁹ 26% ¹⁸ | | |
| BWT ≤3 mm and CDS 0 to 1 | Anti-TNF | | | 21% ¹⁶ 29% ¹⁷ | | | | | | |
| BWT ≤3 small bowel, ≤4 mm colon ^a | Anti-TNF | | | | | | | | | |
| BWT <3 mm small bowel, <4 mm large bowel, CDS 0 ^b | Biologics | | | | | | | | | |
| BWT ≤2 small bowel, ≤3 mm colon, CDS score ≤1 ^c | UST | | 2% ⁵⁷ | 6% ⁵⁷ | 11% ⁵⁷ | | | | | |
| BWT ≤3 mm, normalisation of CDS ^d | Anti-TNF | | | | | | 14% ⁵⁹ 17% ⁸⁸ | 20% ³⁸ | 24% ⁸⁸ | |
| BWT ≤3 mm, normalization of CDS ^e | Anti-TNF ±AZA/6-MP, 5-ASA AZAM/MTX ± Anti-TNF, Anti-integrin, systemic CS | | | | | 32% ³⁶ | | | | |
| BWT ileum ≤2 mm, sigmoid ≤4 mm, rest of colon ≤3 mm, normalization of CDS | AZAM/MTX ± Anti-TNF, Anti-integrin, systemic CS | | | | | 32% ³⁷ | | | | |
| BWT ileum ≤2 mm, sigmoid ≤4 mm, rest of colon ≤3 mm, normalization of CDS, restored BWS and no I-fat [minus one factor that could not be assessed] | AZAM/MTX ± Anti-TNF, Anti-integrin, systemic CS | | | | | 37% ³⁷ | | | | |
| BWT ileum ≤2 mm, sigmoid ≤4 mm, rest of colon ≤3 mm, normalisation of CDS [Limberg 1/2], restored BWS and no I-fat | AZAM/MTX ± Anti-TNF, Anti-integrin, systemic CS | | | | | 24% ³⁷ | | | | |

^aASA, mesalazine; anti-TNF, infliximab; adalimumab; AZA/6-MP, azathioprine/mercaptopurine; biologics, infliximab, adalimumab, ustekinumab, vedolizumab; BWS, bowel wall stratification; BWT, bowel wall thickness; CDS, colour Doppler signals; I-fat, inflammatory fat; UST, ustekinumab; CS, corticosteroid.

^bNo length of disease, absence of fistulae, phlegmons, or abscesses.

^cNo length of disease, normal bowel wall stratification, no inflammatory fat, no active inflammation or fistulising disease.

^dNormal bowel wall stratification and absence of inflammatory fat.

^eNormal five-layer bowel wall stratification, no inflammatory fat, no lymph node enlargement or presence of strictures or pre-stenotic dilation.

^fNormal bowel wall stratification, absence of inflammatory fat, abscesses, and fistulae.

[BWT ≤ 3 mm] was associated with higher rates of steroid-free clinical remission (96%, hazard ratio [HR] 0.87, $p < 0.01$), lower rates of hospitalization [9%, HR 0.88, $p < 0.01$], need for surgery [0%, HR 0.94, $p < 0.01$] compared with ER. Even for patients discontinuing anti-TNF treatment, TR predicted better clinical outcomes compared with ER, $p < 0.01$.³³ Defining TR as BWT ≤ 3 mm for small bowel, ≤ 4 mm for large bowel, no length of disease, and absence of fistulae, phlegmons, or abscess, showed that no patient achieving TR [13/41] underwent surgery, required corticosteroid treatment, or needed hospitalisation during 1-year follow-up.³³ A greater BWT at baseline [$n = 188$] was associated with a lower chance of TR at 3 months, $p = 0.018$, OR 0.69,– and 12 months, $p = 0.006$, OR 0.65.³⁴

3.4.2.6. CDS and its relationship with transmural remission

No study uses CDS alone to define TR. Moreno *et al.* [$n = 30$] defined TR as a combination of BWT ≤ 3 mm together with no CDS [Limerberg grade 0–1] and low perfusion (assessed with contrast-enhanced ultrasound [CEUS]). After a median duration of 14 months [anti-TNF \pm azathioprine], TR demonstrated a good correlation with ER (total CD endoscopic index of severity [CDEIS] < 6 points), $\kappa = 0.73$, $p < 0.001$. BWT showed the best correlation, $\kappa = 0.86$, $p < 0.001$, and CDS showed an almost equally good correlation, $\kappa = 0.85$, $p < 0.001$. The variable with the best prognostic value for predicting endoscopic remission was BWT ≤ 3 mm [96%].²⁵

3.4.2.7. When does transmural remission occur?

The definition of TR varies among studies. Depending on disease severity, the treatment used, disease location, and the IUS parameters included, remission rates vary Table 4. While Castiglione *et al.* showed a significant difference in TR rates between anti-TNF and thiopurines, 26% [17/66] vs. 5% [3/67],¹⁸ no significant differences exist between biologic treatments.^{18,19,34} However, a newly published study by Calabrese *et al.* found that ustekinumab had a lower chance of achieving TR. Authors acknowledge that ustekinumab is offered for refractory diseases, which may influence their findings.³⁴ Further, TR often occurs within the first 3 months of treatment, followed by a minor increase thereafter.^{26,34,87} Paredes *et al.* showed that all patients with TR at Week 12 remained TR at 1 year.¹⁶ At Week 8, BWT had normalised in 29% [5/24], and CDS had normalised in 33% [8/24].¹⁷ This is further supported by the STARDUST study, where BWT and CDS started to normalise at Week 8, and BWS and I-fat first normalised at Week 16.⁵⁷

In two paediatric studies, after 9–12 months of treatment, TR was achieved in 14% [4/32]⁵⁹ and 17% [8/48], respectively.⁸⁸ After 24 and 36 months, the rates were 20% [9/46] and 24% [8/33], respectively.⁸⁸ While CDS, I-fat, and lymph node enlargement improved significantly in the endoscopic response group, strictures and pre-stenotic dilation together with BWS did not. Disruption of BWS was not related to changes in BWT or vascularisation.⁵⁹

These paediatric findings are supported by Orlando *et al.* [$n = 30$], showing that CDS or BWS did not influence variations in BWT and TR at 14 and 52 weeks during follow-up in adults.²⁶ However, BWS may reflect longitudinal ulcers.⁶⁵ In a study by Wilkens *et al.*, segments with histologically proven ulcers were thicker than non-ulcerated segments, $p < 0.01$.⁸⁹ Orlando *et al.* is the only study published to date that has not found CDS influential regarding BWT or TR.²⁶

3.4.3. Other important intestinal ultrasound parameters that are not included in the definition of response and transmural remission

BWT and CDS appear to be the most important parameters when assessing IUS response and remission, based on their relationship

with clinical outcomes. Although deemed important by experts,⁶² I-fat and BWS are not included in our current definition of response or remission/TR. Current data on BWS suggest that up to 53% with active CD will have a loss of BWS,⁹ with gradual restoration of BWS after 3 months of treatment to 29%, followed by 22% at both 6 and 12 months, $p < 0.001$.²⁰ Other studies have not reported a significant restoration of BWS over time.⁵⁹ In active CD, I-fat might be present in up to half of the patients before treatment initiation, with a more apparent decline after 3 months of treatment to 22% followed by 17–18% at 6 and 12 months, respectively, $p < 0.001$.²⁰ Currently, no study has correlated BWS or I-fat with clinical outcomes. However, mesenteric adipose tissue proliferation correlates with increased BWT [OR 7.6] and internal fistulae [OR 13.5].⁹⁰ We believe that the maintained presence of extra-mural inflammation [e.g. I-fat] can be a sign of chronic disease. BWS and I-fat might be included in future definitions of response/remission. However, we suggest that these parameters are mainly contributory to disease activity assessment and could be integrated with more important parameters [BWT/CDS] in an IUS activity score. In patients with strictures, only 6% [1/16]¹⁸ to 16% [1/6],¹⁹ and no patient with penetrating disease, achieved TR.^{18,19} This suggests that normalisation of stricture or penetrating disease is less likely to occur, and TR may only be achievable for predominantly inflammatory disease.

3.5. Ulcerative colitis

3.5.1. Response definition and timing of assessment in ulcerative colitis

- 3.5.1.1. Treatment response in ulcerative colitis is identified by reduction of bowel wall thickness [continues measurements] [$>25\%$] or [>2.0 mm] or [>1.0 mm and one colour Doppler signal reduction]. [InA. 0, Unc. 3, App. 15]
- 3.5.1.2. Ideal assessment of intestinal ultrasound response within the first year of treatment initiation/escalation/change is at baseline, Week 14 ± 2 , and between Weeks 26–52 + intestinal ultrasound depending on elevated faecal calprotectin or symptoms or clinical suspicion of flare. [InA. 0, Unc. 2, App. 14]
- 3.5.1.3. After treatment initiation, response should be measured in all segments that were affected at baseline. [InA. 0, Unc. 0, App. 14]

There are currently only a few studies, most with high risk of bias, examining the relationship between IUS response over time with a reference standard such as clinical scores or endoscopy in UC trials [Table 2; Supplementary Figure 2]. Our recommendations are, therefore, primarily based on our clinical experience and expert opinion. After 2–3 weeks of steroid/cytapheresis treatment, 42% [11/26] showed a BWT reduction by ≥ 2.5 mm. One-year clinical relapse was found in 9% [1/11] in the response group, compared with 47% [9/15] in the non-response group, $p < 0.05$.⁴² After 2 months of treatment with steroids, Maconi *et al.* [$n = 30$] showed a significant decrease in BWT by 2.3 mm [31%] in the response group alone.⁴¹ Already after 10 days of steroid treatment, a significant decrease in BWT meant no risk of surgery at 3 months, $n = 32$ [25 moderate/severe based on the Truelove–Witts score].⁴⁵ In clinical experience, patients receiving steroids tend to respond faster than patients receiving biologics. It is still unclear if transabdominal IUS response

can be measured earlier than at 2 weeks. This doubt reflects the lack of consensus for statements on early response in acute severe ulcerative colitis [Supplementary Material 2, second round voting results, 44.2]. However, a recent pilot study [$n = 10$] on steroid treatment in severe acute UC showed that IUS performed within the first 48 h of hospitalization potentially predicts treatment outcome.⁹¹

Focusing on anti-TNF in UC, a BWT reduction in 34% [15/44] is shown after 6 weeks in the sigmoid and descending colon. Further, patients with an increased CDS at Weeks 6 and 12 had a significantly higher simple clinical colitis activity index [SCCAI], compared with no CDS signal, $p \leq 0.001$.⁴⁴ After 14 weeks of vedolizumab treatment, 57% [4/7] achieved BWT reduction of 1.0 mm, $p = \text{N/A}$, in the response group alone. CDS significantly decreased from 1.3 to 0.5 in responders and increased from 1.3 to 2.7 in non-responders, $p \leq 0.05$.²⁸

After the RAND/UCLA process, De Voogd *et al.* [$n = 29$] published an abstract showing a mean BWT reduction of 2.6 ± 1.4 mm for the sigmoid and 1.8 ± 1.0 mm for the descending colon in patients achieving ER on tofacitinib treatment.⁴⁶ Further, Helwig *et al.* showed that 76% [100/171] achieved a greater than 25% BWT reduction after 12 weeks of mixed treatment.³⁷

This limited available evidence suggests using the exact definition of treatment response in UC as for CD. However, more studies are needed, and no pediatric studies were identified.

3.5.2. Transmural remission, definition, and timing of assessment in ulcerative colitis.

- 3.5.2.1. Transmural remission in ulcerative colitis of the large bowel is defined by bowel wall thickness ≤ 3 mm with normal/0 colour Doppler signal. [InA. 0, Unc. 1, App. 17]
- 3.5.2.2. In some patients, sigmoid colon may contain an enlarged muscularis propria [outer hypoechoic layer—typical in diverticular disease], allowing for bowel wall thickness up to 4 mm without resembling active inflammation. [InA. 3, Unc. 1, App. 13]
- 3.5.2.3. Transmural remission in ulcerative colitis should be assessed after treatment initiation [regardless of treatment] at Week 14 ± 2 . [InA. 0, Unc. 2, App. 16]
- 3.5.2.4. Transmural remission in ulcerative colitis may occur already at Week 4 but with increasing likelihood up to Week 12 [potentially 1 year]. [InA. 1, Unc. 3, App. 14]

Before the RAND/UCLA process, no study had explicitly defined TR for UC. Given the common understanding that UC is not considered a transmural disease, one could argue that no definition of TR is needed [Table 2]. However, numerous examples of extra-mural inflammation, like I-fat and enlarged lymph nodes, in moderate and severe UC challenges the classification of UC as a disease limited to the mucosa only.⁴⁰ As a consequence, we believe that a definition of TR is valid and vital for future studies examining the role of IUS remission and its' relationship with clinical outcomes during follow-up for UC patients. After 2 weeks of variable treatment [$n = 224$], the proportion of patients with increased BWT in the sigmoid colon was reduced from 89% to 39%, $p < 0.001$. A further improvement at Weeks 6 and 12 were shown, at 35% and 32%, respectively,

$p \leq 0.001$. A thickened bowel wall was present in 83% at baseline in the descending colon, followed by a significant decrease to 43% at both Weeks 2 and 6. Endoscopy was not routinely performed during follow-up. However, the IUS findings had a moderate association with SCCAI and faecal calprotectin [FC]. In sigmoid colon, baseline CDS was increased by 35%, followed by 23%, 16%, and 13% at Weeks 2, 6, and 12, $p < 0.001$. The proportion of patients with an increased CDS in the descending colon were 15% at baseline, followed by 7%, 5%, and 7%, $p < 0.001$.⁴⁰ In 5/6 patients with ER and clinical remission, BWT was ≤ 4 mm after 2 months of various treatments. BWT was significantly higher in the pre-treatment group with moderate/severe clinical and endoscopic activity compared with the mild endoscopic group.⁴¹ These findings report a considerable improvement in BWT and CDS within the first 12 weeks of treatment. By combining BWT and CDS in a 0–3 score and comparing it with the 0–3 Baron endoscopic score, Paredes *et al.* showed substantial reliability, $\kappa = 0.76$, at 3 months, and almost perfect $\kappa = 0.88\text{--}0.90$ at 9 months and 15 months, respectively.³⁹ After 8 weeks of treatment with tofacitinib, de Voogd *et al.* [$n = 29$] showed that all patients in the ER group had a BWT cut-off value of ≤ 2.9 mm (area under the receiver operating characteristic curve [AUROC] 0.91 [0.83–0.99], sensitivity 83%, and specificity 100%) in the sigmoid colon and ≤ 2.8 mm (AUROC 0.98 [0.94–1.00], sensitivity 91%, and specificity 92%) for descending colon.⁴⁶ Helwig *et al.* [$n = 171$] examined three different definitions of TR. Focusing on the definition containing BWT and CDS, 12-week TR rates were 53%. This high rate could be explained by a BWT cut-off value of 4 mm in the sigmoid and a CDS score of 1–2 defined as normal.³⁷ A recent systematic review of cross-sectional studies concluded that the most often used criteria to define disease activity were BWT and CDS. The evidence also suggests that BWT in combination with CDS or BWS gives a more accurate correlation with other markers of disease activity.⁴

Although based upon limited evidence, most of the experts in our panel believe that the same definition for TR in CD is applicable in UC.

3.5.3. Additional relevant IUS parameters

The TRUSTandUC study showed that 40%, 23%, and 57% have a presence of I-fat, loss of BWS, and loss of hastration at baseline, respectively. All parameters significantly improved 12 weeks later. These parameters are contributory in the assessment of UC activity by IUS. However, there are no current data on their relationship with clinical outcomes over time and consequently they are not included in our definition. However, they might be included in a validated future score for response and remission, as previously discussed.

3.6. Adults vs. paediatric population

- 3.6.1. The remission/response statements for Crohn's disease may be used in both adult and paediatric populations. [InA. 2, Unc. 1, App. 14]
- 3.6.2. The remission/response statements for ulcerative colitis may be used in both adult and paediatric populations. [InA. 2, Unc. 2, App. 12]

There was only one paediatrician involved in our RAND/UCLA process. However, based on the limited available evidence from paediatric studies presented throughout this article [Supplementary Table 3],^{56,59,61,88,92,93} we find that our recommendations may be used in both populations. Future studies are needed to validate or refute this assumption.

4. Discussion

Cross-sectional imaging, an objective biomarker, currently gains increasing attention and incorporation into clinical trials as a proposed treatment target.⁸⁴ IUS is an accurate, reliable, cost-effective, patient-friendly, non-invasive imaging modality performed by clinicians in a point-of-care setting.² However, definitions for imaging response and transmural remission/healing and optimal assessment timing currently lack international consensus. This systematic review demonstrates the diversity in the current literature of IUS response definitions and reporting. Using a robust methodology, the eligible studies included patients with different disease characteristics [severity and location], treatments, times to follow-up, reference standards, aims, and outcomes. This further highlights the need for an international expert consensus on IUS response assessment and reporting. We now provide clear international expert consensus defining optimal timing and cut-offs for transmural response and remission for CD and UC, using IUS. We also establish consensus recommendations on imaging acquisition, expected transmural response time, disease length, measuring and reporting bowel wall thickness, defining worst bowel segment, the composition of disease activity indices, and paediatric applicability.

Our study has several strengths. Not only did we perform a comprehensive systematic review, we also added a novel and robust RAND/UCLA process, with a panel including many of the world's leading IBD IUS researchers. Using this methodology, panelists are not forced into a majority agreement but individual rating statements on an appropriateness scale. Indeed, statements reached agreement on appropriate definitions for IUS response reporting, preceded by high-level and intense discussions. Not all researchers voted on all statements, and one additional expert was added during the second round. This is reflected by the different total vote counts, especially between CD and UC statements. Due to the small amount of data and the experts' area of expertise limitations, UC statements received fewer votes.

Limitations of this study include the limited amount of high-quality prospective evidence, leaving the panel with an agreement based upon the available literature and expert experience. The applicability of the included research to answer our study questions was high, but so was the risk of bias. A large proportion of the uncertain or unknown biases comes from the included abstracts. Due to the expected low number of full-text studies, the inclusion of abstracts was deemed necessary. Another high risk of bias is the large proportion of clinical scores used as a reference standard. Clinical scores are a subjective rather than an objective measure of inflammation, and results should therefore be considered carefully.^{94,95} With only six studies using ER and/or MRE as a reference standard, definitions of response were influenced by all included studies. In addition, a couple of pivotal studies were published after the first literature search. Since they were aligned with our voting, we chose to add them to the supporting text, although they were not part of the systematic review itself. We aimed at rating individual statements by the Grading of Recommendations, Assessment, Development, and Evaluations [GRADE] terminology. However, observational studies per se are considered low certainty evidence, potentially further downgraded to very low certainty by the limitations reported by the risk of bias. In the absence of any randomised controlled trials using IUS in IBD patients, all our recommendations are considered weak.

The definitions regarding response, TR, and assessment time points need further validation, and more studies regarding IUS's ability to assess and predict treatment response are warranted.

However, we hope these consensus definitions and recommendations will guide future high-quality prospective therapeutic trials using IUS as a secondary or primary endpoint, eventually leading to broad adoption of intestinal ultrasound as the standard of care in objective disease monitoring in IBD striving towards achieving TR.

In conclusion, an agreement was reached on 43 different appropriate statements, including clear definitions on IUS treatment response, transmural remission, optimal timing of follow-up, and general considerations for using transabdominal intestinal ultrasound in inflammatory bowel disease. To ensure a unified approach in routine care and clinical trials, we provide recommendations and definitions for incorporation in future prospective studies.

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Conflict of Interest

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Authors Contributions

JFKFI: conceptualisation, methodology, validation, formal analysis, investigation, data curation, writing—original draft, writing—review and editing, visualization, project administration. TH: validation, investigation, data curation, writing—review and editing. TMG: validation, investigation, data curation, writing—review and editing. JBS: data curation, writing—original draft, writing—review and editing, supervision. HA-F: data curation, writing—review and editing. MA: data curation, writing—review and editing. JB: data curation, writing—review and editing. RVB: data curation, writing—review and editing. DC: data curation, writing—review and editing. BC: data curation, writing—review and editing. MCD: data curation, writing—review and editing. KBG: data curation, writing—review and editing. TK: data curation, writing—review and editing. CL: data curation, writing—review and editing. CM: data curation, writing—review and editing. GM: data curation, writing—review and editing. KN: data curation, writing—review and editing. CP: data curation, writing—review and editing. SRW: data curation, writing—review and editing. KN: conceptualization, methodology, data curation, writing—original draft, writing—review and editing, supervision. RW: conceptualisation, methodology, validation, data curation, writing—original draft, writing—review and editing, visualisation, supervision, project administration.

Supplementary Data

Supplementary data are available at ECCO-JCC online.

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Intestinal Ultrasound in Inflammatory Bowel Disease: A Valuable and Increasingly Important Tool

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Keywords

Intestinal ultrasound · Diagnosis · Disease activity · Monitoring · Therapy response · Point-of-care

Abstract

Background: Intestinal ultrasound is emerging as a non-invasive tool for monitoring disease activity in inflammatory bowel disease patients due to its low cost, excellent safety profile, and availability. Herein, we comprehensively review the role of intestinal ultrasound in the management of these patients. **Summary:** Intestinal ultrasound has a good accuracy in the diagnosis of Crohn's disease, as well as in the assessment of disease activity, extent, and evaluating disease-related complications, namely strictures, fistulae, and abscesses. Even though not fully validated, several scores have been developed to assess disease activity using ultrasound. Importantly, intestinal ultrasound can also be used to assess response to treatment. Changes in ultrasonographic parameters are observed as early as 4 weeks after treatment initiation and persist during short- and long-term follow-up. Additionally, Crohn's disease patients with no ultrasound im-

provement seem to be at a higher risk of therapy intensification, need for steroids, hospitalisation, or even surgery. Similarly to Crohn's disease, intestinal ultrasound has a good performance in the diagnosis, activity, and disease extent assessment in ulcerative colitis patients. In fact, in patients with severe acute colitis, higher bowel wall thickness at admission is associated with the need for salvage therapy and the absence of a significant decrease in this parameter may predict the need for colectomy. Short-term data also evidence the role of intestinal ultrasound in evaluating therapy response, with ultrasound changes observed after 2 weeks of treatment and significant improvement after 12 weeks of follow-up in ulcerative colitis. **Key Messages:** Intestinal ultrasound is a valuable tool to assess disease activity and complications, and to monitor response to therapy. Even though longer prospective data are warranted, intestinal ultrasound may lead to a change in the paradigm of inflammatory bowel disease management as it can be used in a point-of-care setting, enabling earlier intervention if needed.

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Ecografia intestinal na doença inflamatória do intestino: uma ferramenta valiosa e de importância crescente

Palavras Chave

Ecografia intestinal · Diagnóstico · Atividade de doença · Monitorização · Resposta à terapêutica · Point-of-care

Resumo

Contexto: A ecografia intestinal na doença inflamatória intestinal tem ganho importância crescente como exame não invasivo para monitorizar a atividade de doença, pelos seus custos reduzidos, excelente perfil de segurança e disponibilidade. Neste artigo realizamos uma revisão sobre o papel da ecografia intestinal no manejo destes doentes.

Sumário: Na doença de Crohn, a ecografia intestinal tem uma boa acuidade no diagnóstico, avaliação da atividade e extensão da doença, assim como na avaliação de complicações, como estenoses, fístulas e abcessos. Apesar de não estarem validados, vários scores têm sido desenvolvidos para avaliar a atividade de doença. É de realçar a importância da ecografia intestinal na avaliação da resposta à terapêutica. A melhoria dos parâmetros ecográficos é observada tão precocemente como quatro semanas e persiste durante o seguimento a curto e longo prazo. Os doentes sem melhoria ecográfica parecem ter uma maior necessidade de intensificação terapêutica, corticóides, internamento ou cirurgia. À semelhança da doença de Crohn, a ecografia intestinal tem uma boa acuidade na avaliação ao diagnóstico, atividade e extensão da doença na colite ulcerosa. Na colite ulcerosa grave, um maior espessamento da parede intestinal à admissão está associado a maior necessidade de terapêutica de resgate e a ausência de melhoria deste parâmetro pode predizer a necessidade de colectomia. A ecografia também permite a avaliação da resposta à terapêutica na colite ulcerosa, com alterações observadas após duas semanas de tratamento e mantendo melhoria significativa após 12 semanas.

Mensagem-chave: A ecografia intestinal é um método importante para avaliar a atividade de doença, complicações e monitorizar a resposta à terapêutica na doença inflamatória intestinal. Apesar de serem necessários mais estudos prospectivos, a ecografia intestinal pode levar a uma mudança de paradigma no manejo destes doentes, uma vez que pode ser utilizada no momento de prestação de cuidados, permitindo uma intervenção precoce quando necessário.

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Introduction

Objective evidence of bowel inflammation is a key feature in the management of inflammatory bowel disease (IBD) patients, since clinical-based assessment is insufficient to make adequate therapeutic decisions [1]. Endoscopic mucosal healing (MH) has emerged as a major therapeutic endpoint, as it has been associated with long-term clinical remission, steroid-free remission, and reduced risk of surgery [2, 3]. However, endoscopy is a time-consuming, expensive and invasive technique, not always tolerated by patients. Therefore, a growing interest has risen regarding non-invasive monitoring tools, such as intestinal ultrasound (IUS) and faecal calprotectin (FCal). IUS is a widely available imaging modality associated with low costs, an excellent safety profile, and lack of preparation [4]. It is increasingly recognised as an accurate technique as part of the armamentarium for IBD diagnosis, but also for assessing disease activity and extent, detecting complications, and monitoring response to therapy [5]. Moreover, IUS can be performed in a point-of-care setting, leading to therapy optimisation without delay, allowing repeated evaluations to monitor lesions over time, and even replacing invasive examinations, such as endoscopy [6]. Moreover, due to lack of radiation, good availability, and because it is an easy exam to perform for both patients and physicians, in experienced hands IUS can also replace other cross-sectional image modalities, such as computerised tomography (CT) or magnetic resonance (MR) [3]. When compared to other non-invasive monitoring tools such as FCal or C-reactive protein, IUS offers additional information, namely on disease extension, location, severity, and complications [4, 6]. Finally, in an era of shared decision-making with our patients, it is important to consider their acceptance when proposing follow-up examinations. In a recent systematic review, IBD patients preferred non-invasive techniques, particularly IUS, to monitor disease activity, when compared to endoscopy [7].

There is a clear need to consider IUS as a non-invasive monitoring tool in IBD, with recent ECCO-ESGAR recommendations supporting the use of IUS in the diagnosis and management of IBD patients [3]. In this review, we comprehensively discuss the role of IUS for: (a) screening and diagnosis of IBD; (b) evaluating disease activity and postoperative recurrence in Chron's disease (CD); (c) evaluating disease-related complications; and (d) monitoring response to therapy, both in CD and ulcerative colitis (UC) patients.

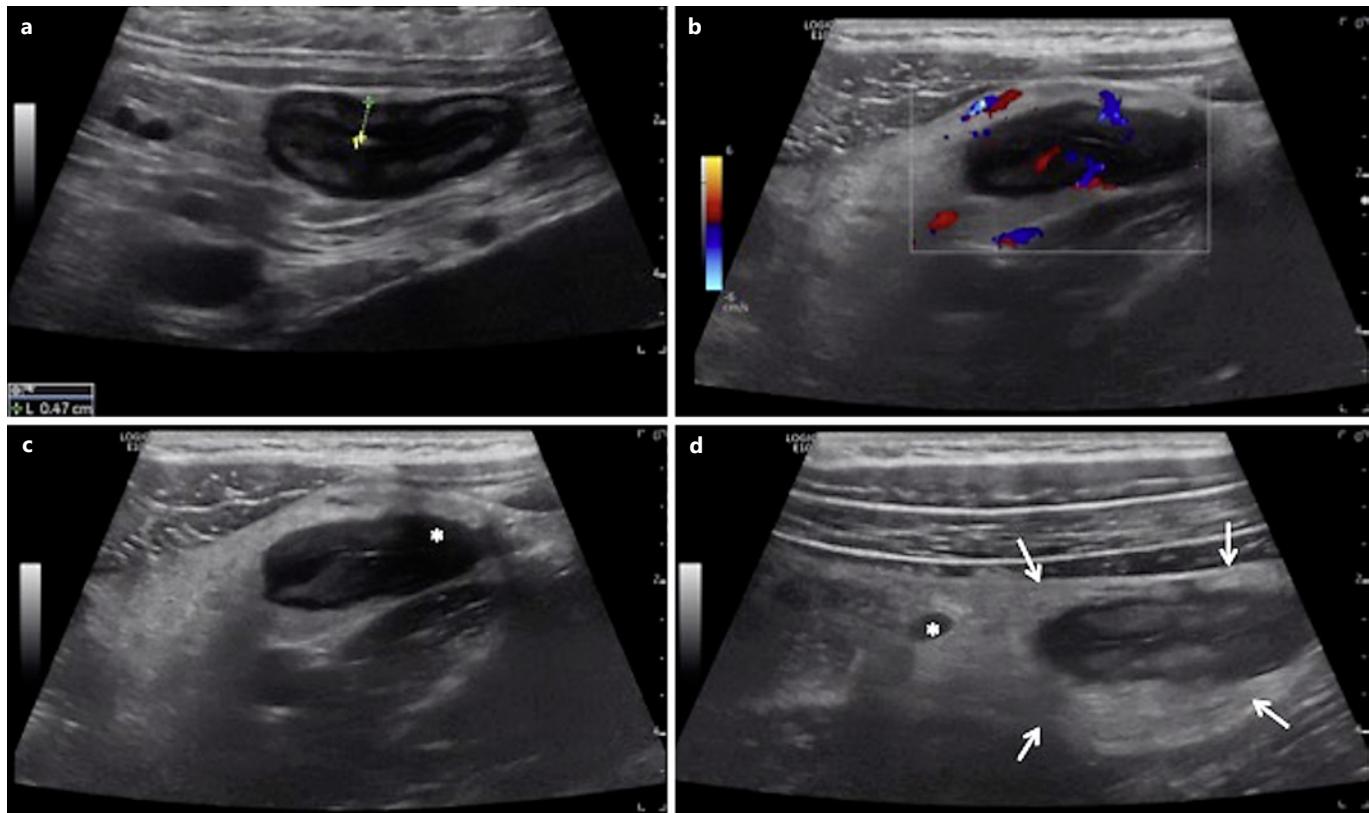


Fig. 1. Examples of IUS parameters. **a** Measurement of increased BWT (4.7 mm). **b** Increased CDF (Limbberg score 4). **c** Areas of focal loss of BWS (asterisk). **d** Extramural findings, including mesenteric fat proliferation (arrows) and mesenteric lymph node (asterisk).

Screening and Diagnosis of IBD

IUS has been used as a screening tool in patients with gastrointestinal (GI) symptoms but without severe signs of disease (such as weight loss, anaemia, or elevated FCal), showing a good accuracy to distinguish IBD from irritable bowel syndrome patients in primary care settings [8]. Additionally, in a recent prospective study including 37 patients with low-risk abdominal symptoms, the use of IUS reduced the number of colonoscopies and appointments, improving health service outcomes [9]. Furthermore, GI infections can also mimic IBD. IUS has been shown to be an accurate method in the diagnosis of infectious enteritis when compared to CT or MR, and the major findings include hypoechoic small bowel wall thickening and lymph node enlargement. Similarly, IUS can also detect inflammation in infectious colitis. Importantly, all these IUS features may overlap with IBD, and IUS alone cannot diagnose GI infections. Therefore, an ultrasound control can be performed in these patients to exclude IBD [10].

The most frequent IUS parameter used to detect intestinal inflammation is bowel wall thickness (BWT; Fig. 1a). Common cut-off values are 2–3 mm for the small bowel and 3–4 mm for the colon [11]. Loss of bowel wall stratification (BWS) and increased vascularisation assessed through colour Doppler flow (CDF) are also associated with active inflammation (Fig. 1b, c) [11]. Finally, extramural features are also important, such as mesenteric fat proliferation and lymph nodes (Fig. 1d).

Therefore, IUS can be a very helpful tool for IBD diagnosis. For instance, CD patients at diagnosis should undergo small bowel assessment, either by MR enterography (MRE), IUS, and/or capsule endoscopy. CT enterography is another valid option, though it is associated with radiation exposure [3]. In a systematic review, including 1,558 CD patients, endoscopic, histologic, barium examination, and/or intraoperative findings were used for the reference standard. The overall pooled sensitivity of IUS was 88% and specificity 97% [12]. When specifically evaluating small bowel disease, the overall sensitivity of IUS ranged from 54 to 93%, with a specificity of 97–100% [13].

Table 1. Prospective studies evaluating IUS scores to predict disease activity or complications in CD

| Index assessed (study) | n | Aims of the study | Segments assessed | Reference standard | Index parameters and cut-offs | Severity grades | Outcomes |
|-------------------------------------|----|---|--|-----------------------------|---|--|--|
| UAI/CD (Futagami et al. [29], 1999) | 55 | To develop an IUS index of intestinal inflammatory activity | Duodenum Jejunum Ileum Ascending colon Transverse colon Descending colon Sigmoid colon Rectum | Colonoscopy Radiology | BWT >4 mm BWS Compressibility Peristalsis | A: Decreased compressibility and peristalsis with loss of hastration, but normal BWT B: BWT >4 mm and presence of BWS C: BWT >4 mm and loss of BWS | Strong correlation with endoscopy or barium contrast studies ($r = 0.62, p < 0.01$) |
| MS (Maconi et al. [35], 2003) | 43 | To establish whether IUS can assess histologic features of ileal stenosis in CD | NS | Surgical specimen Histology | Stenosis: BWT >4 mm with pre-stenotic dilation >25 mm BWS Sinus tract or fistulae | BW echo pattern: Hypoechoic pattern: increased BWT with loss BWS Stratified pattern: increased BWT with preserved BWS Mixed pattern: Co-existence of tracts with/without stratification | IUS detection of moderate-severe or intermediate degree of fibrosis: sensitivity 100%, specificity 63% ($k = 0.91, 95\% \text{ CI } 0.83-0.98$) |
| NYS (Neye et al. [31], 2004) | 22 | To evaluate diagnostic criteria of power Doppler sonography | Terminal ileum Caecum Ascending colon Transverse colon Descending colon Sigmoid colon | Ileocolonoscopy | BWT >5 mm CDF: no vessel/cm ² , 1-2 vessels/cm ² , >2 vessels/cm ² | Inactive: BWT <5 mm and no vessels Mild activity: BWT <5 mm and 1-2 vessels or BWT ≥ 5 mm with no vessels Moderate activity: BWT <5 mm and >2 vessels or BWT ≥ 5 mm with 1-2 vessels High activity: BWT ≥ 5 mm with 2 vessels | High concordance of power Doppler sonography and ileocolonoscopy (higher agreement in descending colon: $k = 0.91, 95\% \text{ CI } 0.83-0.98$) |
| PPRS (Paredes et al. [34], 2010) | 33 | To evaluate accuracy of IUS compared with endoscopy in the diagnosis and grading of postsurgical recurrence of CD | Anastomosis | Ileocolonoscopy | BWT (T1) >3 mm CDF: absent (0), barely visible (1), moderate vascularity (2), marked vascularity (3) | Recurrence: T1 BWT >3 mm and/or positive CDF Moderate to severe recurrence: T1 BWT >5 mm and/or CDF grade 2 or 3 | Recurrence: sensitivity 76.9%, 95% CI 57.9-89; specificity 57.1%, 95% CI 25-84.2% Moderate to severe recurrence: sensitivity 86.7%, 95% CI 62.1-96.3; specificity 66.7%, 95% CI 43.7-93.7 |
| LZS (Lenze et al. [36], 2012) | 30 | To compare FDG-PET/CT in stricture detection and stricture differentiation with IUS, endoscopy, and MRE | NS | Colonoscopy Histology | Stricture diagnosis: BWT >4 mm Bowell wall echogenicity CDF (Limbberg score) | Stricture differentiation: Fibromatous: hyperechogenic BWT and Limberg 1 Mixed: mixed hypo and hyperechogenic BWT and Limberg 2 Inflammatory: hypoechogenic BWT and Limberg 3 or 4 | Sensitivity of IUS to detect strictures: 68%, 95% CI 53-84 Correct diagnosis according to stricture differentiation: 40% ($p = 0.0001$) |
| PCPRS (Paredes et al. [22], 2013) | 60 | To assess if CEUS can increase the value of IUS in the study of postoperative CD | Anastomosis | Ileocolonoscopy | BWT (T1) >3 mm CDF: absent (0), barely visible (1), moderate vascularity (2), marked vascularity (3) CEUS: % of wall brightness | 0: normal BWT and CEUS enhancement >34.5% 1: BWT 3-5 mm with CEUS enhancement <46% 2: BWT >5 or CEUS enhancement >46% 3: BWT >5 mm or enhancement >70%, presence of fistulae | Strong correlation between IUS and endoscopy ($k = 0.64, p = 0.0001$) IUS sensitivity 89.8%, 95% CI 78.2-95.6; specificity 81.8%, 95% CI 52.3-94.9 CEUS sensitivity 98% (89.3-99.6), specificity 81.8% (52.3-94.5) |

Table 1 (continued)

| Index assessed (study) | n | Aims of the study | Segments assessed | Reference standard | Index parameters and cut-offs | Severity grades | Outcomes |
|---------------------------------------|-----|--|---|-----------------------|--|--|---|
| US-LI (Rispo et al. [37], 2017) | 71 | To investigate the concordance between IUS-based Lémann Index (US-LI) and RME-based Lémann index (MR-LI) | Small bowel Colon Rectum | Ileocolonoscopy | BWT > 3 mm BWS Stricture Abscesses and fistulae | Structure: 1: BWT > 3 mm or segmental enhancement without pre-stenotic dilation (SB; C) 2: BWT > 4 mm or mural stratification without pre-stenotic dilation (SB; C) or <50% of the lumen (C) 3: BWT > 4 mm narrowed lumen and fluid distended (SB)/stricture with pre-stenotic dilation or >50% of the lumen (C) Penetrating disease: 2: Deep transmural ulceration 3: Hypoechoic duct-like structures with fluid or air (SB)/phlegmon or any type of fistulae (C) | High concordance between US-LI and MR-LI ($r = 0.90, p < 0.001$) |
| SUS (Novak et al. [30], 2017) | 63 | To identify IUS parameters contributing to inflammatory disease activity, develop a simple score, and validate this score prospectively | Small bowel Terminal ileum Caecum Ascending colon Transverse colon Descending colon Sigmoid colon Rectum | Ileocolonoscopy | BWT (ileum > 3 mm; colon > 4 mm) CDF Mesenteric fat and lymph nodes Complications Overall impression of disease activity | Continuous score: [0.0563 * BWT1] + [2.0047 * BWT2] + [3.0881 * BWT3] + [1.0204 * CDF1] + [1.5460 * CDF2] | IUS overall sensitivity 92.1%, 95% CI 78.6–98.3, with 81.6% specificity, 95% CI 68–91.2 Score accuracy: AUC 0.836 |
| RMS (Ramaswamy et al. [46], 2019) | 35 | To assess the utility of IUS in assessing disease activity in CD | Ileum Right colon Transverse colon Left colon Rectum | Ileocolonoscopy | BWT > 3 mm CDF BWS Mesenteric fat Intestinal motility | Median BWT; Doppler activity and loss of BWS | Strong correlation with SES-CD ($r = 0.8, p = 0.009$) |
| IBUS-SAS (Novak et al. [33], 2021) | 30 | To establish the core parameters defining active intestinal inflammation in CD, to evaluate inter-rater reliability and propose a segmental activity score | NS | Visual analogue scale | BWT CDF BWS Inflammatory fat | Continuous variable (ranging from 0 to 100) IBUS-SAS = 4 × BWT + 15 × i-fat + 7 × CDF + 4 × BW | Inter-rater reliability: BWT 0.96, 95% CI 0.94–0.98 CDF 0.60, 95% CI 0.48–0.72 BWS 0.39, 95% CI 0.24–0.53 i-fat 0.51, 95% CI 0.34–0.67 IBUS-SAS 0.97, 95% CI 0.95–0.99 |
| BUSS (Alloca et al. [32], 2021) | 225 | To assess the predictive value of bowel US findings and prospectively follow them up for a period of 12 months | Ileum Cecum-ascending colon Transverse colon Descending-sigmoid colon Rectum | Ileocolonoscopy | BWT CDF (0: absent; 1: present) | Continuous score (BUSS = 0.75 × BWT + 1.64 × CDF) BUSS > 3.52 to predict endoscopic disease activity (AUC 0.864, 95% CI 0.812–0.906; sensitivity 83%, specificity 85%). | BUSS correlated significantly with SES-CD ($r = 0.55, p < 0.001$) BUSS > 3.52 predicted negative CD course (steroids, therapy optimisation, surgery, and hospitalisation) |

BUWT, bowel wall thickness; BWS, bowel wall stratification; CDF, colour Doppler flow; CEUS, contrast-enhanced ultrasound; MRE, magnetic resonance enterography; FDG-PET, fluoroo-2-deoxy-D-glucose positron emission tomography; CT, computerised tomography; TI, terminal ileum; SB, small bowel; C, colon; BW, bowel wall; NS, not specified.

Several studies have assessed the value of BWT to support the diagnosis of UC [4]. Even though UC is a mucosal disease, a BWT >4 mm had a sensitivity of 62–89% and specificity of 77–88% for its diagnosis [4]. Nevertheless, the best cut-off at diagnosis is not established and values >3 mm have also been reported.

In patients with active IBD, UC patients have a prominent thickening of the mucosal layer, whereas CD patients have a significant thickening of the submucosal layer and a higher rate of lymph node enlargement [14]. In UC, the thickening of the bowel wall is mostly proportional and BWS is usually present [11]. The mesenteric proliferation is a prominent feature in CD, although it can also occur in UC, especially during severe episodes [11]. Hence, IUS is an accurate method to screen for intestinal inflammation and to support the diagnosis of both CD and UC.

Evaluating Disease Activity in IBD

Disease Activity and Postoperative Recurrence in Crohn's Disease

IUS has shown a good accuracy in detecting disease activity in CD. In a systematic review, the overall sensitivity of IUS for assessing CD activity when compared to ileo-colonoscopy, barium-contrasted exams, CT, MRE, capsule endoscopy, or surgical specimens was 89%, with a specificity of 94.3% [5], as previously reported [15]. When compared to MRE, IUS has an accuracy of 91% for localisation and 89% for bowel wall flow [16]. Similarly, in a recent prospective study, the accuracy of IUS was not significantly different from MRE, regarding BWT, loss of BWS and CDF, also highlighting the concordance between IUS and other cross-sectional exams [17]. The METRIC trial was a prospective multicentre trial including 284 patients (133 newly diagnosed; 151 relapsed) to evaluate MRE and IUS performance in assessing disease extent and activity in CD. A constructed referenced standard was used to compare the two techniques. Both MRE and IUS were highly accurate for detecting small bowel disease, even though a higher sensitivity and specificity in detecting disease activity and evaluating disease extent was observed with MRE [18]. Nonetheless, an expert panel highlighted some methodological limitations of this study such as bias in the constructed reference standard model, absence of information on time between MRE and IUS, and use of high BWT cut-offs [19]. Importantly, the sensitivity of IUS seems to be lower for jejunal lesions (55.6%) when compared to ileal (92.7%) or colonic involvement (81.8%) [5].

Regarding postoperative recurrence, even though ileo-colonoscopy remains the gold standard examination, non-invasive tools may be considered, especially after small bowel resection [20]. In a recent systematic review, the pooled IUS sensitivity and specificity for detecting postoperative recurrence was 94 and 84% [21]. Small intestine contrast ultrasonography (SICUS) had a higher sensitivity (99 vs 82%), but lower specificity (74 vs. 88%) than IUS. Also, a higher concordance between contrast-enhanced ultrasound (CEUS) and colonoscopy has been observed when compared to IUS alone ($k = 0.82$ vs. 0.64 , $p < 0.001$), suggesting that both SICUS and CEUS can improve anastomosis evaluation [22]. Moreover, perianastomotic BWT correlated with Rutgeerts' endoscopic score ($r = 0.67$, $p = 0.0001$), with higher BWT in patients with a score $\geq i3$ [23]. A cut-off BWT above 5.5 mm predicted severe endoscopic recurrence ($\geq i3$) [21].

Finally, a growing interest has emerged with the use of transperineal ultrasound (TPUS) to assess perianal disease as a simple and painless method. TPUS showed a sensitivity of 90.6% and a positive predictive value (PPV) of 93.4% in detecting perianal fistulae when compared to pelvic MR [24]. Extrasphincteric and suprasphincteric fistulae were less detected by TPUS, when compared to transsphincteric and rectovaginal/anovulvar fistulae. Regarding perianal abscesses, TPUS showed a sensitivity of 50% and PPV of 79% [25]. Importantly, although not completely studied, the steep learning curve of TPUS may limit the current use of this resource in clinical practice [26]. According to previous studies, physicians may achieve competency in TPUS after 12 months of training [27].

Accompanying the increasing evidence of IUS as an accurate tool to assess disease activity, several IUS scores have been published (Table 1). Six studies [28–33] evaluated inflammatory disease activity and showed a strong correlation between IUS score and endoscopy [28, 29, 31, 32]. Additionally, an expert consensus developed the International Bowel Ultrasound Segmental Activity Score (IBUS-SAS), with an almost perfect intraclass correlation coefficient (ICC 0.97 [0.95–0.99], $p < 0.001$) [33]. Nevertheless, the BWT definition varied between the studies, ranging from 3 mm [28], to 4 mm [29], or even 5 mm [31] in the colon. Additionally, two studies evaluated postoperative recurrence [22, 34], two compared stricture detection and echo pattern between IUS and MRE or histology [35, 36], and one investigated the concordance between IUS and MRE scores based on the Lémann index (LI) [37]. Interestingly, a high concordance was found between US-LI and MR-LI ($r = 0.90$, $p < 0.001$), suggesting

Table 2. Prospective studies evaluating IUS scores to predict disease activity in UC

| Index assessed (study) | n | Aims of the study | Segments assessed | Reference stan- dard | Index parameters and cut-offs | Severity grades | Outcomes |
|---|---|---|---|--|--|--|--|
| Ultrasound activity index (UAI) (Arienti et al. [65], 1996) | 57 (severe or moderately severe pts) | To investigate IUS assessment of disease activity and extent | Ascending colon Transverse colon Descending colon Rectosigmoid colon | Tc-99m scintigraphy Surgical specimen | BWT | Continuous scale (sum of maximum BWT in four segments of the colon) | Strong correlation between Tc-99m scintigraphy and IUS ($r = 0.78$, $p < 0.001$) UAI sensitivity 90.3%, specificity 96% |
| US score (Parente et al. [45], 2009) | 74 (E1 pts excluded) | To evaluate colonoscopy and IUS as indexes of response to short-term therapy | Terminal ileum Colon | Colonoscopy | BWT >4 mm CDF | 0: BWT <4 mm and no/scarse CDF 1: BWT 4–6 mm and CDF 2: BWT 6–8 mm and CDF 3: BWT >8 mm and CDF | Consistent concordance between endoscopy and IUS score in all visits (3, 6, and 9 months; k ranging from 0.76 to 0.90) |
| US score (Ishikawa et al. [47], 2011) | 37 | To evaluate the association between son elastography (EG) and colonoscopy in assessing disease activity | Descending colon | Colonoscopy | BWT >4 mm BWS (presence or absence) EG (homogeneous, random, hard) | Normal: BWT <4 mm Homogenous: BWT >4 mm, unclear BWS, Random: BWT >4 mm, unclear BWS, thickened wall EG with various colours Hard: BWT >4 mm, unclear BWS, homogenous blue EG | Significant association between EG and colonoscopy ($p < 0.001$) |
| US score (Civitelli et al. [43], 2014) | 50 (paediatric E1 pts excluded) | To evaluate usefulness of IUS in assessing disease extent and activity | Right colon Transverse colon Left colon | Colonoscopy | BWT >3 mm CDF (presence or absence) BWS (yes or no) Absence of haustra coli (yes or no) | Index calculation: sum of four components per segments 1: mild disease 2: moderate disease 3 or 4: severe disease | Strong correlation between IUS and endoscopy ($r = 0.94$, $p < 0.001$) US score >2 had a sensitivity of 100% and specificity of 93% to predict severe endoscopic disease |
| US score for UC (UCUS) (Hashimoto et al. [44], 2018) | 116 | Identify IUS parameters that can predict UC endoscopic activity and develop a simple US score | Ascending colon Transverse colon Descending colon Sigmoid colon | Colonoscopy | BWT (0: <3 mm; 10: 3–5 mm; 20: >5 mm) BWS (0 preserved, 2 obscure, 4 disappearing) | Continuous score ranging from 0 to 39 CDF (Limberg score 0: 0; 1: 5; 2: 10; 3: 15) | UCUS showed a strong correlation with endoscopy (Mayo score: $r = 0.83$, $p < 0.001$; UCES score: $r = 0.85$, $p < 0.001$) |
| Hata index (Kinoshita et al. [48], 2018) | 133 | To evaluate IUS for assessing disease activity compared to colonoscopy | Caecum Ascending colon Right transverse colon Left transverse colon Descending colon Sigmoid colon | Colonoscopy | BWT BWS Ulceration | 1: Normal BWT 2: Thickened mucosa and submucosa without hypochoic changes of the submucosa 3: BWT with loss BWS 4: BWT with loss BWS and irregular mucosa or hyperechogenic shallow concavity in mucosa | IUS sensitivity 78.9%, specificity 63.8% Moderate concordance between IUS and colonoscopy ($K = 0.55$, $p < 0.001$) This study was posteriorly validated (Omotehara et al. [82]) |
| Humanitas Ultrasound Criteria (HUC) (Alloca et al. [39], 2018) | 53 (E1 pts excluded) | To assess diagnostic accuracy of IUS in detecting disease activity/ severity and develop a non-invasive quantitative criteria of disease activity based on IUS findings | Ileum Ascending colon Transverse colon Descending colon Sigmoid colon | Colonoscopy | BWT >3 mm BWS (0 normal, 1 hypoechogetic, 2 hyperechogetic, 3 loss) CDF (presence or absence) Lymph nodes Mesenteric hypertrophy | Index calculation: 1.4 BWT + 2 \times CDF Active disease (Mayo endoscopic score ≥ 2): HUC ≥ 6.3 points CDF (presence or absence) Lymph nodes Mesenteric hypertrophy | BWT >3 mm and presence of CDF had a sensitivity of 68% and specificity of 100% compared to colonoscopy HUC ≥ 3 points (sensitivity 71%, specificity 100%) to detect endoscopic active disease |

Table 2 (continued)

| Index assessed (study) | n | Aims of the study | Segments assessed | Reference standard | Index parameters and cut-offs | Severity grades | Outcomes |
|--|--|---|--|--------------------|---|--|---|
| RM (Ramaswamy et al. [46], 2019) | 102 colonic segments (number of patients not reported) | To develop a new IUS score in UC patients and assess its correlation with Mayo endoscopic score (MES) | Caecum Ascending colon Transverse colon Descending colon Sigmoid colon Rectum | Colonoscopy | BWT (0; <3 mm; 2; 3–5 mm; 4; >5 mm) BWT (0; present; 4; absence) CDF (0; no vessels; 2; 1–2 spots; 4; stretch- es in wall; 6; extend- ing beyond the wall) | Continuous score Total score >4 = MCES 0/1 Total score 4–8 = MCES 2 Total score >8 = MCES 3 | Excellent correlation between IUS and MES; caecum ($r = 0.95$), ascending colon ($r = 0.9$), transverse colon ($r = 0.96$), descending colon ($r = 0.85$), sigmoid colon ($r = 0.82$), rectum (0.76), $p < 0.001$) |
| UC-IUS (Bots et al. [83], 2021) | 60 | To develop an ultrasound activity index | Ascending colon Transverse colon Descending colon Sigmoid colon | Colonoscopy | BWT >2 mm CDF (spots or stretch- es) Abnormal hastra- tions Fat wrapping | Continuous score ranging from 0 to 7 points | UC-IUS index showed a strong correlation with endoscopic Mayo score ($p = 0.83$, $p < 0.001$) and UCEIS index ($p = 0.759$, $p < 0.001$) |

BWT, bowel wall thickness; BWS, bowel wall stratification; CDF, colour Doppler flow; CEUS, contrast-enhanced ultrasound; MCES, Mayo clinic endoscopic sub-score; Pts, patients; T, terminal ileum; UCEIS, ulcerative colitis endoscopic index of severity.

that IUS was not inferior to MRE to evaluate bowel damage.

Therefore, IUS is an accurate method to assess disease activity, even though a lower sensitivity when evaluating the jejunum has been shown. Regarding the postoperative setting, IUS is a useful method in detecting and grading the severity of recurrence in CD. Nevertheless, for patients with BWT <5.5 mm, IUS alone may not be sufficient to guide their management, as an accurate distinction between cicatrisation and mild to moderate recurrence may not be achieved and, therefore, cannot replace endoscopy yet [38]. Finally, several endoscopic scores have been developed but none is fully validated. Accordingly, no specific IUS score is currently recommended to evaluate CD.

Disease Activity in UC

Although the role of IUS is less well established in UC, its value in evaluating disease activity has also been explored. In a prospective study, 53 UC patients underwent colonoscopy and IUS within 1 week. Patients with endoscopic active disease had higher BWT, presence of CDF, loss of BWS, and enlarged lymph nodes [39]. In a recent systematic review, most studies showed an association between IUS findings, either defined by BWT alone or in combination with other features, and disease severity on endoscopy [4]. Moreover, the accuracy of IUS to evaluate disease extension compared to endoscopy was reported as 88.5–95% (sensitivity 95%; specificity 96%) [4]. Assessments of the sigmoid and descending colon had the higher accuracy [40], in contrast to the rectum, where trans-abdominal IUS had a poor sensitivity (15%) [41]. Nevertheless, this limitation could be exceeded using TPUS. In a cross-sectional study, 57 UC patients underwent trans-abdominal and TPUS evaluation simultaneously, 7 days before or after colonoscopy. Rectal BWT ($r = 0.72$, $p < 0.001$) and CDF ($r = 0.66$, $p < 0.001$) correlated well with the Mayo endoscopic score, suggesting that TPUS can be a good tool to evaluate patients with proctitis [42].

Considering IUS scores, nine indices have been prospectively developed in UC (Table 2). All studies were based on BWT and usually complemented by CDF [39, 43–46] and/or BWS [39, 4, 44, 46, 48]. Most studies considered a normal BWT when below 3 mm, even though two studies considered 4 mm to define normal BWT [45, 47]. Overall sensitivity of UC scores ranged from 71 to 100% and specificity from 63.8 to 100%. A strong correlation was found between IUS scores and endoscopy [43–45, 47], especially in severe disease ($r = 0.94$, $p < 0.001$) [43].

Thus, IUS has shown a good performance in assessing disease activity in UC, although a lower sensitivity has been reported when evaluating the rectum, which could be exceeded using TPUS. Similar to CD, no IUS score has been formally validated.

Evaluating Disease-Related Complications

Crohn's Disease

Several studies have assessed IUS accuracy to detect intestinal strictures, with a sensitivity ranging from 74.4 to 100% and a specificity of 63–100% [35, 49–53]. Strictures have been defined by a thickening and stiffness of the bowel wall, accompanied by a proximal dilation >2.5 cm (Fig. 2) [54]. In a prospective study including 249 CD patients, the concordance between MRE and IUS for stricturing disease was high when compared to intraoperative findings ($k = 0.86$) [55]. SICUS seems to have higher sensitivity for detecting strictures when compared to IUS (89–94 vs. 74–76%) [56, 57] and showed a good accuracy in detecting ileal stenosis and prestenotic dilation [58, 59]. However, it is still not clear if IUS, including SICUS, can distinguish inflammatory from fibrotic stenosis. Nevertheless, assessment of the wall echo pattern at the stricture level may suggest the degree of fibrosis. Maconi et al. [35] concluded that strictures with a stratified echo pattern had a higher degree of fibrosis compared to those characterised by a hypoechoic echo pattern. Moreover, a reduced CDF has also been associated with a fibrotic phenotype [60]. Importantly, CEUS has also been reported as an adjuvant method to characterise strictures in CD. When compared to surgical specimens, the concordance between CEUS with inflammatory or fibrostenotic phenotype was good ($k = 0.63$), with a good correlation between sonographic and pathology scores for both inflammatory ($r = 0.53$, $p = 0.004$) and fibrotic stenosis ($r = 0.50$, $p = 0.007$) [60]. Finally, conflicting data have been published when evaluating sonoelastography as a possible method to distinguish fibrotic from inflammatory strictures in CD, and this modality requires further investigation [61].

Penetrating disease is another potential complication in CD. Abscess appears as an irregular hypoechoic lesion without vascularisation. Fistulae are hypoechoic tracts, originating from the bowel wall and connecting to other tissues, such as the urinary bladder, skin, vagina, or other intestinal segments (Fig. 3) [54]. In a meta-analysis, the pooled sensitivity and specificity of IUS in detecting fis-

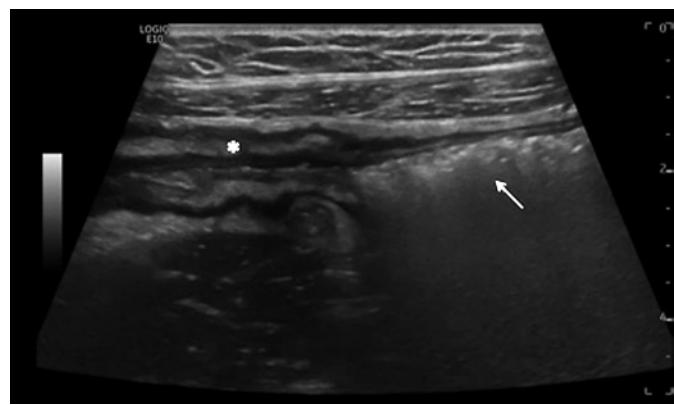


Fig. 2. IUS showing an ileal stenosis, with thickened bowel wall with narrow lumen (asterisk) and prestenotic dilation (arrow).

tulae was 74 and 95% and in diagnosing abscesses was 84 and 93%, respectively [15]. Ripollés et al. [62] showed that CEUS was able to differentiate between phlegmon and abscess in 57 CD patients, showing a high concordance ($k = 0.972$) with CT, MR, percutaneous drainage, or surgery. Similar findings have been previously reported, highlighting the role of CEUS as a sensitive method for differential diagnosis between phlegmon and abscess (Fig. 4) [63].

Therefore, IUS is an accurate method to evaluate CD-related complications. SICUS can help evaluating patients with strictures. CEUS supports the differential diagnosis of an inflammatory mass and is a promising tool in differentiating inflammatory from fibrotic strictures.

Ulcerative Colitis

A particular important scenario is acute severe UC (ASUC), treated with high-dose systemic corticosteroids, which is associated with an increased risk of colectomy. Nowadays, therapy response is based on clinical symptoms and biochemical markers (Oxford criteria) [64]. In hospitalised patients with moderate to severe UC, a significant decrease in BWT was observed in all patients who did not require colectomy, whereas patients who underwent colectomy had no BWT improvement between admission until day 10 [65]. In a recent pilot study including 10 patients, higher BWT (6.2 vs. 4.6 mm, $p = 0.009$) and any colonic segment with BWT >6 mm at admission were also associated with the need for infliximab salvage therapy. Additionally, after 3 days of high-dose steroid therapy, steroid-responsive patients had lower BWT (4.0 vs. 6.3 mm, $p = 0.009$) [66]. Similarly, in a retrospective study including 69 ASUC episodes in 52 paediatric patients, sal-



Fig. 3. IUS showing entero-enteric fistulae: hypoechoic tracts connecting small bowel loops (arrows).

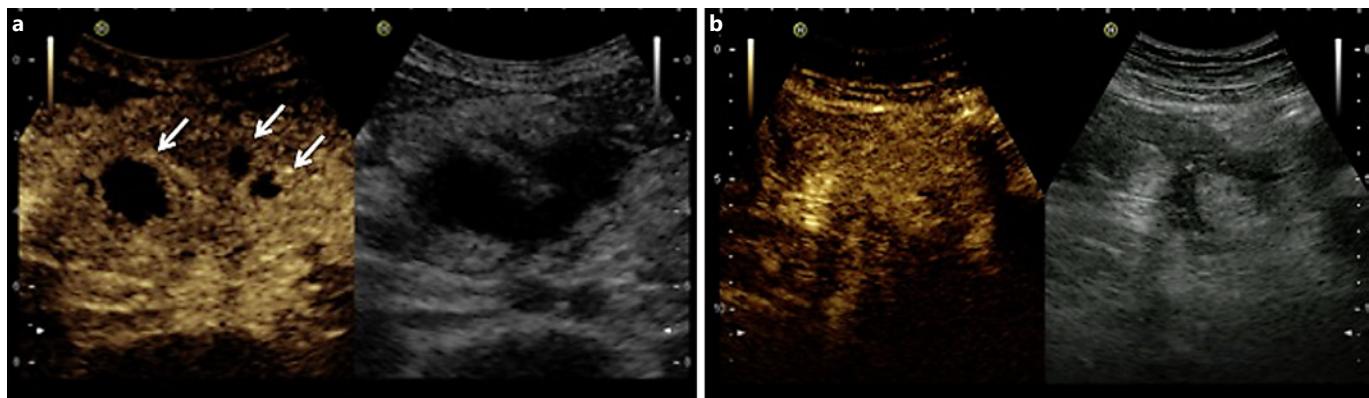


Fig. 4. Two examples of CEUS showing differentiation between abscess and inflammatory mass. **a** Using CEUS this hypoechoic mass shows three areas completely devoid of microbubble signal, repre-

senting three abscesses. CEUS can be very helpful for defining the size of the abscesses. **b** Using CEUS this hypoechoic structure shows intralesional enhancement and corresponds to an inflammatory mass.

vage therapy was more frequently needed in patients with higher BWT, higher vascularisation, and loss of BWS at admission. A thickened wall (>3.4 mm) and loss of BWS were independent predictors of steroid resistance [67]. Thus, if IUS parameters prove to be independent predictors of response to systemic steroids in the ASUC setting, early IUS could enable a timelier introduction of salvage therapy.

Monitoring Response to Therapy

Crohn's Disease

Several studies have assessed IUS as a monitoring tool in CD to evaluate the response to therapy [45, 68–70]. The definition of ultrasonographic remission, or transmural healing (TH), is not yet established, although it has been defined by some authors as a complete normalisation of

BWT (<3 mm) with normal CDF or a complete normalisation of all IUS parameters. Additionally, definitions for ultrasonographic response have also been proposed when a sonographic improvement occurs [71]. In a prospective study, TH was associated with higher rates of steroid-free remission, lower rates of clinical relapse, and longer intervals until hospitalisation when compared to MH, suggesting that TH may be a more accurate target than MH alone in CD [72]. In the recently published STRIDE-II update, TH is considered as a potential therapeutic target but not a formal one yet [1].

The TRUST study was a 12-month prospective study to assess the value of IUS in monitoring CD, including 243 patients with at least moderately active CD (Harvey Bradshaw index >7). A significant proportion of patients had an improvement in BWT, CDF, BWS, and mesenteric fat proliferation at the end of follow-up. These ultrasonographic changes were accompanied by

Table 3. Studies evaluating IUS as a monitoring tool to evaluate therapy response in CD and UC patients

| Study | Participants and duration of follow-up | Study type | Primary endpoint | Inclusion criteria | IUS features | Response to treatment | Outcomes |
|---|--|--|---|--|--|--|---|
| <i>Crohn's disease</i> | | | | | | | |
| Ripollés et al. [68] (2016) | 51 CD Median follow-up 16 months (IQR 12.2–32) | Multicentre prospective study | Assess long-term effect of biological treatment on transmural lesions by IUS (including CEUS) | Active CD pts with clinical indication for anti-TNF | BWT (>3 mm) CDF (0:absent; 1: barely visible; 2: moderate vascularity; 3: marked vascularity) Wall brightness after contrast enhancement | Clinical-biological response: Remission: HBI <5 and normal CRP levels, without steroids Partial response: HBI decrease >3 points and CRP levels decreased but without normalisation, without steroids Lack of response: HBI and/or CRP increased or did not change when other treatments were needed to control the disease IUS remission: BWT ≤3mm, CDF 0, no complications IUS improvement: BWT decrease ≥2 mm, CDF decrease 1 grade; decrease ≥20% enhancement, no complications | Week 12: Significant reduction in BWT in patients with clinical remission/ partial response (4.66 vs.1.79 mm, p = 0.01). Week 52: 96% of patients who showed a clinical remission or response had IUS improvement or normalisation Good IUS response at week 12 predicted good IUS response at week 52, with a sensitivity of 75.9% and specificity of 81.8% Follow-up: Patients without IUS improvement at week 52 had a higher need for therapy/intensification or surgery (65 vs. 11%, p < 0.001) |
| Kucharzik et al. [70] (2017) TRUST study | 234 CD 12 months | Multicentre prospective study | Change in IUS parameters within 12 months | CD pts who experienced a flare: HBI ≥7 points | BWT (TI >2 mm; colon >3 mm) CDF (Limberg score) | Clinical response: decrease in HBI score of 3 points Clinical remission: HBI <4 | Changes in IUS parameters (p < 0.001) BWT: TI 75.4 vs. 35.8% SC 47 vs. 23.1%; CDF (L5 ≥3) 44 vs. 9.7%; BWS: 53% vs. 21.6%; mesenteric fibro-fatty proliferation 47 vs. 17.9%. Improvement in IUS was accompanied by clinical (median HBI 10 vs. 2, p < 0.001) and biochemical response (median CRP 50.5 vs. 16.1 g/dL, p < 0.001) |
| Kucharzik et al. [73, 74] (2020) STARDUST IUS sub-study | 82 CD week 16 71 CD week 48 | Phase 3b randomised trial of CD patients treated with UST, comparing T2T vs. SoC | Changes in IUS parameters, including transmural response to UST | Moderate to severe active CD (CDAI 220–450), who failed conventional therapy and/or 1 biologic | BWT CDF BWS IF | IUS response: ≥25% BWT reduction from BL IUS remission: normal BWT, CDF, BWS, and absence of IF | IUS response: ≥33.8% (week 16); 35.8% (week 48) IUS remission: 11.3% (week 16); 18.3% (week 48) Mean BWT improvement from BL was observed as early as week 4 (p = 0.0002). BWT and CDF sign started to normalise at week 8; IF and BWS at week 16 |
| Calabrese et al. [75] (2021) | 188 CD | Multicentre prospective study | Assess changes in IUS parameters, including TH, induced by different biological therapies | Patients eligible for biological therapies | BWT (small bowel <3 mm; large bowel <4 mm) CDF BWS Disease length Lymph nodes Fibro-fatty proliferation | Improved lesions: improvement (>1 mm) or normal BWT; decreased length of disease; Limberg score improvement; no worsening of other parameters TH: normalisation of all parameters | 3 months: improved lesions: 36%; TH 16.4% 6 months: improved lesions: 38%; TH 24.5% 12 months: improved lesions: 36%, TH: 27.6% Colon lesions: higher risk of TH at 3 months (OR 3.18, 95% CI 1.16–7.75) Greater BWT: lower rates of TH at 3 and 12 months (OR 0.70, 95% CI 0.5–0.97; 0.58, 95% CI 0.38–0.89) |

Table 3 (continued)

| Study | Participants and duration of follow-up | Study type | Primary endpoint | Inclusion criteria | IUS features | Response to treatment | Outcomes |
|---|---|-------------------------------|--|--|---|--|--|
| <i>Ulcerative colitis</i> | | | | | | | |
| Maconi et al. [69] (1999) | 30 UC 2 months (E1 patients excluded) | Prospective study | Determine whether IUS evaluation of BWT may be useful in follow-up of UC | Active UC | BWT >4 mm Absence of regular hastruation | Remission: no symptoms and/or no signs of disease activity on endoscopy | BWT decreased in patients who achieved clinical remission (7.3 vs. 5.1 mm, $p < 0.001$) after treatment and did not change in those patients without significant clinical improvement (7.0 vs. 7.0, $p = \text{NS}$) |
| Parente et al. [45] (2009) | 74 UC 15 months (E1 patients excluded) | Prospective study | Evaluate the accuracy of IUS as a surrogate of colonoscopy in monitoring response to medical therapy | Recently diagnosed or flare-up UC patients, with moderate-to-severe disease and needing high-dose systemic steroids (oral or IV) | BWT BWS CDF | Endoscopic remission: Bs: 0 Endoscopic relapse: Bs >1 US severity: 0: BWT <4 mm and no/scarce CDF 1: BWT 4–6 mm and CDF 2: BWT 6–8 mm and CDF 3: BWT >8 mm and CDF | Consistent concordance between 0–1 Baron scores and US scores in the 3rd, 9th, and 15th months (k ranged from 0.76 to 0.90). Severe IUS scores (2–3) after 3 months of therapy had a higher risk for severe endoscopic activity in the 15th month (OR 9.1, 95% CI 2.5–33.5) |
| Maaser et al. [79] (2020) TRUST&UC study | 224 UC 12 weeks | Multicentre prospective study | Proportion of patients with normalisation of BWT in patients with clinical response | UC patients in clinical relapse (SCCAI ≥5 points) | BWT (>3 mm, except in sigmoid colon >4 mm) CDF (present or absent) | Clinical response: decrease ≥3 points in SCCAI | Significant reduction at week 12 in BWT (SC 18.9 vs. 32.6% and DC [83 vs. 37.6%] and in CDF (SC [34.8 vs. 12.9%] and DC [15.2 vs. 7.3%]) Patients with a normalisation of BWT had higher rates of clinical response (SC: 90.5 vs. 68.9%; DC: 96.4 vs. 68.8%, $p < 0.001$) |
| Sacarollo et al. [67] (2020) | 52 UC (paediatrics) | Retrospective | Evaluate the potential role of IUS in predicting the need for second-line therapy in ASUC | ASUC patients (PUCAI >55) | BWT BWS Lymph nodes | Steroid treatment failure: need for second-line therapy (infliximab or calcineurin inhibitor) | Patients requiring a second-line therapy had higher BWT values (5.14 vs. 3.89 mm, $p < 0.001$) Loss of BWS was more frequent in steroid-resistant patients (47 vs. 3%, $p < 0.001$) BWT >3.4 mm predicted steroid treatment failure, with a sensitivity of 92% and specificity of 52% |
| Smith et al. [66] (2021) | 10 UC | Prospective study | IUS can predict steroids-refractory disease | ASUC patients (>6 bowel wall movements/day) | BWT (>4 mm) CDF (Lindberg score) BWS Extra-intestinal features | Steroid treatment failure: need for salvage therapy with infliximab | At admission BWT was higher in patients with steroid treatment failure (6.2 vs. 4.6 mm, $p = 0.009$). Patients with any colonic segment >6 mm were more likely to require salvage therapy (100 vs. 25%, $p = 0.03$) At day 3, steroid responsive group had lower BWT (4.0 vs. 6.3 nm, $p = 0.009$) |

BWT, bowel wall thickness; BWS, bowel wall stratification; CDF, colour Doppler flow; CEUS, contrast-enhanced ultrasound; Pt_s, patients; TI, terminal ileum; SC, sigmoid colon; DC, descending colon; T2T, treat to target; So_c, standard of care; UST, ustekinumab; CDAl, Crohn's disease activity index; IF, inflammatory fat; SCCAI, Short Clinical Colitis Activity Index; IV, intravenous; Bs, Baron score; ASUC, acute severe ulcerative colitis; Bl_r, baseline.

clinical and biochemical improvement [70]. Similarly, in a multicentre prospective study, improvement of BWT and CDF were observed after 12 weeks, increasing even more after 12 months of therapy, highlighting that IUS response at week 12 was associated with maintenance of the IUS response at week 52 [68]. Importantly, patients without IUS improvement after 1 year of therapy had a higher need for therapy intensification or surgery (65 vs. 11%, $p < 0.001$) [68]. Likewise, in an interim analysis of the STARDUST trial IUS sub-study including 88 CD patients, IUS response and remission after ustekinumab induction were assessed. IUS response was defined by a BWT reduction of 25% from baseline and IUS remission by normalisation of BWT, CDF, BWS, and inflammatory mesenteric fat. At week 16, IUS response and remission rates were 33.8 and 11.3%, respectively. BWT improvement was observed as early as week 4, suggesting that IUS could be a useful method to detect early response to treatment [73]. A consistent decrease in BWT was observed up to week 48. Furthermore, the overall IUS response progressively increased over time (week 48 46.3%), accompanied by a higher rate of TH (week 48 24.1%). Interestingly, normalisation of BWT was more frequent when the colon was affected compared to the ileum (50 vs. 15.8% at week 48), reflecting a faster cicatrisation of the colon [74]. A recent multicentre prospective study, including 181 CD patients treated with different types of biologic therapies, assessed IUS improvement (decrease ≥ 1 mm or normalisation of BWT, decrease in length of disease, Limberg score improvement, and no worsening of other IUS parameters) and TH (normalisation of all parameters) during 12 months of follow-up. After 3 and 12 months, 36.7 and 36% of the patients showed IUS improvement, with 16.4 and 27.6% achieving TH, respectively. Patients in clinical and biochemical remission had higher rates of TH. Predictive factors of TH included colonic location (aOR 3.18, 95% CI 1.11–9.10), whereas greater BWT at baseline was associated with lower rates of TH at 3 (aOR 0.70, 95% CI 0.5–0.97) and 12 months (aOR 0.58, 95% CI 0.38–0.89) [75]. Similarly, in a recent prospective study, baseline BWT and CDF, presence of disease-related complications, FCal (>250 $\mu\text{g/g}$), and male gender were associated with a higher need for steroids, optimisation therapy, hospitalisation, or surgery after 12-months of follow-up [31]. Thus, IUS features at baseline and IUS improvement during follow-up seem to be associated with disease-related outcomes. In a prospective study, including 80 consecutive CD patients, baseline and follow-up SICUS

were performed (after a median of 18 months). Patients with IUS response (improvement or normalisation of BWT, decreased length of disease, without complications) had lower need for steroids, hospitalisation, and/or surgeries at 1 and 5 years of follow-up [76]. Regarding CEUS, differences in kinetic parameters derived from time intensity curves, such as peak enhancement, wash-in perfusion index, wash-in and wash-out rate, significantly improved in patients with clinical or endoscopic response, after 6 weeks of therapy [77]. Similarly, in a prospective study of IBD patients treated with vedolizumab, amplitude-derived CEUS parameters of mural microvascularisation also decreased in clinical responders after 14 weeks of therapy [78]. Altogether, these data emphasise the role of IUS as a method for monitoring the response to treatment in CD patients (Table 3).

Ulcerative Colitis

In the TRUST&UC prospective study, IUS findings in UC patients after initiating therapy for clinical relapse were evaluated during a 12-week period [79]. Overall, 178 patients with left-sided or pancolitis completed follow-up at week 12. Patients with normalisation of BWT in the sigmoid or descending colon had higher rates of clinical response. Moreover, clinical responders showed a significant reduction in BWT and CDF at week 12. These changes could be observed as early as after 2 weeks of therapy [79]. Finally, other IUS parameters, such as mesenteric fat proliferation, BWS, hastration, and ascites also improved after 12 weeks. Clinical symptoms accompanied IUS improvement, with a lower Simple Clinical Colitis Activity Index (SCCAI) at week 12 (9 vs. 2 points, $p < 0.001$). Similarly, a higher proportion of patients with BWT normalisation at week 12 had normal FCal values (<250 $\mu\text{g/g}$; sigmoid colon: 48.9 vs. 22.2%, $p = 0.02$; descending colon: 50 vs. 25%, $p = 0.03$) [79]. Parente et al. [45] also evaluated moderate to severe UC patients during a 15-month follow-up period. Patients who had severe IUS activity in the third month after corticosteroids therapy had a higher risk of severe endoscopic activity at 15 months (OR 9.1, 95% CI 2.5–33.5; Table 3).

Even though studies with longer follow-up are needed, these data support the use of IUS as a non-invasive monitoring tool to assess therapy response in UC. Importantly, the IUS response can be observed as early as 2–4 weeks after treatment initiation.

| Current role of IUS in IBD |
|--|
| Screening and diagnosis of IBD Differential diagnosis with IBS and GI infections Small bowel assessment in CD |
| Disease activity assessment in IBD Evaluation and grading of disease activity and extent Severe postoperative recurrence in CD Perianal disease in CD-TPUS |
| Disease-related complications in CD Strictures, fistula such as and inflammatory masses, such as phlegmon and abscesses Monitoring response to therapy in IBD |
| Future directions |
| Validation of IUS scores to allow its use in clinical practice and clinical trials Improve IUS assessment of mild to moderate CD postoperative recurrence CEUS as a promising tool differentiating fibrotic from inflammatory strictures Transmural healing as potential target in CD Uniform time points for IUS evaluation based on a treat-to-target strategy IUS in ASUC: predict need for salvage therapy and colectomy Correlation of IUS with histology in UC |

Fig. 5. The current role and future directions of IUS in IBD. ASUC, acute severe ulcerative colitis; CD, Crohn's disease; GI, gastrointestinal; IBS, irritable bowel syndrome; TPUS, transperineal ultrasound; UC, ulcerative colitis.

Future Directions and Conclusions

Nowadays, IUS is a very useful tool in the management of IBD patients, with a good accuracy in detecting disease activity, extent, and complications in CD. Besides, although being a mucosal disease, recent published data also endorse its use in UC to assess disease activity and extension. Emerging data have supported the use of IUS as a promising tool to assess response to treatment in both UC and CD, reporting changes in IUS features as early as 2–4 weeks of treatment and that persist in short- and long-term follow-up (Fig. 5). In fact, this could lead to a paradigm change in IBD, as IUS can become a routinely used tool in the management of these patients in a point-of-care setting and enabling early intervention if needed. Nevertheless, the use of IUS is not yet universal and its performance is highly dependent in the operator's experience. Inter-observer agreement of IUS in UC and CD patients is excellent for BWT and good for CDF, with fair to moderate agreement in other IUS parameters, such as lymph nodes and inflammatory fat [80, 81]. Moreover, IUS can have lower accuracy in specific bowel locations, such as the proximal jejunum and rectum. Other possible limitations of IUS include the patient's biotype, as evaluation in obese patients is difficult [82], evaluation of disease activity/extent in the postoperative setting, due to anatomical changes, and the lower capacity to detect superficial lesions in the small bowel. Therefore, it is important to train IBD-specialised gastroenterologists in this technique, as proposed by the International Bowel Ultrasound (IBUS) group. Additionally, future studies are

needed to improve IUS capacity in differentiating the severity of endoscopic recurrence in the postoperative setting, as well as to deepen the knowledge on elastography and better characterisation of stricture subtype in CD. Regarding UC, the real accuracy of IUS to predict histologic remission has never been formally studied. In an era of strict endpoints like endoscopic Mayo score of zero or even histological remission, IUS parameters might not be sensitive enough to capture subtle inflammatory mucosal changes. Finally, no IUS score has been fully validated and a homogenous approach of IUS parameters is warranted to spread its use in IBD clinics and hospitals, as well as in clinical trials.

In conclusion, IUS is an accurate non-invasive monitoring tool not only to assess IBD diagnosis, disease extent, and activity in CD and UC, but also to monitor response to therapy. In experienced hands, IUS adds extraordinary value to the management of IBD patients.

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Statement of Ethics

This article does not contain any studies with humans or animal subjects performed by the authors.

Conflict of Interest Statement

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The Use of Transabdominal Ultrasound in Inflammatory Bowel Disease

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Transabdominal ultrasound (TAUS) is useful in all aspects of lesion screening, monitoring activity, or treating/diagnosing any related complications of inflammatory bowel disease. Its ability to screen or diagnose complications is almost the same as that of other methods, such as CT or MRI. Moreover, its noninvasiveness makes it a first-line examination method. A TAUS image depicting ulcerative colitis will show large intestinal wall thickening that is continuous from the rectum, which is mainly due to mucosal layer thickening, while for Crohn's disease, a TAUS image is characterized by a diversity in the areas affected, distribution, and layer structure. Indicators of activity monitoring include wall thickness, wall structure, and vascular tests that use Doppler ultrasound or contrast agents. While all of these have been reported to be useful, at this time, no single parameter has been established as superior to others; therefore, a comprehensive evaluation of these parameters is justified. In addition, evaluating the elasticity of lesions using elastography is particularly useful for distinguishing between fibrous and inflammatory stenoses. However, the lack of objectivity is the biggest drawback of using ultrasound. Standardizing and popularizing the ultrasound process will be necessary, including scanning methods, equipment settings, and image analysis.

Keywords: Crohn's disease; Ulcerative colitis; Ultrasound; Monitoring; Diagnosis

INTRODUCTION

Inflammatory bowel disease (IBD) is a global disease of the 21st century, and the number of patients is increasing rapidly, including in Asian countries [1-4]. To date, there is not much disagreement between endoscopy and endoscopic mucosal healing as the basis of morphological diagnosis for IBD [5]. However, in addition to the invasiveness of this procedure, including pretreatment, as well as the inability to observe the distal side of stenosis and obtain information outside the wall, such as fistulas, the importance of transmural healing has also been emphasized, especially with regard to Crohn's disease (CD) [6,7]. Furthermore, since

this disease frequently occurs in relatively young people and requires long-term, almost lifelong, medical care, simpler and less invasive screening and medical follow-up procedures are required. In recent years, tomographic diagnostic methods, such as CT, MRI, and transabdominal ultrasound (TAUS), have gained attention [8-10]. In particular, TAUS has many advantages, such as not requiring any pretreatment or exposure to radiation, simplicity of the technique, relatively inexpensive equipment, and widespread use. Thus, its usefulness in the diagnosis and treatment of this disease is gaining attention [11-13]. Moreover, compared to other methods, such as MRI or endoscopy, TAUS has been reported to have higher patient acceptability than when taking a blood sample [14,15]. This study describes the usefulness of TAUS in the medical diagnosis and treatment of IBD.

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Screening IBD Using TAUS

TAUS Equipment Used for Gastrointestinal Tract Examination

While devices commonly used for abdominal USs may be adequate, using a high-frequency (7–12 MHz) probe for detailed observation of the lesion alongside a low frequency

Transabdominal Ultrasound in Inflammatory Bowel Disease

(3–4 MHz) probe for screening is desirable. In addition, a more accurate evaluation is expected if functions, such as color Doppler US, contrast-enhanced US, and elastography, are equipped. In contrast, highly portable devices, such as those used for point-of-care US (POCUS), are inferior to general devices in terms of image quality and functionality; these devices do not produce sufficient evidence to diagnose IBD.

Gastrointestinal Tract Screening Scanning Method

For the examination, special pretreatment such as colonic lavage or the use of an anticholinergic agent is not required. Performing scans requires an understanding of the gastrointestinal anatomy [16,17]; therefore, to detect gastrointestinal lesions efficiently on US, a scanning method that reliably identifies areas that consistently appear in certain parts of the body, such as the stomach, duodenum, ascending and descending colon, and rectum, and continuously tracks the lumen (which we refer to as systematic scanning of the gastrointestinal tract) is recommended. For example, the ascending colon is located on the far-right side of the abdominal cavity, with the dorsal side fixed to the retroperitoneum. Additionally, the descending colon is bilaterally symmetrical to the ascending colon and is located on the far-left side of the abdominal cavity, with the dorsal side fixed to the retroperitoneum. However, since the small intestine, mainly the jejunum, is located on the ventral side, unlike the ascending colon, it is necessary to ensure that it occupies the deepest position in the abdominal cavity when performing a scan. Systematic scanning of the small intestine is difficult, but the jejunum and ileum can be distinguished from each other, in terms of the shape (density and height) of their folds and their location.

The gastrointestinal screening procedure used at our facility is as follows: first, the region from the abdominal esophagus to the duodenal bulb is scanned, followed by a continuous scan from the ascending colon to the rectum. As the practitioner gets used to this technique, it takes between a minute or two to complete the procedure. When there is possibility of small intestinal lesions, light pressure is applied to extend the intestinal tract. Then, a scan is carefully conducted from the upper left abdomen (mainly the jejunum) to the lower abdomen (mainly the ileum), which takes a few minutes. Therefore, the total time required for the screening of the entire gastrointestinal tract is five minutes or less when the operator is

experienced in gastrointestinal ultrasonography. Figure 1 shows the affected ileal loop detected during the screening of the small intestine.

There are some tips to successfully screen and evaluate the lesions. The detection of a suspicious lesion starts with the use of a 4-MHz convex probe to visualize the entire abdomen since it permits better penetration of the US beam. Applying adequate pressure to the probe is crucial to minimize artifacts, such as multiple reverberations from the abdominal wall and sidelobe artifacts from the adjacent gastrointestinal tract. Application of pressure such that the examiner can visualize the lesion, at a depth of approximately 4–6 cm with a 4-MHz convex probe and at a depth of approximately 2–3 cm with a 7-MHz linear probe, can be helpful. The convex probe is switched to a 7-MHz linear probe after detecting a suspicious lesion to obtain detailed information regarding the lesion, including the wall stratification. Zooming in on the lesion with a 4-MHz convex probe can be an alternative when the 7-MHz probe cannot provide an image suitable for analysis because of beam attenuation caused by the patient's constitution.

Demonstration of the wall layer structure is key to judging the suitability of an US image. The image is considered suitable to evaluate the lesion if the layer structure of the lesion or the adjacent unaffected bowel segment can be appreciated when the lesion has lost the wall stratification. US can be used as a substitute for frequent CT or MRI examinations if a good quality image can be obtained.

TAUS Images of a Normal Gastrointestinal Tract

Regardless of the part of the body, a TAUS image of a normal gastrointestinal wall has the following five-layer structure: starting from the luminal side, hyperechoic (interface echo and part of the mucosal layer), hypoechoic (mucosa and muscularis mucosa), hyperechoic (submucosa),

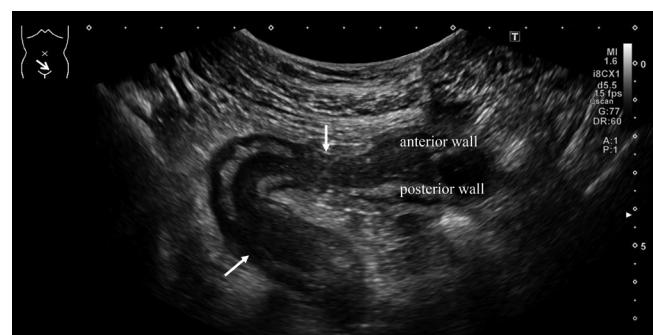


Fig. 1. Crohn's disease. An affected ileal loop in the pelvic cavity. There are two bowel segments showing loss of wall stratification (arrows), representing severe transmural inflammation.

hypoechoic (muscularis propria), and hyperechoic (serous membrane and interface echo) [18,19].

In inflammatory diseases, lesions are depicted as areas with wall thickening, but there are some reports of lesions with normal wall thickness. At the same time, lesions are also affected by factors, such as the degree of the wall stretch or the frequency used. Therefore, setting a strict cutoff value for wall thickness is difficult [20]. Therefore, as a guide, an abnormality in the small or large intestine was suspected when the wall thickness was 4 mm or greater. However, in chronic inflammatory diseases, such as IBD, active lesions may be found endoscopically, even if they are less than 4 mm. Moreover, even if everything is normal, if the lumen is empty, the wall thickness may be 4 mm or greater. Therefore, it is necessary to make a comprehensive judgment that considers other factors, such as how that area compares to other areas, the normal parts of the body, and the layer structure.

TAUS Images of UC

A typical US image of ulcerative colitis (UC) depicts a

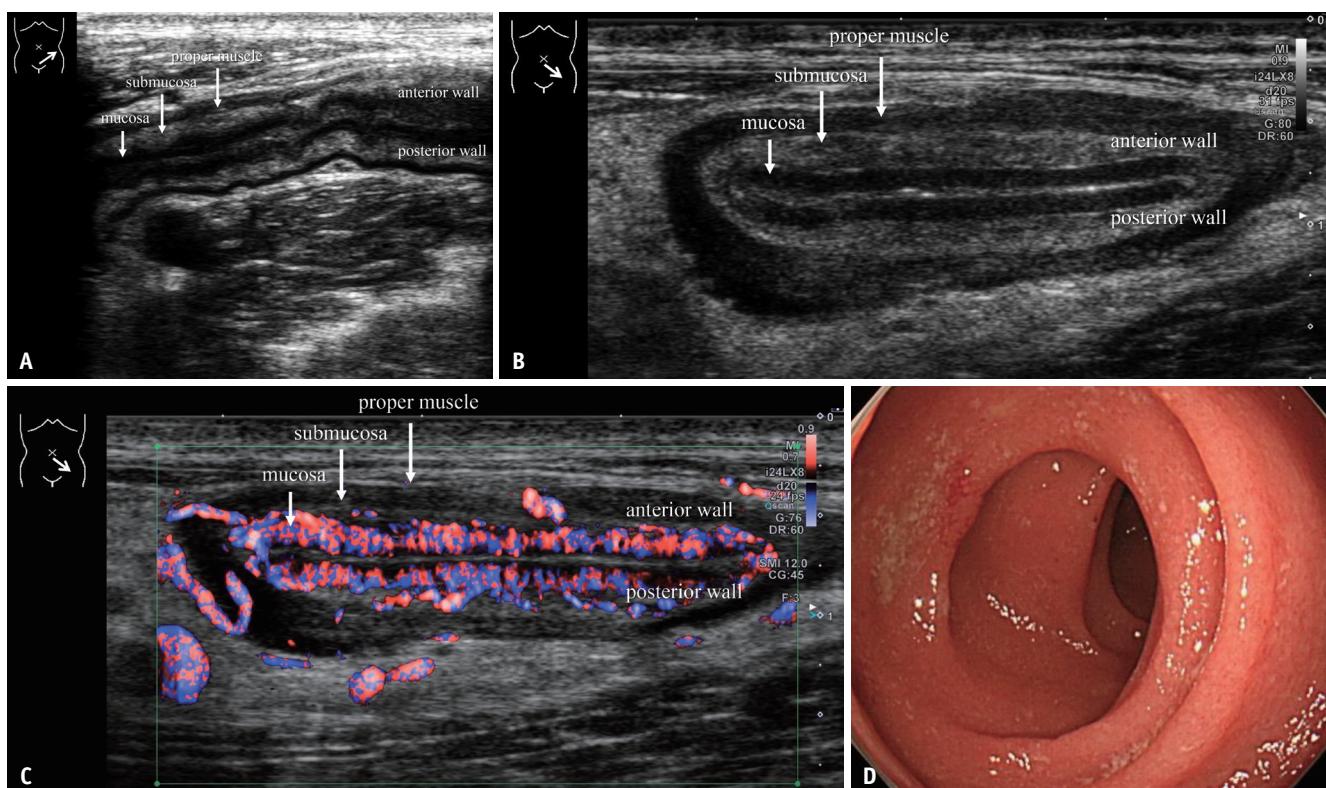


Fig. 2. Ulcerative colitis.

A. Longitudinal view of the sigmoid colon. The wall layer structure and thickening of the mucosal layer are clearly demonstrated (probe: 7 MHz linear). **B.** Transverse view of the same lesion using a 24-MHz linear probe. Each layer of the lesion is clearly visible. **C.** Blood flow signals using Superb Microvascular Imaging. Increased blood flow signals, mainly in the mucosal layer as the focus of inflammation, are noted (probe: 24 MHz linear). **D.** Endoscopic figure of the same lesion. Endoscopy shows mild inflammation of the mucosa, with an endoscopic Matts score of grade 2.

are interspersed along a normal gastrointestinal tract, can be found between them, and there are narrow and deep longitudinal ulcers (Fig. 3) that occur on the mesenteric side of the intestine. These are considered characteristic findings of this disease [27].

IBD Detection and Diagnostic Ability Using TAUS

Although there are some reports on the ability of TAUS to detect and diagnose IBD lesions, they generally show a good diagnostic ability that is almost equivalent to other modalities [28-35]. While normal equipment (not the portable type) was used in these studies, the usefulness of POCUS in IBD diagnosis and treatment in clinics has also been reported [36,37]. Hence, for patients who complain of symptoms that suggest IBD, such as chronic diarrhea and bloody stool, TAUS could be the first-line testing method because of its simple technique and non-invasiveness, despite an associated lack of objectivity.

Evaluation of IBD Activity Using TAUS

Since IBD is a disease that repeatedly goes through a cycle of remission and exacerbation for more than a year at a time, repeated endoscopy is a heavy burden on patients, as well as the medical staff and the medical economy. The

number of endoscopies that must be performed can be significantly reduced by using TAUS to evaluate IBD activity.

The following indicators should be considered when evaluating IBD activity using TAUS. There are many reports on the usefulness of the following: 1) wall thickness, 2) wall layer structure, 3) intramural blood flow measured using Doppler US, 4) intra-intestinal blood flow measured using contrast-enhanced US, and 5) elastography. In extreme cases, when the inflammation becomes severe, the following trends occur: 1) the wall becomes thicker, 2) the submucosal thickening becomes more noticeable, and with extreme inflammation or fibrosis, the layer structure disappears, 3) the color Doppler signal increases (more blood vessels are displayed), and 4) the wall appears enhanced earlier with the contrast US. Although 1) and 2) are indicators that can be compared between different patients, they do not always accurately reflect the patient's condition as the lesions are modified by fibrosis or other factors in the process of chronic inflammation. In contrast, intra-intestinal blood flow measured using Doppler US and intra-intestinal blood flow measured using contrast-enhanced US are relatively sensitive indicators that reflect the degree of inflammation. However, since the measurement of intramural blood flow using Doppler US or contrast US is also affected by other factors such as the

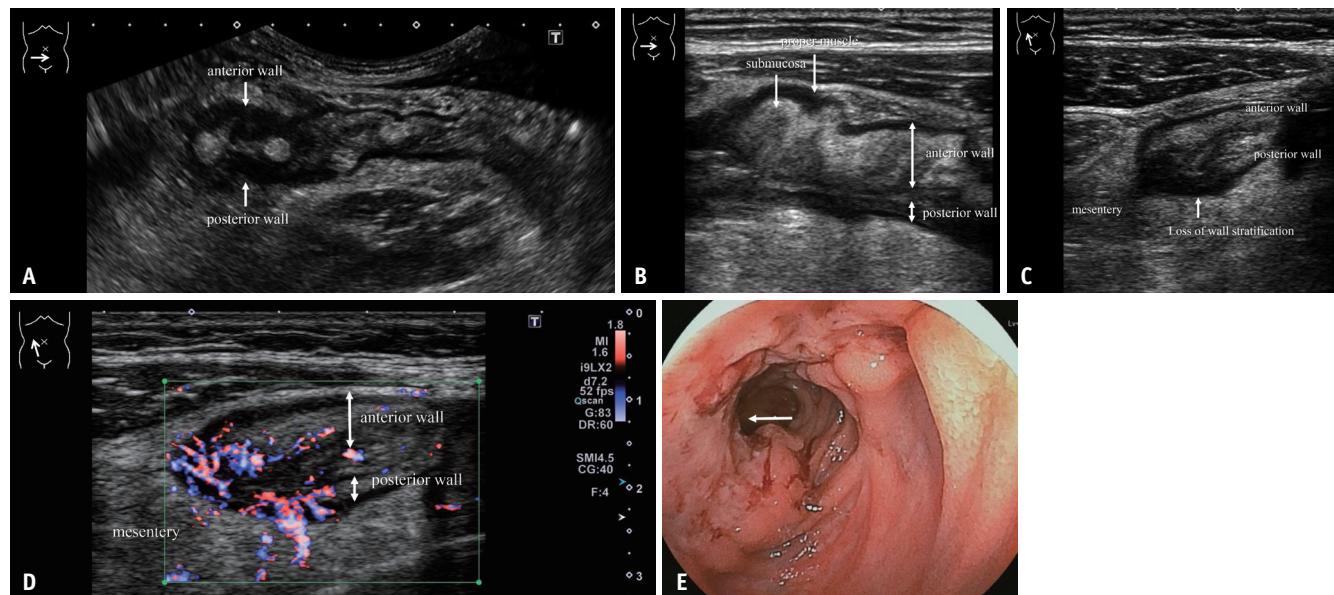


Fig. 3. Crohn's disease.

A. Super-wide view of the terminal ileum in a patient with Crohn's disease. The wall thickness, as well as the wall stratification, varies according to the location (probe: 4 MHz convex). **B.** Close-up view of the lesion using a 7-MHz linear probe. The loss of wall stratification of the posterior wall is demonstrated. **C.** Transverse view of the same lesion. The focal loss of wall stratification on the side of the mesentery represents longitudinal ulcer (probe: 7 MHz linear). **D.** Transverse view of the same lesion using Superb Microvascular Imaging. Increased blood flow signals are prominent on the mesenteric side. **E.** Endoscopic figure of the same lesion. A longitudinal ulcer is demonstrated (arrow). Loss of wall stratification on the mesenteric side is one of the specific findings of Crohn's disease.

device performance, the patient's physique, and the location of the lesion in the body, these measurements should, in principle, be used for follow-up examinations of the same part of the body in the same patient.

Wall Thickness

Wall thickening and the degree to which it has thickened are the simplest and most reproducible among examiners [38], and the measured values are not significantly affected by influences such as the patient's condition or device performance, making them suitable for use as a global standard. As previously mentioned, it has been reported that there is a relatively good correlation between the wall thickness and the degree of inflammation in both CD and UC [39-44]. However, the following points should be noted: in CD, it takes time to improve the wall thickness with treatment, and the proportion of the wall that reduces in thickness is not high [45,46]. In addition, since the

mucous membrane is the main cause of inflammation in UC, the wall is not as thick as that of CD. Therefore, it is not always easy to judge the therapeutic effect by only looking at the wall thickness [47]. Figure 4 shows an example of this phenomenon. With a wall thickness of approximately 3 mm, it is not necessarily pathological, but the layer structure makes it unclear. In addition, abundant blood flow signals were observed using Superb Microvascular Imaging (SMI), suggesting high activity, which was confirmed by endoscopy.

Layer Structure

The layered structure reflects the histopathological changes of all layers and is an important piece of information that cannot be obtained by endoscopy. Loss of this layered structure in both CD and UC suggests a more severe and poor prognosis [48-52]. The disappearance of the local layered structure in CD also indicates a deep

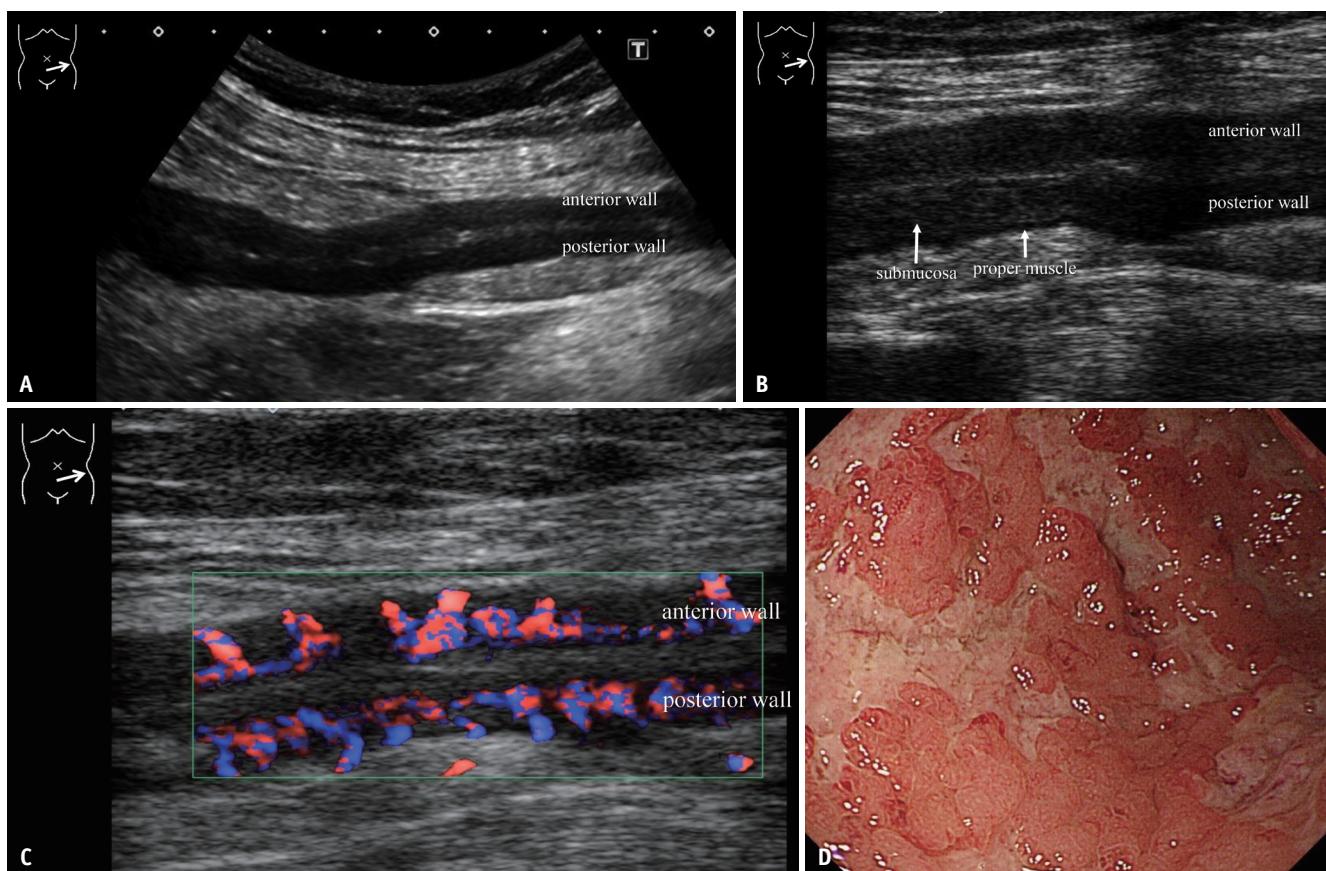


Fig. 4. Ulcerative colitis.

A. Longitudinal view of the sigmoid colon in a patient with ulcerative colitis. Although the wall thickening is mild (3 mm), the wall layer structure is blurred (probe: 4 MHz convex). **B.** Close-up view of the lesion using a 7 MHz linear probe. Thickening of the submucosal layer is demonstrated, while the mucosal layer is not clearly recognized. **C.** Evaluation of blood flow using Superb Microvascular Imaging of the same lesion. Increased blood flow, especially on the side of the lumen, is demonstrated (probe: 7 MHz linear). **D.** Endoscopic view of the same lesion. Although the wall thickness observed with ultrasound is mild, endoscopy shows severe inflammation, classified as Matts grade 4.

Transabdominal Ultrasound in Inflammatory Bowel Disease

longitudinal ulcer [27, 53]. Meanwhile, some disadvantages of considering the layered structure as a parameter are that it may be affected by factors such as the frequency of the probe being used, the physical condition of the patient, and the fact that this evaluation metric cannot be quantified and lacks objectivity. Therefore, these obstacles need to be overcome to standardize the utilization of this parameter.

Doppler US

It has long been known that inflammation increases blood flow, and it is reasonable to consider that blood flow evaluation using Doppler US is likely to be useful for IBD. As the use of Doppler US has become widespread, there have been reports on the evaluation of blood flow in the superior mesenteric artery and/or vein, but contradictory results have been reported [54-57]. Theoretically, blood flow in these vessels depends more on physiological conditions than on inflammation in certain parts of the intestinal tract. Moreover, measurement errors between examiners cannot be ignored [58, 59]. Accordingly, it would be reasonable to consider it unsuitable as a parameter for assessing lesion activity. Meanwhile, evaluating the degree of local inflammation mainly from the amount of blood flow signals using a color Doppler US seems to be a more appropriate method; its usefulness has been reported for both CD and UC [38, 60-65]. However, from the perspective of ultrasonic engineering, Doppler US sensitivity is affected by various factors such as the frequency used, display flow velocity range (folded frequency), and brightness of the background B-mode image. It also depends greatly on the path (acoustic pathway) leading to the target

organ. Therefore, it should be kept in mind that although these conditions are offset by comparing groups with large numbers of patients and certain tendencies can be observed, the results obtained for a lesion in one patient are not theoretically valid for comparison with lesions in other patients or even in the same patient at different sites. In addition, in the evaluation of intra-intestinal blood flow, the recently developed SMI has superior sensitivity, especially for a slower blood flow compared to the conventional color Doppler US [66-68]; although it is expected to be useful in assessing the activity of this disease, no clear evidence has been reported about its superiority over the conventional color or power Doppler US. Figure 5 shows an image of a patient follow-up that was conducted using SMI that looked at the same part of the body. It can be seen that the blood flow signal is reduced, reflecting an improvement in the pathological condition of the patient with treatment.

Contrast-Enhanced US

Various indicators such as maximum peak intensity, area under the curve, and time until the enhancement reaches the maximum value (time to peak) when the time-course of contrast enhancement of the wall is displayed as a time-intensity curve (TIC), are used as parameters for evaluating activity when using contrast-enhanced US. For these parameters, compatibility between patients is not necessarily guaranteed. This is because if the ultrasonic wave is strongly attenuated by the time it reaches the target organ, parameters such as maximum peak intensity and area under the curve, will naturally be affected by this

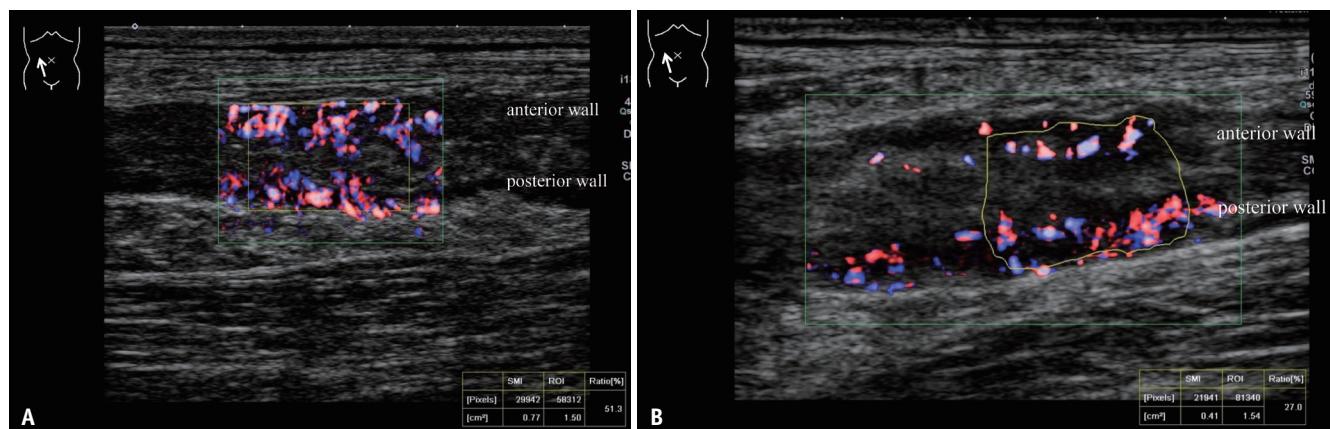


Fig. 5. Crohn's disease.

A. SMI image of a lesion in a patient with Crohn's disease before treatment. Transmural increase of blood flow is demonstrated, and the ratio of the pixel counts of the colored area to those of the range of interest is 51.3% (probe: 7 MHz linear). **B.** SMI image of the lesion after successful treatment. The blood flow signals decrease as the ratio decreases to 27.0% (probe: 7 MHz linear). SMI = Superb Microvascular Imaging

and decrease as a result; the time to peak may also be shortened if the time when the shading starts to appear on the US (zero point) is delayed. Therefore, the slope of the line connecting the peak from the zero point (coefficient of the enhancement wash-in slope) is theoretically considered to be the most compatible indicator. However, meta-analyses and systematic reviews have reported that contrast-enhanced US exhibits high sensitivity and specificity in the evaluation of CD activity [69,70]; hence, it is possible that it may be useful. Figure 6 shows the TIC of the contrast-enhanced US of CD. On the other hand, there are few reports on the usefulness of contrast-enhanced US for UC [71,72], and there is currently little evidence at the meta-analysis or systematic review level, regarding its usefulness.

Contrast-enhanced US is more cost-effective than other scanning methods such as CT or MRI [73]; however, these

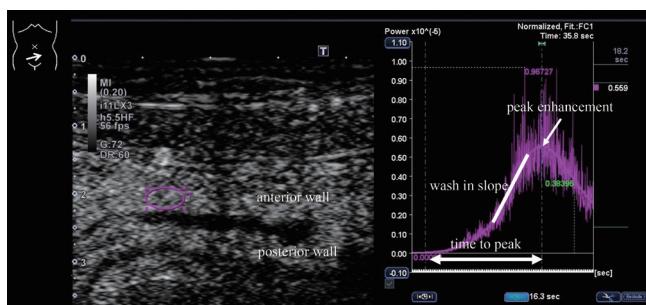


Fig. 6. Contrast ultrasound of a lesion of Crohn's disease.
Contrast ultrasound images using Sonazoid™ and the time-intensity curve of the enhancement with some parameters are shown on the right (probe: 7 MHz linear).

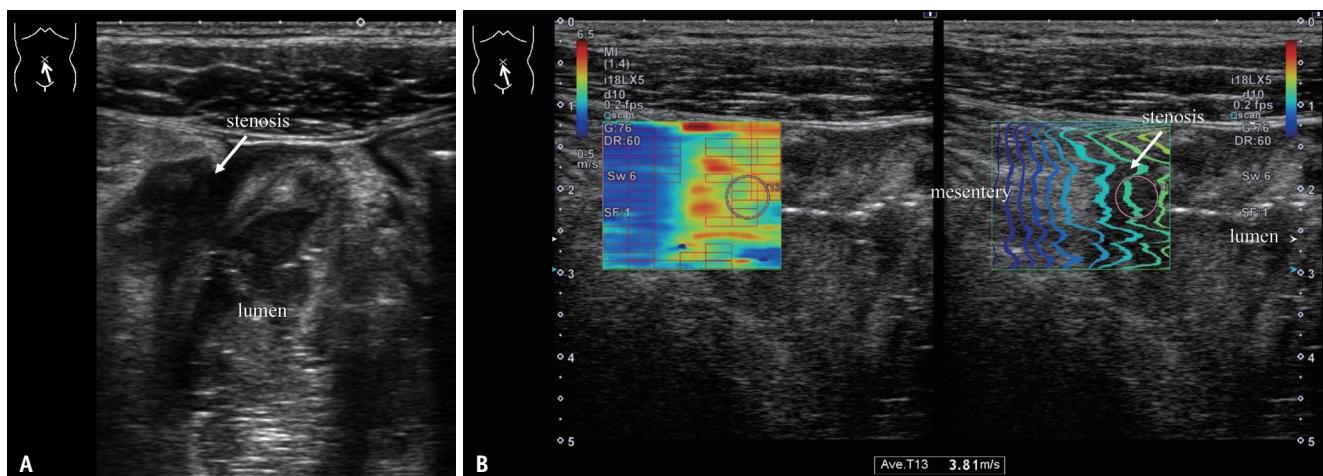


Fig. 7. Bowel stenosis is seen in a patient with Crohn's disease.

- A. Marked luminal narrowing with dilatation of the oral side. The wall stratification of the stenotic segments is lost (probe: 7 MHz linear).
- B. Shear-wave elastography of the stenotic lesions. The stenotic area is orange-colored, while the adjacent mesentery is blue, which indicates that the lesion has higher elasticity. The shear wave speed is as high as 3.81 m/s (probe: 7 MHz linear).

reports were for masses found in the liver. In addition to other factors such as a longer examination time, the invasiveness of the procedure due to the use of an intravenous contrasting agent on the patient as well as the increased financial burden, a drawback of this method is that it requires equipment that can handle contrast-enhanced US and its TIC analysis. In addition, since the strongest enhancement of the lesion is observed only during the early vascular phase, it is difficult to evaluate multiple lesions at a time using contrast US. Therefore, we must decide the lesion of interest that is the most affected bowel segment, before performing contrast US. Thus, there is uncertainty as to whether this method will become widespread as a global standard.

Hence, at present, it is considered more realistic to comprehensively judge wall thickness, layer structure, and Doppler US findings and, if necessary, perform contrast-enhanced US [44,46,74]. While we have previously published a report outlining a scoring system for CD activity using wall thickness and layer structure [49], it unfortunately never became widespread due to its complexity. In the future, the development of a simpler and more useful scoring system is desirable.

Diagnosis of Complications

It is not always easy to use an endoscope to diagnose complications related to IBD, but the usefulness of US, which is a tomographic diagnostic method, is promising. Stenosis is a complication often encountered in CD that

Transabdominal Ultrasound in Inflammatory Bowel Disease

requires surgical or endoscopic interventions [75]. US stenosis is defined as luminal narrowing (< 10 mm) with oral dilation (> 25–30 mm) [76,77]; however, it may not always be accompanied by pathological thickening of the

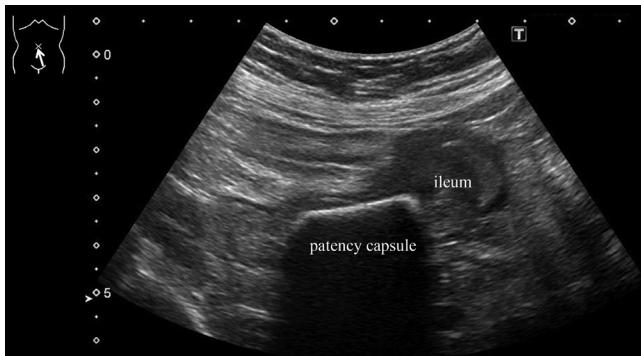


Fig. 8. Retention of a patency capsule in a patient with Crohn's disease. The patency capsule demonstrated as a linear, strong echo accompanied by an acoustic window is trapped at the oral side of the stenotic lesion (probe: 4 MHz convex).

stenotic site. Although only one end of the stenotic site can be evaluated with an endoscope, it is possible for the US to evaluate the length of the stenosis and the properties of

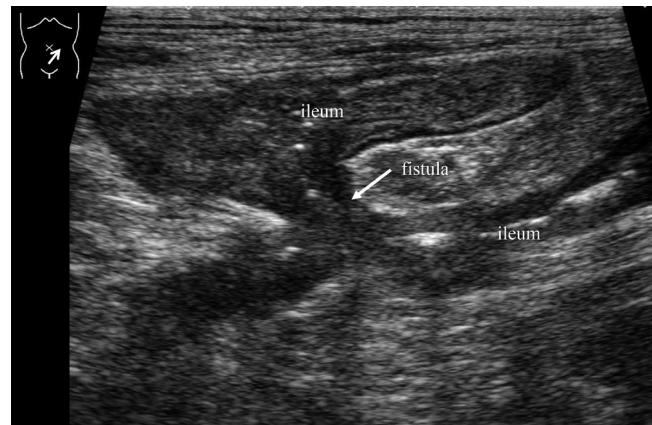


Fig. 9. Ileo-ileal fistula in a patient with Crohn's disease. The fistula between the two bowel segments is demonstrated as a hypoechoic band with small air bubbles inside (probe: 7 MHz linear).

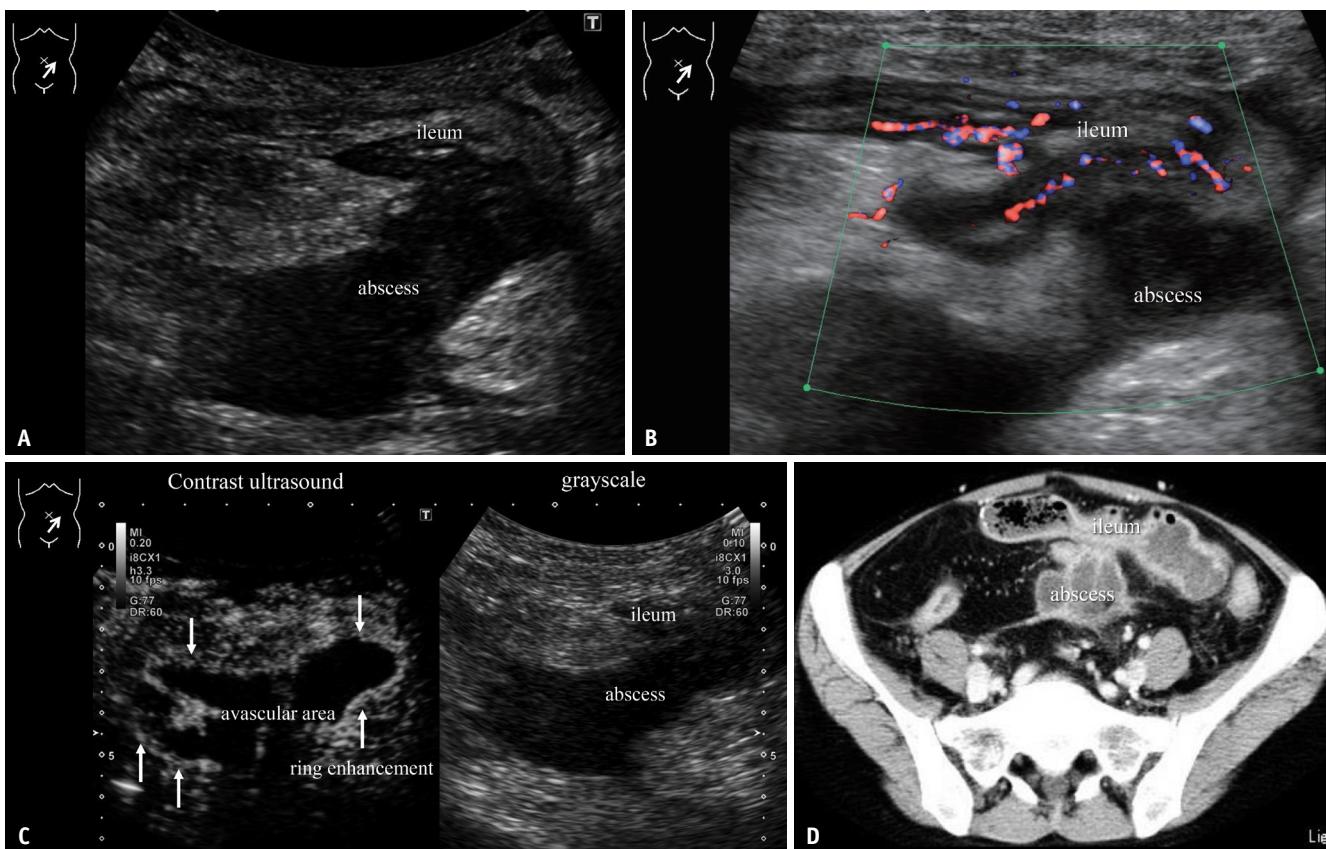


Fig. 10. Abscess in a patient with Crohn's disease.

A. An abscess is identified as a hypoechoic area attached to the bowel lesion. Fluctuations in the contents can be noticed by real-time observation (probe: 4 MHz convex). **B.** Superb Microvascular Imaging of the same lesion. The abscess is identified as an avascular area (probe: 7 MHz linear). **C.** Contrast ultrasound of the same lesion. The image on the right shows the contrast ultrasound image and the image on the left shows the monitoring grayscale image. The abscess shows no contrast enhancement, while the surrounding area shows increased enhancement, which is known as ring enhancement (arrows) (probe: 4 MHz convex). **D.** Contrast-enhanced computed tomography image. The abscess is identified as an area without enhancement.

the wall, including its relationship with surrounding tissues. The mechanism of stenosis is complicated, including hyperplasia of smooth muscle that is associated with chronic inflammation as well as the compression of adipose tissue outside the wall due to wall thickening. However, it is generally necessary to determine whether the stenosis is predominantly due to inflammation or fibrosis, as the former is likely to improve with conservative treatment, while the latter requires surgical treatment or endoscopic dilatation [78]. Regarding the differentiation between inflammation and fibrosis using TAUS, there are reports that, in B-mode, the hypoechoic pattern is more typical in inflammatory stenosis, while the stratified or nonhomogeneous echo pattern indicates fibrosis [79,80]. At the same time, it is important to note that factors such as the appearance and uniformity of the layered structure differ depending on the

frequency used or the patient's condition. Additionally, reports using color Doppler and contrast-enhanced US indicated more blood flow with inflammatory stenosis compared to fibrous stenosis, and the finding is believed to be useful in differentiating between inflammatory and fibrous stenosis [81-85]. Recently, it has been reported that evaluation of lesion hardness using methods such as strain elastography or shear-wave elastography (SWE) is useful for diagnosing fibrosis [86-90]. In particular, SWE is expected to be used as an objective and quantitative indicator as well as for lesion activity evaluation in the future. Figure 7 shows stenotic lesions in CD. Clear stenosis of the upper lumen and dilation of the oral intestinal tract were observed in B-mode. When SWE was used, the lesion appeared hard, suggesting that the stenosis was accompanied by a high degree of fibrosis. TAUS can also be used to diagnose areas

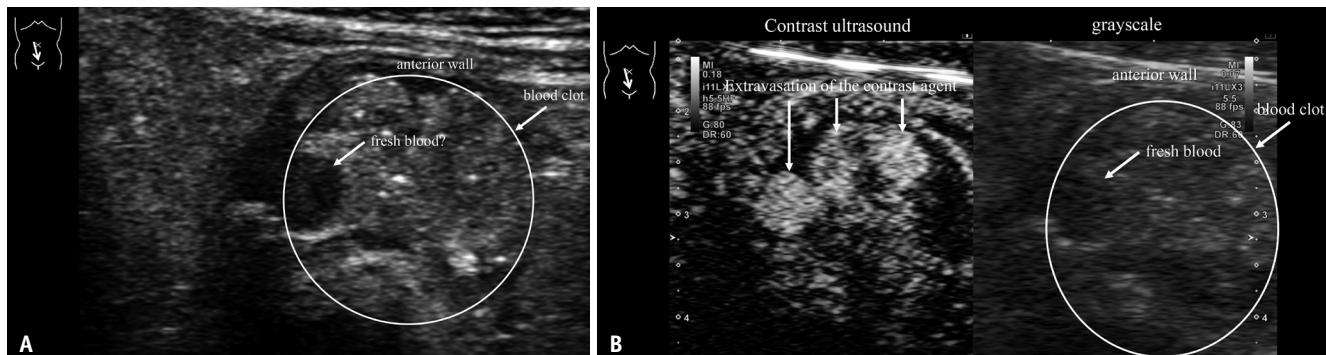


Fig. 11. BBowel hemorrhage seen in a patient with Crohn's disease.

A. An echogenic mass in the ileal lumen with a small, rounded, hypoechoic area inside is detected. The echogenic mass (circled area) might represent a blood clot, and the hypoechoic area may represent fresh blood (probe: 7 MHz linear). **B.** Contrast ultrasound of the same lesion. The image on the right shows the contrast ultrasound image and the image on the left shows the monitoring grayscale image. Extravasation of the contrast agent into the hypoechoic area (arrows) is immediately demonstrated, and the contrast agent gradually spreads into the mass, which represents the blood clot (circled area) (probe: 7 MHz linear).

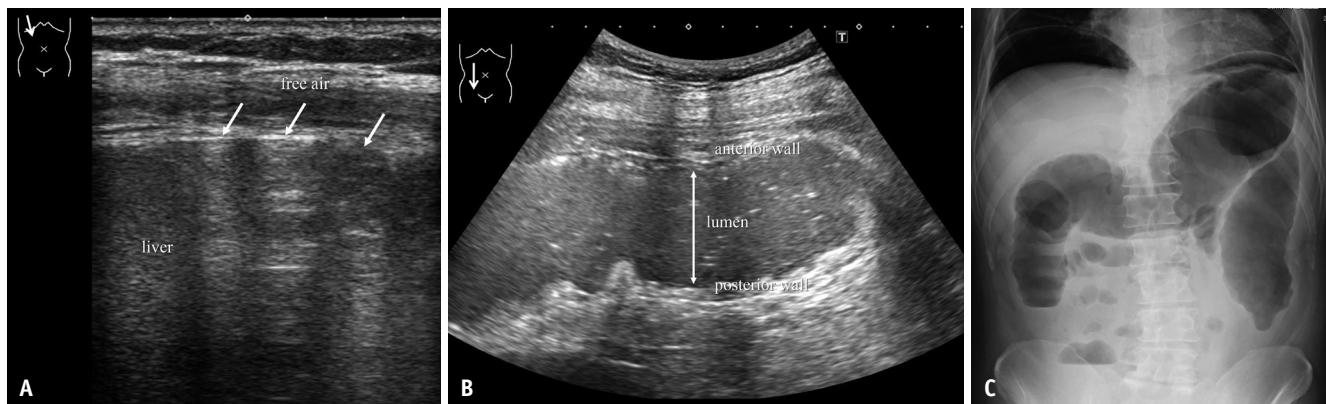


Fig. 12. Colonic perforation seen in a patient with ulcerative colitis.

A. Free air is demonstrated as hyperechoic bands accompanied by multiple echoes beneath the parietal peritoneum (probe: 7 MHz linear). **B.** Longitudinal view of the ascending colon. The wall thickness is thin, and dilatation of the colonic lumen filled with watery stool is demonstrated, which indicates toxic megacolon (probe: 4 MHz convex). **C.** Abdominal X-ray. Colonic dilatation, suggesting toxic megacolon, as well as free air, is demonstrated.

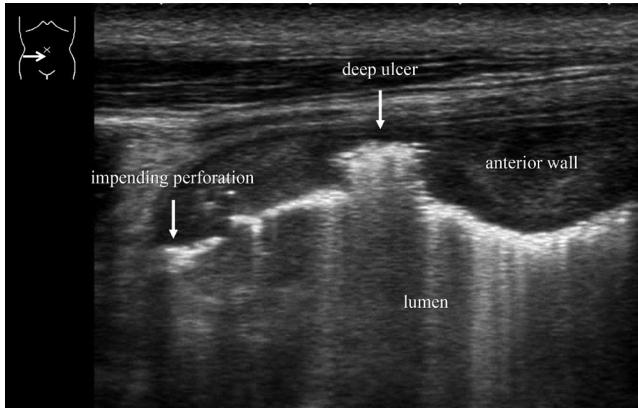


Fig. 13. Impending perforation of the cecum in a patient with ulcerative colitis. Deep ulcers are demonstrated, and an ulcer is as deep as the subserosa, indicating a high risk of perforation (probe: 7 MHz linear).

of stasis for capsule endoscopy and patency capsules [91]. Figure 8 shows an image of a patency capsule retained in the ileum in the case of CD.

The sinus and fistula are depicted as linear or band-shaped hypoechoic lesions, continuing from the superior intestinal lesions of the TAUS; air may also be observed inside (Fig. 9) [92,93]. Abscesses are also considered to be low to non-echoic regions with liquid components and sometimes aeration (Fig. 10) [94]. Since it has been reported that the diagnostic abilities of TAUS are almost the same as those of other methods such as CT and MRI scans [95], this method should be tried first.

Meanwhile, it is not easy to diagnose bleeding with B-mode (black and white images) or color Doppler; hence, we have reported a method for showing extravasation of a contrast agent using a contrast-enhanced US and making a diagnosis [96]. However, no IBD-specific papers have been found, and this method is not commonly used, as yet. Figure 11 shows a case of CD in which evidence of active bleeding was found using contrast-enhanced US.

Toxic megacolon is a serious intestinal complication that can occur in a case of UC, but there are very few reports on this complication, in which TAUS was used. In these cases, the large intestine was dilated (> 6 cm), the wall was thinned (< 2 mm), and the lumen was filled with watery stool (Fig. 12) [97]. Evidently, perforation is determined by detecting free air on US. In addition, TAUS can determine the perforation site and the risk of perforation; however, there are no reports on this. Figure 13 shows a case of UC in which a perforation occurred 12 hours after the examination, and deep subserosal ulcers in the cecum and turbid ascites

in the surrounding area, signifying imminent perforation.

CONCLUSION

TAUS is considered to be extremely useful in the diagnosis and treatment of IBD as a non-invasive and simple tomographic diagnostic method. It is an indispensable examination method at our facility for the diagnosis of IBD and several other gastrointestinal diseases, such as acute inflammatory diseases and neoplasm. Since TAUS is non-invasive and does not require any special preparation, it can be easily performed and repeated at any time, whenever necessary. In addition, TAUS can provide detailed information regarding the transmural changes of the lesion, extramural complications, and even minute blood flow changes of the lesion, with its high spatial and temporal resolution. Therefore, we believe that TAUS has great potential to be the first-line morphological examination method in the diagnostic strategy of gastrointestinal diseases. However, there are some issues that need to be resolved related to the universalization and standardization, as for such a technique, the biggest drawback could be regarding equipment selection and settings, parameters used for evaluation, and lack of objectivity. In the future, discussions between facilities, academic societies, and nations would be necessary.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Jiro Hata. Resources: Jiro Hata. Supervision: Hiroshi Imamura. Validation: Jiro Hata. Writing—original draft: Jiro Hata. Writing—review & editing: Jiro Hata.

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Abbreviation:
 SROC = summary receiver operating characteristic

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Role of US in Detection of Crohn Disease: Meta-Analysis¹

PURPOSE: To evaluate the accuracy of ultrasonography (US) in the detection of Crohn disease in adults by systematically reviewing both cohort studies (those including patients whose clinical characteristics were consistent with those caused by an inflammatory bowel disease) and case-control studies (those in which patients with Crohn disease were compared with patients with other bowel diseases or healthy control subjects).

MATERIALS AND METHODS: The MEDLINE, EMBASE, and Cochrane Library databases were used to retrieve all the cross-sectional studies that assessed the diagnostic accuracy of US against that of one of several predefined reference standards (ie, radiologic, endoscopic, or histologic findings). The studies that fulfilled the inclusion criteria were identified, and their methodological quality was evaluated. Of the 2860 primary studies identified, two case-control and five cohort series fulfilled the inclusion criteria. Statistical analysis was performed by using the summary receiver operating characteristic (SROC) model.

RESULTS: The ranges of US sensitivity and specificity for the diagnosis of Crohn disease reported for the included series were 75%–94% and 67%–100%, respectively; the heterogeneity of these values prevented the calculation of a cumulative value. The SROC curve revealed a clear cutoff effect that depended on the chosen bowel wall thickness threshold. Sensitivity and specificity of 88% and 93%, respectively, were achieved when a bowel wall thickness threshold greater than 3 mm was used, and sensitivity and specificity of 75% and 97%, respectively, were achieved when a threshold greater than 4 mm was used.

CONCLUSION: US examination seems appropriate for confirming or excluding Crohn disease as a diagnosis in a clinical context characterized by a pretest probability of Crohn disease that ranges from 12% to about 60%. In particular, for Crohn disease limited to the ileum, US may represent a valid alternative to the small-bowel series, while for colonic involvement US may be useful in ruling out the diagnosis.

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Crohn disease is an inflammatory bowel disease that may involve various portions of the gastrointestinal tract, although ileal and/or colonic involvement is most frequent. In addition to relying on clinical findings, the diagnosis of Crohn disease relies on information yielded by a combination of various imaging and endoscopic techniques and/or histologic examination (1). In particular, ultrasonography (US) of the bowel loops is a noninvasive procedure whose ability to depict bowel wall abnormalities has recently been improved by the availability of high-frequency transducers.

The role of US in the diagnosis of Crohn disease has been investigated extensively (2–47), but the estimates of its diagnostic accuracy have been based on the results of studies that differed in terms of design, population characteristics, and reference standards. Furthermore, most of the currently available data have been obtained from studies that included patients with a previous diagnosis of Crohn disease but lacked an appropriate control population, thus making it possible to calculate only the positive predictive value of US examination.

The purpose of our meta-analysis was to evaluate the accuracy of US in detection of Crohn disease in adults by systematically reviewing both cohort studies (those including patients whose clinical characteristics were consistent with those of an inflammatory bowel disease) and case-control studies (those in which patients with Crohn disease were compared with patients with other bowel diseases or healthy control subjects).

MATERIALS AND METHODS

Data Sources

The primary study retrieval sources were MEDLINE (which, at the time we performed our literature search, included articles published from January 1966 through the 1st week of April 2004); EMBASE (which included articles published from January 1988 through the 1st week of April 2004); the Cochrane Library database (which included systematic reviews published from January 1988 through the 1st issue of 2004); and reference lists from all available review articles, primary studies, and proceedings of major meetings published between January 1995 and the 1st week of April 2004. The search was not restricted to articles published in a certain language or languages. In cases of incomplete data, the original material was directly requested from the study authors.

The search strategy, which included the use of both Medical Subject Headings, or MeSH, and free terms, is detailed in Figure 1.

Study Selection Criteria

The aim of our search was to identify cross-sectional studies that met the following two criteria: First, the study had been performed with patients who had clinical (eg, chronic diarrhea, abdominal pain) and/or laboratory data (increased levels of acute phase reactants) that were suggestive of an inflammatory bowel disease. Second, the study examined compared the accuracy of US in the diagnosis of Crohn disease with the accuracy of one of the following reference standards: (a) radiologic evidence, at small-bowel series, of a peculiar ileal pattern whose severity increased with the stage of the disease, with a characteristic cobblestone appearance of the mucosa, luminal narrowing with retrodilation, and possible coexistence of fistulas and/or sinus tracts in the more advanced stages of disease (1); (b) a pattern macroscopically consistent with that of Crohn disease at endoscopy (1); and/or (c) appropriately classified histologic findings obtained after colonic or ileal surgery or endoscopic procedures (1).

Consideration was given to both cohort studies aimed at detecting Crohn disease among patients whose clinical characteristics were consistent with those of inflammatory bowel disease and case-control studies aimed at assessing the accuracy of US in discriminating patients with Crohn disease from patients with

Search strategy

- 1 exp Crohn Disease
- 2 exp DIAGNOSIS
- 3 exp ULTRASONOGRAPHY
- 4 2 or 3
- 5 1 and 4
- 6 exp ENDOSCOPY
- 7 exp COLONOSCOPY
- 8 exp RADIOGRAPHY, ABDOMINAL/ or exp RADIOGRAPHY
- 9 exp HISTOLOGY
- 10 6 or 7 or 8 or 9
- 11 5 and 10
- 12 (crohn dis\$ or IBD or inflammatory bowel diseas\$).mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
- 13 diagnos\$.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
- 14 (ultraso\$ or echograph\$ or sonograph\$ or ultra-sound\$ or ultra sound\$).mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
- 15 13 or 14
- 16 12 and 15
- 17 (endoscop\$ or colonoscop\$).mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
- 18 (histol\$ or biop\$ or pathol\$).mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
- 19 (radio\$ or small bowel series).mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
- 20 17 or 18 or 19
- 21 16 and 20
- 22 11 or 21

Figure 1. MEDLINE search strategy used in the study.

other bowel diseases or healthy individuals or in enabling exclusion of an underlying disease.

Types of Participants and Interventions

The cohort studies included patients with clinical (eg, chronic diarrhea, abdominal pain) and laboratory features that were possibly related to an underlying inflammatory bowel disease, whereas the case-control studies included patients known to have Crohn disease as well as either patients with other organic or functional bowel diseases or healthy control subjects. Both study types assessed the diagnostic accuracy of US against at least one of the reference standards defined above.

Inclusion and Exclusion Criteria

In this systematic review, we included studies with the following features: (a) involvement of either a population representative of the spectrum of the disease or a population of patients with Crohn

disease and either patients with other bowel diseases or healthy control subjects; (b) use of an appropriate reference standard; and (c) presence of data regarding sensitivity and specificity values or the possibility of deriving such values from the results analysis. Reports of studies involving children and duplicate reports were not included.

Quality Assessment of Primary Studies

The included studies were assessed in terms of their methodologic quality to explain the possible sources of heterogeneity. In agreement with previously defined standards (48,49), the criteria we used to rate the quality of the studies were as follows: spectrum composition (whether the sample composition [ie, clinical population or case control] was properly described); verification (whether exhaustive details concerning the method of applying the reference standard were given; verification was considered complete when all patients

TABLE 1
Characteristics of Seven Studies of Diagnostic Performance of US in Crohn Disease

| Reference | Year of Publication | Type of Study* | Disease Location† | Reference Standard | No. of Patients with Crohn Disease/ No. of Other Subjects‡ | Bowel Wall Thickness Cutoff Used (mm) |
|-----------------------|---------------------|----------------|-------------------|---|---|---------------------------------------|
| Sheridan et al (3) | 1993 | PC | I | Small-bowel series | 24/96 (25) | >5 |
| Bozkurt et al (4) | 1994 | PC | IC | Endoscopy or surgery and histologic results | 31/240 (12.9) | >4 |
| Solvig et al (42) | 1995 | PC | I | Small-bowel series | 20/59 (33.8) | >3 |
| Tarjan et al (43) | 2000 | PC | I | Small-bowel series and clinical findings | 47/73 (64.3) | >3 |
| Astegiano et al (44) | 2001 | PC | ND | Endoscopy, radiology, and 2-year follow-up | 61/313 (19.4) | ≥7 |
| Sonnenberg et al (45) | 1982 | CC | IC | Endoscopy, histologic results, and small-bowel series | 51/124 | >5 |
| Reimund et al (46) | 1999 | CC | IC | Endoscopy, histologic results, and radiology | 48/70 | >3 for ileum, >4 for colon |

* CC = case control, PC = prospective cohort.

† I = ileal, IC = ileocolonic, ND = not defined.

‡ Numbers in parentheses, which are given only for patients in prospective cohorts, are percentages of patients with Crohn disease. The other subjects in the studies of Sheridan et al, Bozkurt et al, Solvig et al, Tarjan et al, and Astegiano et al were patients with clinical findings of inflammatory bowel disease; those in the studies of Sonnenberg et al and Reimund et al were control subjects without Crohn disease.

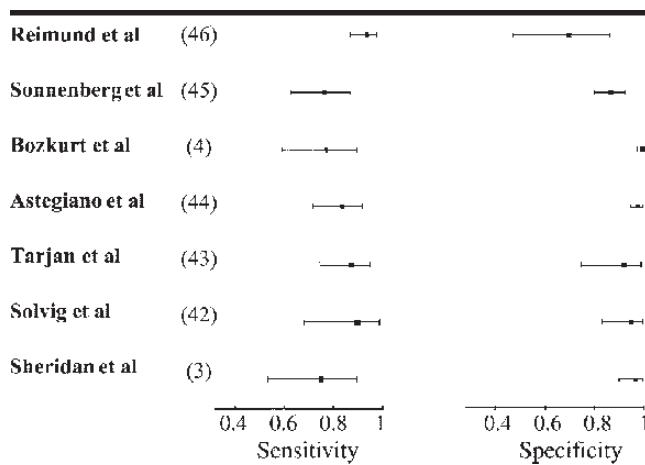


Figure 2. Graph shows the sensitivity and specificity of US in the detection of Crohn disease reported for the seven studies. Reimund et al (46) and Sonnenberg et al (45) were case-control studies; the other five studies were prospective cohort studies. Mean values (■) and 95% confidence intervals (error bars) are indicated; the heterogeneity of the results prevented the calculation of a cumulative value.

were examined by using the same reference standard and partial when all patients were not thus examined); interpretation of test results (whether blinded or not); method of patient selection (whether consecutive or not); methods of data collection and reporting (whether data collection was prospective, retrospective, or “unknown” [in case of doubt]); and whether details concerning the test, reference standard, or population were provided (sufficiently or insufficiently). In addition, data concerning intra- and interobserver variability, when detailed in the studies, were considered as quality parameters.

Outcome Measures

The outcome measures for diagnostic accuracy were sensitivity and specificity.

Review Methods

The search was independently performed by two reviewers (M.F. and S.P.). The review included all of the studies that were initially identified in the manner described above, and the results of the review were analyzed by five reviewers (M.F., S.P., A. Colli, S.M., and A. Colucci). In addition, each of the five reviewers reexamined the selected studies

to identify those that fulfilled the inclusion criteria and then evaluated the methodologic quality of the studies by using reported parameters, as defined above (49). The data concerning the types of participants, the interventions, and the outcome measures were independently extracted by each reviewer. Any discrepancy was openly discussed by the reviewers, and, in cases of further disagreement, the judgment of an independent gastroenterologist with 30 years of clinical experience (D.C.) was considered final.

Statistical Analysis

The sensitivity (true-positive rate) and specificity (true-negative rate) of each study was recorded, and exact 95% confidence intervals based on a binomial distribution were calculated. The homogeneity of the true-positive and the true-negative rates was evaluated by using the χ^2 or exact test (50) and a significance level of .1 (51). In cases of heterogeneity, the relationship between sensitivity and specificity was evaluated by using the Spearman correlation coefficient, ρ (52), and assuming a between-study variation in cutoff points when ρ was less than -0.3 (53).

When a between-study variation in cutoff points was observed, the summary receiver operating characteristic (SROC) curve was calculated (52). Maximum joint sensitivity and specificity was defined as the point on the SROC curve that intersected a diagonal line running from the top left corner to the bottom right

TABLE 2
Results of Assessment of Methodological Quality of Seven Studies of Diagnostic Performance of US in Crohn Disease

| Reference | Year of Publication | Spectrum Composition* | Verification | Blinded Interpretation of Test Results | Consecutive Patients Enrolled | Equipment and Procedures Detailed | | Data on Intra- and Interobserver Variability Included |
|-----------------------|---------------------|-----------------------|--------------|--|-------------------------------|-----------------------------------|--------------------|---|
| | | | | | | US | Reference Standard | |
| Sheridan et al (3) | 1993 | PC | Complete | Yes | Yes | Yes | No | ND |
| Bozkurt et al (4) | 1994 | PC | Partial | Yes | Yes | Yes | No | ND |
| Solvig et al (42) | 1995 | PC | Complete | Yes | Yes | Yes | Yes | ND |
| Tarjan et al (43) | 2000 | PC | Partial | ND | ND | Yes | No | ND |
| Astegiano et al (44) | 2001 | PC | Partial | Yes | Yes | Yes | No | ND |
| Sonnenberg et al (45) | 1982 | CC | Complete | Yes | ND | Yes | No | Yes |
| Reimund et al (46) | 1999 | CC | Partial | Yes | Yes | Yes | No | ND |

Note.—ND = not defined.

* CC = case control, PC = prospective cohort.

corner of the diagram and represented the point at which sensitivity and specificity had the same value. A perfect test has a maximum joint sensitivity and specificity score of 1.0, whereas a nondiagnostic test has a score of 0.5 or less.

A subgroup analysis was predefined to explain the possible sources of clinical heterogeneity between studies on the basis of the study design, the percentage prevalence of Crohn disease (ie, the pretest probability) (<10%, 10%–40%, or >40%), the reference standard used, the percentage prevalence of irritable bowel syndrome (<10%, 10%–40%, or >40%), the bowel wall thickness cutoff (>3 vs >4 mm [a value of ≤ 3 mm is considered normal]) used, the disease location (ileal, ileocolonic, or colonic), the percentage frequency of ulcerative colitis (<10%, 10%–40%, or >40%), the frequency of the US transducer used (≤5 vs >5 MHz), and the year of study publication (before or during 1990 vs after 1990).

So that we could analyze the presence of a publication bias, we constructed a funnel plot of the individual studies, with log diagnostic odds ratios plotted against sample size. An asymmetric funnel plot would suggest that other small studies may have been conducted but not published because of unfavorable results (54).

The data were analyzed by using SAS, version 8.2 (SAS Institute, Cary, NC).

RESULTS

Included Studies

Of the 2860 primary study reports identified, 2147 represented nonduplicated study reports and were retrieved in abstract form because of a 25% overlap between the MEDLINE and EMBASE da-

tabases. Because 2103 of these abstracts were considered not pertinent, only 44 of the studies were retrieved as full texts. Of these 44 studies, 27 were excluded because of the inappropriateness of the population studied (eg, there was a lack of control subjects) ($n = 12$) (6,11, 14,15,18,22,25–28,35,40), a lack of or use of an inappropriate reference standard ($n = 6$) (10,12,16,21,34,36), the unavailability of sensitivity or specificity values ($n = 4$) (23,24,32,47), data duplication ($n = 1$) (20), or the involvement of a pediatric population ($n = 4$) (9,17,31,33). So that we could obtain a pooled value, we excluded an additional 11 studies (2,5,7,13,19,29,30,37–39,41) in which the US sign of bowel wall thickness was not considered as a single variable and/or a precise bowel wall thickness threshold level was not provided. Thus, at the end of the process, the final analysis included five cohort (3,4,42–44) and two case-control studies (45,46) whose main characteristics are detailed in Table 1. In detail, the prevalence of Crohn disease (ie, the pretest probability of the disease) in the five cohort studies ranged between 12% and 64%.

Sensitivity and Specificity

The sensitivity and specificity values of US for the diagnosis of Crohn disease in the seven studies, together with their 95% confidence intervals, are detailed in Figure 2. Because of the heterogeneity of the values, we could not calculate a pooled value; however, the presence of an inverse correlation between the sensitivity and specificity values ($\rho = -0.43$) allowed us to construct an SROC curve of summary data (Fig 3) that revealed overall sensitivity and specificity ranges of

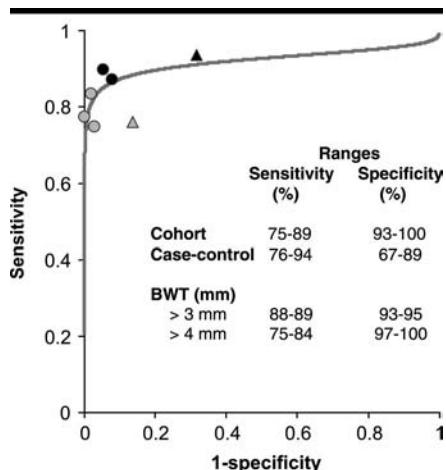


Figure 3. SROC curve for detection of Crohn disease with US according to both study design and bowel wall thickness (BWT) cutoff level. Black circles = prospective cohort studies with a bowel wall thickness cutoff of greater than 3 mm, black triangles = case-control study with a bowel wall thickness cutoff of greater than 3 mm. Gray circles indicate prospective cohort studies with a bowel wall thickness cutoff of greater than 4 mm, and the gray triangle indicates a case-control study with a bowel wall thickness cutoff of greater than 4 mm. Overall, data revealed a clear cutoff effect that depended on the chosen bowel wall thickness threshold. Sensitivity decreased and specificity increased when the bowel wall thickness threshold changed from greater than 3 to greater than 4 mm.

75%–94% and 67%–100%, respectively. More specifically, for a bowel wall thickness cutoff value of greater than 3 mm, sensitivity and specificity, respectively, were 88% and 93% (positive likelihood ratio, 12.5; negative likelihood ratio, 0.12), whereas for a thickness greater than 4 mm, the values were 75% and 97% (positive likelihood ratio, 25; nega-

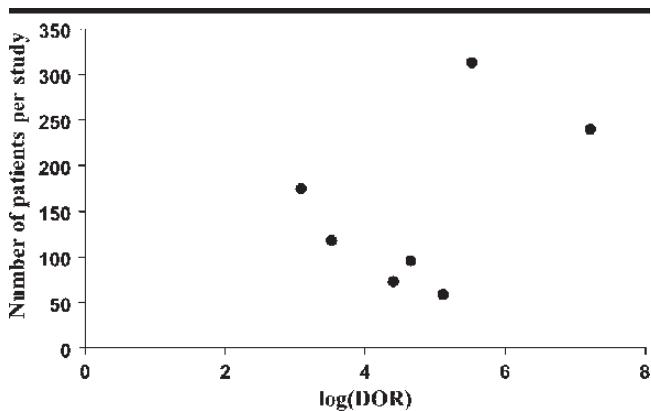


Figure 4. Inverted funnel plot of individual studies with log diagnostic odds ratio, or $\log(DOR)$, plotted against sample size (ie, number of patients in study). The lack of studies with a limited number of patients (ie, <100) and log diagnostic odds ratios of less than 4 accounts for the evident asymmetry of the funnel plot and suggests that other small studies may have been conducted but not published because of unfavorable results.

tive likelihood ratio, 0.25). In addition, the maximum joint sensitivity and specificity of the SROC curve was 0.882. Furthermore, analysis of the data according to study design (Fig 2) revealed that the degree of variability between values was even greater for the case-control studies. The presence of a clear cutoff effect related to the chosen bowel wall thickness threshold was more evident when only the cohort studies, which better fit the curve, were taken into account.

Bias and Observer Variability

Furthermore, so that we could assess a possible publication bias, we designed an inverted funnel plot (Fig 4). As is evident from the figure, the lack of studies with a limited number of patients (ie, <100) and a log diagnostic odds ratio of less than 4 accounted for the asymmetry of the curve.

Results of the quality assessment (Table 2) revealed that the same reference standard was used with all patients in three studies (3,42,45), thus leading to complete verification corresponding to a lack of bias; in the remaining four studies (4,43,44,46), the verification was partial in that different reference standards had been used for different subsets of patients. Blinding was practiced in all but one study (43), and patient recruitment was consecutive in five studies (3,4,42,44,46). All study reports detailed the characteristics of both the equipment and the procedures used for US, whereas the characteristics of the reference standard examination were properly described in only one report (42).

Finally, all but one study lacked details concerning intra- and interobserver variability; when these variables were reported, they had been calculated only for a subset of patients (45).

DISCUSSION

Data from primary studies that assessed the accuracy of US in the detection of Crohn disease in adults were summarized in the present review.

Different findings at US—for example, bowel wall thickness, the pattern of vascularization, the presence of abdominal fluid, and/or the presence of enlarged mesenteric lymph nodes—have been used for the diagnosis of Crohn disease. However, because not all such findings were reported for all of the included studies, we considered only the accuracy of bowel wall thickness and decided to include only those studies that involved use of a precise bowel wall thickness cutoff level so that we could obtain a pooled value of the operative characteristics of the test itself.

The significant heterogeneity of the estimates of sensitivity (75%–94%) and specificity (67%–100%) precluded the possibility of obtaining a cumulative value of diagnostic accuracy. The SROC analysis revealed the presence of a clear cutoff effect based on the different bowel wall thickness thresholds (>3, >4, >5, and ≥ 7 mm, respectively) used in different studies (3,4,42–46). This threshold effect became even more evident in the predefined subgroup analysis of the cohort studies. When a bowel thickness

cutoff value of greater than 3 mm was used, the sensitivity of the test increased to 88%–89% (negative likelihood ratio, 0.1), supporting the use of this cutoff value in a diagnostic strategy of exclusion; conversely, the use of a cutoff value of greater than 4 mm led to a high specificity value (97%–100%) (positive likelihood ratio, 25), making the use of this value highly appropriate for a confirmatory strategy.

On the basis of the above findings, the actual role of US in the diagnosis of Crohn disease depends on the prevalence of the disease (ie, the pretest probability); in the five cohort studies included in the present review, the pretest probability ranged from 12% to 64%, mainly as a consequence of differences in both the selection criteria and the characteristics of the referral center. For example, if a pretest probability of the disease of 12% is assumed—that is, if a hypothetical patient with low risk is considered—US evidence of a bowel wall thickness of 3 mm or less could enable one to rule out the disease because the posttest probability of the disease would decrease to about 1%. Conversely, US evidence of a bowel wall thickness of greater than 4 mm in a high-risk population with a pretest probability of 64% would increase the posttest probability of Crohn disease to up to 97%.

As far as the relevance of the study design to the study results is concerned, our SROC curve analysis revealed that the variability of the estimates was related mainly to the case-control studies (45,46), whose position was more distant from the curve. In fact, case-control studies lead to less reproducible estimates and usually result in overestimation of the accuracy of a diagnostic test (49).

We performed an ad hoc subgroup analysis to consider the possible relationships between clinical heterogeneity and differences in population characteristics, US features or technical characteristics, and type of reference standard used. Differences in Crohn disease prevalence can unpredictably affect US sensitivity and specificity values owing to the variability of prevalence across settings (55). The disease location could also have influenced the diagnostic estimates, as suggested by the results of three series (6,40,47). Another factor with a possible effect on US sensitivity and specificity could be the use of a recently introduced high-frequency probe responsible for a time-related technical improvement. A high-frequency transducer was used in two of the included series (44,46), but

comparison of these series with the other series was precluded by different study designs and thresholds of normal bowel thickness.

In cases of colonic Crohn disease, another factor that is potentially relevant in modifying US operative characteristics could be the prevalence of ulcerative colitis, which is the most frequent cause of chronic colonic inflammation and is often characterized by the presence of bowel wall thickening, in the evaluated population; this prevalence could possibly account for confusing results. However, in the cohort studies included in the present review, the actual prevalence of ulcerative colitis (<10%) was lower than would be expected in an unselected population. Because most of the included studies were conducted at tertiary referral centers, it is highly probable that patients presenting with chronic bloody diarrhea would have been immediately examined and given a diagnosis with endoscopy. A low sensitivity value (38%) and a high specificity value (98%) were reported for the single study (to our knowledge) that evaluated the operative characteristics of US in the detection of ulcerative colitis (44). At present, however, data in a population that reflects a more realistic clinical scenario—that is, a population with a higher prevalence of ulcerative colitis—are lacking.

Overall, the lack or paucity of data for all of the predefined variables considered in our study made it impossible to evaluate their possible influence on study outcome.

Furthermore, our present study had possible limitations that should be considered. First, this study lacked an adequate reference standard for the confirmation of Crohn disease. For example, in case of ileal Crohn disease, even when results of small-bowel series (currently considered the reference standard for Crohn disease with ileal involvement) are consistent, the diagnosis must eventually rely on histologic findings if false-positive results are to be avoided. In addition, the sensitivity and specificity estimates derived from our systematic review were limited to the diagnostic role of US, and no inferences were made concerning disease staging. A second limitation of this review was the lack of data on the performance of US in differentiating Crohn disease from other organic bowel diseases (eg, intestinal tuberculosis, ulcerative colitis, indeterminate colitis) that are also characterized by increased bowel wall thickness (41,56). As an example, if we consider a different clinical context,

such as that in an area with a high prevalence of intestinal tuberculosis, the accuracy of US in the diagnosis of Crohn disease will obviously be reduced as a consequence of a reduction in the specificity of the technique that is related to the increase in the frequency of false-positive results. Properly designed primary studies (57) should be performed to overcome this limitation.

Finally, the asymmetry of the funnel plot, which was consistent with the lack of studies that both had a small sample size and revealed a low diagnostic accuracy of US, suggests the presence of a possible publication bias in that it is highly probable that such series are less likely to be published than are small studies with more appealing results.

In conclusion, in the presence of both clinical and laboratory findings leading to a pretest probability of Crohn disease that ranges from 12% to about 60%, as in the series analyzed in our systematic review (3,4,42–46), the operative characteristics of US bowel examination, especially in the presence of two different bowel wall thickening thresholds, seem appropriate for confirming or ruling out the diagnosis. In particular, in cases of ileal Crohn disease, US could represent a valid alternative to small-bowel series, not only in predicting the presence of ileal Crohn disease but also in revealing the extent of the disease (a strong correlation between US and radiographic findings of extent of disease has recently been demonstrated [47]). Furthermore, compared with small-bowel series, US has the advantage of being noninvasive, less costly, and easily repeatable and thus can be very useful in following up patients, especially in monitoring the response to treatment. Additionally, in the setting of colonic Crohn disease, US examination may be useful in ruling out the disease, even if the final diagnosis still must rely on endoscopic findings.

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TOPIC HIGHLIGHT

Dr. Jonas Mudter, MD, Series Editor

Diagnostics in inflammatory bowel disease: Ultrasound

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Abstract

Diagnosis of chronic inflammatory bowel diseases (IBD) is based on a combination of clinical symptoms, laboratory tests and imaging data. Imaging of the morphological characteristics of IBD includes the assessment of mucosal alterations, transmural involvement and extraintestinal manifestations. No single imaging technique serves as a diagnostic gold standard to encompass all disease manifestations. Ultrasound, computed tomography (CT) or magnetic resonance imaging (MRI) allow cross-sectional imaging of the transmural alterations and extraintestinal manifestations. While in the USA the technique of choice is CT, in Europe the focus is more on MRI and ultrasound (US). Most patients with chronic IBD are diagnosed at a young age. After baseline diagnosis many of these young patients have to undergo repetitive imaging procedures during the variable clinical course of the disease, characterized by alternate periods of remission and active disease, and in monitoring the response to treatment. US has the advantage of being noninvasive, less costly, and easily repeatable, and thus can be very useful in following up patients with IBD. In addition, rising concern about radiation exposure in young adults indicates the demand for radiation-sparing techniques like US and MRI. This article focuses on the current clinical practice of US in IBD, describing the current technologies used in transabdominal intestinal US and the characteristic sonographic findings in Crohn's disease and ulcerative colitis.

ULTRASOUND TECHNOLOGY

Ultrasound (US) for inflammatory bowel diseases (IBD) requires high-frequency (5-17 MHz) linear array probes. High-frequency linear-array probes provide increased spatial resolution of the intestinal wall, which is essential for the assessment of wall diameter and wall layer discrimination. In modern high-frequency probes the creation of special modulated US pulses in transmission results in greater penetration of high frequency US. Compounding technology allows image reconstruction using signal responses from different frequencies or from viewing indifferent directions that results in an increase in contrast resolution and border definition of bowel wall architecture. Color or power Doppler imaging and contrast-enhanced US (CEUS) provide detailed information on mural and extraintestinal vascularity, which reflect inflammatory disease activity.

US EXAMINATION

Conventional transabdominal US with a conventional 3.5-5 MHz convex probe is recommended prior to high-frequency US of the intestinal tract so as not to overlook

underlying extraintestinal causes of abdominal discomfort. Special attention should be paid to the lower abdomen (urogenital tract) and the individual patient's pain location. High-frequency US of the intestinal tract requires extra time and patience of the examiner. With the exception of emergency situations the standard US examination should be performed preprandial in the morning or at least after 4 h fasting to diminish peristaltic movements and the amount of intraluminal air. Gradual compression of the bowel with the US probe helps to reduce intraluminal air. The application of intraluminal fluid as used in bowel preparation for colonoscopy or the use of enteral contrast medium^[1-4] has been shown to improve the delineation of the wall architecture and the detection of jejunal and colonic lesions in patients with IBD, but these more sophisticated techniques have not been transferred into routine clinical practice. For US diagnosis of IBD, an understanding of the anatomical location of Crohn's disease (CD) and ulcerative colitis (UC), and of the more difficult or non accessible parts of the small and large bowel is essential for a systemic US approach to the patient. Transabdominal high-frequency US does not provide a continuous and complete examination of the small and large bowel. The ileocecal region and the sigmoid colon can be identified in all patients. The left and right colon can be adequately evaluated in most of patients. The colonic flexures (especially the left flexure) are more difficult to visualize due to their cranial position and ligamentous fixation to the diaphragm. The colon transversum can be identified in most patients, but complete examination is not easy to achieve because of its variable anatomy. The rectum and anal region cannot be visualized accurately by the transabdominal route due to their pelvic location. Transperineal US is useful in the evaluation of the perianal region and the distal rectum^[5]. A proposal for a systematic approach in IBD patients could be to start in the left lower abdomen with transverse scans using the left iliac artery and vein as landmarks to visualize the sigmoid colon. The sigmoid colon can be easily identified by its prominent hypoechoic muscle layer (muscularis propria). Examination of the left colon can then be adequately performed by continuous scanning from the rectosigmoid transition along the colon descendens upwards to the left costal arch. Gradual compression is recommended to follow the left-sided colon along. The next step of a systematic examination could be visualization of the ileocecal region with transverse scans in the right lower abdomen using the right iliac artery and vein as landmarks and gradual compression. A variable location of ileocecal region in the right middle abdomen (also a frequent location of the neoterminal ileum after surgical resection) can be identified after manual palpation of the right spina iliaca anterior superior as a landmark. Moving the US probe in transverse sections from the right spina iliaca anterior superior upwards to the right costal arch with graded compression helps to find the lumen of the colon ascendens with its characteristic broad lumen (hyperechoic air filled lumen or hypoechoic fluid filled lumen). The cecum can easily be found by turning the probe towards a longitudinal position to follow the colon ascendens down-

Table 1 Sonoanatomy of the normal intestinal wall

| Layer echogenicity | Anatomic structure |
|---|---|
| Hypoechoic (fluid) or hyperechoic (air) lumen | |
| Hyperechoic entrance | Transition lumen/mucosa |
| Hypoechoic | Mucosa |
| Hyperechoic | Submucosa |
| Hypoechoic | Muscularis propria |
| Hyperechoic | Transition muscularis propria/serosa, surrounding structures (fat, peritoneal wall) |

wards until the broad luminal echo disappears. The distal part of the ileum can also be identified by transverse scanning from the cecum towards the middle and lower parts of the abdomen, again using the right iliac artery and vein and the urinary bladder as landmarks. Whereas the distal part of the small intestine (terminal ileum) can be evaluated in all patients, a complete and continuous evaluation of the proximal parts of the ileum and jejunum is not possible due to multiple overlying bowel loops. However, for a systematic approach to the proximal small intestine, four scanning positions in the upper and lower, right and left abdominal quadrants are recommended as final steps of a systematic approach to search for thickened intestinal wall segments.

SONOMORPHOLOGY OF THE INTESTINAL WALL

With the use of high US frequencies in the range from 7.5 MHz to 17 MHz, the wall of the intestine usually exhibits five different layers (Table 1). The small and large bowel can usually be distinguished in various stages of filling during movement by scanning the haustra of the colon and/or the circular folds of Kerckring in the small intestine. Measurement of the wall thickness is crucial for the diagnosis of IBD. Discrepancies in the measurements are mainly due to the presence or absence of graded compression during the examination by the operator in addition to various technical causes (US frequency, equipment). With modern high-frequency linear array probes the normal intestinal wall thickness is generally ≤ 3 mm (using mild compression) ranging from small diameters in the jejunum, ileum and proximal colon to larger diameters in the sigmoid colon (due to the hypertensive function of the sigmoid zone). Physiological contraction of the intestine leading to a thickened wall segment may cause misinterpretation, therefore bowel motions have to be taken into account before measurements are performed. In addition to wall thickening, echomorphology (integrity of wall architecture) and surrounding structures have also to be considered in the interpretation of the intestinal wall diameter.

CROHN'S DISEASE

CD can be localized in any part of the gastrointestinal tract, although the main location is the terminal ileum.

Small intestinal localization of the disease is found in 30%-40% of patients with CD (with involvement of the terminal ileum in 90%), and 40%-55% of the patients show an ileum and colonic localization. Only in a minority of patients (15%-25%) is colonic localization only observed. A systematic examination in patients with IBD should include complete scanning of the ileocecal region and sigmoid colon as well as the remaining parts of the colon, and evaluation of the small intestine (in sections) and surrounding mesenteric structures.

Assessment of bowel wall involvement

The most widely used diagnostic criterion for the diagnosis of IBD is bowel wall thickening with increased vascularization (with maintenance or loss of wall stratification).

In most studies, the bowel is considered to be thickened when the wall diameter exceeds 3 mm (Figure 1). The diagnostic accuracy of different cut-off values in CD were compared in a metaanalysis by Fraquelli *et al*^[6]. Sensitivity and specificity of 88% and 93%, respectively, were achieved when a bowel wall thickness threshold greater than 3 mm was used, and sensitivity and specificity of 75% and 97%, respectively, were achieved when a threshold greater than 4 mm was used. Several studies report a relation between bowel wall thickness and clinical disease activity using the Crohn's Disease Activity Index (CDAI) or Harvey Bradshaw Index (HBI) at initial diagnosis and during the clinical course of CD and in relation to endoscopic findings^[7-9].

Bowel ultrasonographic signs used in CD can be standardized as most show a fair to good reproducibility. In particular, bowel wall thickness, the most relevant parameter for CD detection, showed an excellent reproducibility^[10]. Color or power Doppler imaging of the vascularity of thickened wall segments using semiquantitative scores has proved useful in the distinction between remission or the active phase in CD and correlated with the clinical and endoscopic activity scores in adults^[9,11] and children^[12]. A reduction in wall thickness and mural vascularity (color Doppler imaging) could be shown in patients with a positive clinical-biological response to anti-tumor necrosis factor- α induction therapy in a small study in 24 patients. Maintenance of wall thickness and increased mural vascularity were seen in all non-responders ($n = 7$). Sonographic normality (defined as wall thickness ≤ 3 mm and Doppler flow grade = 0) was only seen in 5 of 17 patients with a positive clinical-biological therapeutic response (29%)^[13]. Most studies on Doppler US include a subjective semiquantitative assessment of mural vascularity, e.g. grade 0 = no vascular signal, grade 1 = barely visible signals, grade 2 = moderate vascularity, grade 3 = marked vascularity. Currently there is no objective scale to determine the degree of disease activity on Doppler US.

CEUS is the most sensitive technique to visualize microperfusion and has been shown to be superior to conventional color or power Doppler imaging in determining tumor vascularity^[14]. Currently, the clinical value of CEUS in IBD is not well defined. Most studies on

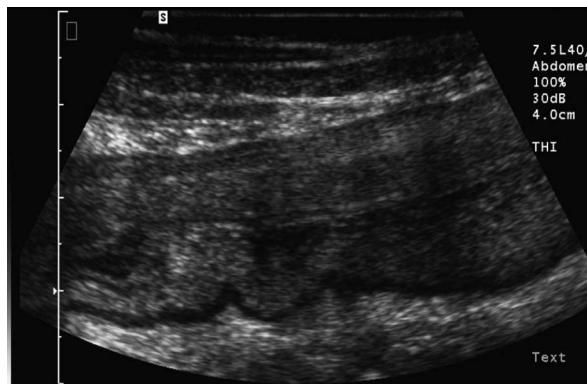


Figure 1 Sonographic appearance of an inflamed colon segment in Crohn's disease. Characteristic appearance: thickened wall diameter (almost 1 cm), partial loss of wall stratification, prominent submucosal layer, narrowed lumen and mesenteric fat hypertrophy.

CEUS have been feasibility or pilot studies.

In a small study (21 patients) with histologically confirmed CD and bowel wall diameters > 5 mm, contrast enhancement was observed after a mean of 13.4 s (± 4.2 s; range, 7-19 s) with a maximum vascularity after 30 s^[15]. In addition, the length of contrast-enhanced bowel segments in US correlated significantly with the length of thickened bowel segments in magnetic resonance imaging (MRI)^[16]. In a retrospective analysis, the assessment of the bowel wall vascularization in CD was performed using quantification software, indicating that CEUS data can not only be analyzed in a semi-quantitative way, but also in a reproducible, quantitative manner^[17]. Using time-intensity curves, patients with CD showed a maximum enhancement 36 s after injection with 9 dB (range, 5.9-13.2 dB), while healthy volunteers reached the maximum level of 2.8 dB (range, 2-3.8 dB) after 23 s ($P < 0.05$)^[18].

Correlation of CEUS with disease activity (endoscopy, histology, CDAI) indicate that active disease can be identified by CEUS)^[19,20]. Characterization of the enhancement pattern in relation to wall thickness was shown to distinguish CD patients with active and inactive disease^[21]. Lower levels of bowel contrast enhancement were observed in some patients who responded to anti-inflammatory treatment^[22,23], as was shown in power Doppler imaging a few years ago. CEUS may be a useful method to assess the therapeutic effectiveness of specific medical anti-inflammatory treatment in patients with CD, or to differentiate inflammatory from fibrotic bowel wall changes. In addition, CEUS was suggested to be helpful in surgical management, in deciding upon conservative *vs* surgical treatment^[24,25]. However, the role of CEUS in addition to conventional Doppler imaging is not yet well defined in clinical studies. Pilot studies on CEUS are promising, but studies on larger patient numbers, including the objective contrast enhancement score are needed before CEUS can be considered a clinical useful tool.

Mesenteric blood flow parameters

Patients with CD had significantly higher portal vein and mesenteric flow and a lower resistance index than con-

trols^[26]. Blood flow in the superior mesenteric artery (SMA) has shown an increase in the postprandial pulsatility index (PI) in remission^[27] in Doppler US. A decrease in PI predicted a non responder to azathioprine therapy and clinical relapse in a 12-mo follow-up^[28]. Contrast enhancement in the SMA and vein, and calculation of splanchnic transit time showed a reduction in transit time (4.0 s vs 6.9 s) in patients with active CD^[29]. However, in our own experience splanchnic transit time measurement in CEUS was not correlated with clinical disease activity (HBI) in mild stages of CD.

Extraintestinal findings

In addition to the assessment of bowel thickness and increased mural vascularity, the surrounding structures (fat, lymph nodes, free fluid accumulation) may indicate a peri-intestinal inflammatory reaction. Mesenteric fat hypertrophy correlated with biochemical and clinical activity of CD and with internal fistulas and increased bowel wall thickness. In quiescent CD, mesenteric hypertrophy does not appear to be a risk factor for relapse^[30]. US is very sensitive for the detection of free fluid in CD^[31]. The presence of regional lymph nodes shows only a weak correlation with clinical and biochemical CD activity^[32]. Furthermore, the finding of mesenteric lymph nodes is non-specific and may reflect disease activity, but infectious intestinal diseases have to be excluded by stool and serologic tests.

Since US can find both intraluminal and peri-intestinal pathological features, it is a particularly valuable tool for the detection of complications of CD, such as stenosis, fistulas, and abscesses. Sensitivity and specificity for detecting fistulae in transabdominal US have been reported as 50%-89% and 90%-95%, respectively^[33]. Sensitivity and specificity for detecting abscesses in transabdominal US is even higher with sensitivities of 71%-100% and specificities of 77%-94%^[33-36]. In a series of 58 patients with CD, including 28 patients with bowel stenosis, 23 patients with fistulas and 10 patients with abscesses, high-resolution US showed a high diagnostic accuracy in comparison to clinical, endoscopic, radiological and operative findings^[37]. The sensitivity, specificity, positive predictive and negative predictive values for US were 86%, 90%, 83% and 92%, respectively, for stenosis and 78%, 95%, 86% and 91%, respectively, for fistulas. The highest diagnostic accuracy was found for abscesses with sensitivity, specificity, positive predictive and negative predictive values 90%, 99%, 90% and 99%, respectively.

ULCERATIVE COLITIS

UC exclusively affects the colon with a predictable way of spreading from distal to proximal colon in a continuous manner. UC is classified by disease extent into proctitis, left-sided colitis and extensive colitis beyond the splenic flexure. A solitary rectal location of UC cannot be visualized accurately due to the pelvic location of the rectum. Mural stratification is preserved in most UC patients due to the superficial pattern of inflammation. The spatial resolution of US is not high enough to allow detection

of mucosal pathology but bowel wall thickening is also a characteristic feature of UC^[38].

The clinical role of US in UC is less well established as compared with CD. In contrast to CD, bowel thickening in UC could not be correlated with clinical disease activity in some studies^[39,40]. However, compared with endoscopic findings, with an overall accuracy of 89% for US (bowel wall thickness > 3 mm and increased Doppler signal) and 73% for MRI (contrast enhancement in bowel wall) in identifying active IBD, the diagnostic accuracy was better in patients with UC than in patients with CD for both US and MRI^[41].

Mucosal healing (MH) after short-term medical treatment is being considered as an important step in the therapeutic work-up of IBD patients due to the potential prognostic role of MH in predicting disease outcome. However, IBD patients are reluctant to be re-endoscopes during follow-up; therefore, there is a need for a non-invasive alternative index of MH which can replace endoscopy in clinical practice. In a prospective trial in 83 patients with UC with a follow-up of 15 mo, a high and consistent concordance between endoscopic and US scores was shown. In patients with UC, moderate-to-severe endoscopic and US scores at 3 mo were associated with a high risk of endoscopic activity at 15 mo, indicating that bowel US may be used as a surrogate of colonoscopy in assessing the short-term response of severe forms of UC to therapy. In addition, the US score and endoscopic score after 3 mo of steroid therapy predicted the outcome of disease at 15 mo^[42,43].

Splanchnic flow measurements in the inferior mesenteric artery have been shown to be closely related to clinical and endoscopic disease activity in patients with UC^[44,45]. In a small trial, CEUS showed entire bowel wall vascularity in correlation to clinical nonresponders to cytapheresis for steroid-refractory or -dependent UC^[46]. So far CEUS is not routinely used in UC.

CONCLUSION

Transabdominal US is currently accepted as a clinically important first-line imaging technique in IBD in initial diagnosis and during the clinical course of the disease.

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Bowel Ultrasonography in the Management of Crohn's Disease. A Review with Recommendations of an International Panel of Experts

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Background: Bowel ultrasonography (US) is considered a useful technique for assessing mural inflammation and complications in Crohn's disease (CD). The aim of this review is to appraise the evidence on the accuracy of bowel US for CD. In addition, we aim to provide recommendations for its optimal use.

Methods: Publications were identified by literature search from 1992 to 2014 and selected based on predefined criteria: 15 or more patients; bowel US for diagnosing CD, complications, postoperative recurrence, activity; adequate reference standards; prospective study design; data reported to allow calculation of sensitivity, specificity, agreement, or correlation values; articles published in English.

Results: The search yielded 655 articles, of which 63 were found to be eligible and retrieved as full-text articles for analysis. Bowel US showed 79.7% sensitivity and 96.7% specificity for the diagnosis of suspected CD, and 89% sensitivity and 94.3% specificity for initial assessment in established patients with CD. Bowel US identified ileal CD with 92.7% sensitivity, 88.2% specificity, and colon CD with 81.8% sensitivity, 95.3% specificity, with lower accuracy for detecting proximal lesions. The oral contrast agent improves the sensitivity and specificity in determining CD lesions and in assessing sites and extent.

Conclusions: Bowel US is a tool for evaluation of CD lesions in terms of complications, postoperative recurrence, and monitoring response to medical therapy; it reliably detects postoperative recurrence and complications, as well as offers the possibility of monitoring disease progression.

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Key Words: inflammatory bowel disease, detection, cross-sectional imaging technique, inflammation, ultrasound, small intestine contrast ultrasonography, contrast-enhanced ultrasound

Clinical symptoms of Crohn's disease (CD) do not reliably reflect the severity, extent, or character of intestinal inflammation. This disconnect has led to monitoring paradigms, necessitating multiple assessments including endoscopy and cross-sectional imaging techniques. Composite data aid in directing clinicians to objectively detect, stage, and classify disease patterns, select treatment options, and assess response to therapy.

Increasing availability of biological agents offers the opportunity to redefine treatment goals in CD, evolving from control of symptoms to healing of ulcerative lesions and preventing progression of structural bowel damage. Thus, the need to assess and depict structural bowel changes exists, to initiate and optimize therapy and potentially alter the natural history. Mucosal healing is emerging as an important therapeutic endpoint in clinical trials¹ and increasingly in clinical practice.

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Ileocolonoscopy has been and remains the gold standard for evaluation of luminal lesions in the colon and terminal ileum. However, evaluation of lesion extent may be challenging given proximal location and inaccessibility by retrograde ileoscopy. Moreover, CD can lead to stricturing of the terminal ileum and/or ileocecal valve, precluding endoscopic assessment in a significant proportion of patients.² CD is a transmural process involving the whole thickness of bowel wall leading to mural and transmural structural damage. Damage can persist despite improvement of symptoms with therapy. Evaluation of structural involvement may help in defining treatment goals and monitoring therapy.³

The American College of Gastroenterology (AGC) and European Crohn's and Colitis Organisation (ECCO) guidelines^{4,5} consider computed tomography (CT) or magnetic resonance enterography/enteroclysis as the cross-sectional imaging technique with the highest accuracy for the detection of intestinal involvement of CD including extramural complications. Bowel ultrasonography (US) is an additional technique for assessing bowel inflammation in CD.⁶ Bowel US does not involve radiation and its low cost provides an attractive alternative to other techniques, especially for children and young patients. Much like other imaging modalities, including magnetic resonance and CT, the successful evaluation with bowel US depends on the acquisition of certain skills and experience, which may vary among individual operators. Bowel US has been largely promoted in parts of continental Europe, where US is performed by physicians; in these countries, abdominal US is an integral part of the training curriculum for gastroenterology and training is mandatory for physicians. Although the use of bowel US is less widespread in North America and other parts of the world, related to lack of training opportunities of gastroenterologists and reimbursement, it is still regarded as a useful diagnostic tool for the assessment of CD.⁷ However, consensus guidelines or recommendations about the use of US in CD from North America are still lacking.

The aim of this review is to critically appraise the evidence on the use of bowel US in assessment of CD and produce recommendation levels about its use from a panel of experts from Europe and North America.

METHODS

A comprehensive literature search was conducted to identify all relevant citations. Keyword searches in MEDLINE and EMBASE were conducted, supplemented by manual review of the reference list of included studies. Only published articles were considered. Because of significant advances in sonographic equipment in the 1990s, we restricted our research to studies after 1992. The literature dated from January 1992 to June 2014 was included, using the following search criteria (all fields): (“Crohn Disease” or “Crohn’s”) and (“ultrasound” or “ultrasonography” or “sonography”). References from the articles selected were examined in search of additional studies meeting inclusion criteria. The final selection of published articles was performed according to the following criteria: (1) 15 or more patients were included; (2) bowel

US was used to diagnose CD, detecting complications, assessing postoperative recurrence and disease activity, evaluating techniques, interobserver agreement, training and learning curves, identifying ultrasonographic prognostic factors, and monitoring therapeutic response; (3) adequate reference standard, including ileocolonoscopy, CT/magnetic resonance enteroclysis/enterography, capsule endoscopy, enteroscopy, or surgical or pathological findings for evaluating small and large bowel were considered; (4) a prospective study design; (5) data reported to allow calculation of sensitivity, specificity, accuracy, agreement, or correlation values (in the case of disease extent, disease activity, and techniques comparison); (6) full-text articles published in English. The patient population comprised both patients suspected of having CD and patients known to have CD. In patients with confirmed CD, either active or inactive patients were considered. For each study, the imaging criteria used to diagnose CD with the given imaging test were considered according current guidelines.^{6,8} The reference-standard examination used to verify the imaging findings was also recorded for each study. All studies fulfilling the selection criteria were included in the review, without performing any additional formal quality assessment. Four reviewers (E.C., F.Z., C.M., and K.K.) independently assessed the eligibility of the articles for inclusion. Disagreements between the reviewers regarding study inclusion were resolved by consensus of all authors.

For each of studies, the following variables were extracted in a predefined data extraction form: author, publication year, number of patients included, population (adult or children), cohort or case-control studies, gold standards, number of patients positive and negative for the variable examined, sensitivity and specificity. The mean sensitivity and specificity were calculated and expressed as a weighted mean (and corresponding 95% CI) to make allowances for the number of patients included in each study. The evidence level (EL) and grade of recommendation (GR) were established according to the Oxford Centre for Evidence-based Medicine-Levels of Evidence (<http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009>). Statements in bold are followed by comments on the evidence and opinion of the experts. Statements reflected consensus of all authors. Statistical analysis was performed using STATA 11.2 (STATA Corp., College Station, TX).

RESULTS

The search yielded a total of 655 articles, of which 63 were found to be eligible and retrieved in full-text for conspicuous analysis (Fig. 1).

Accuracy of Bowel US in the Diagnosis of CD

Suspected CD

Studies were considered only if they included patients with suspected CD; when both suspected and established CD were reported, the studies were selected if accuracy results were available for suspected CD alone (Table 1).

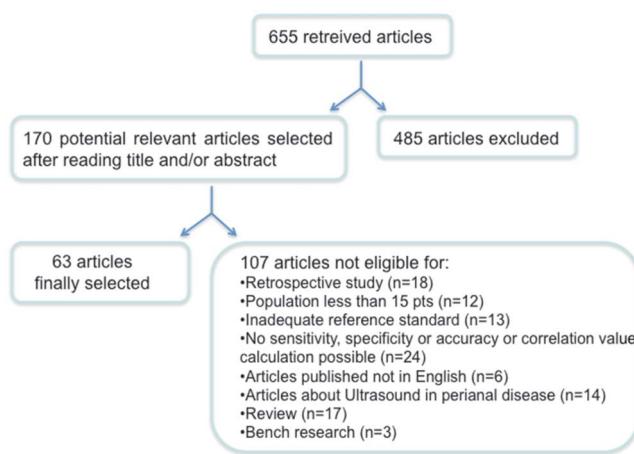


FIGURE 1. Flowchart for the selection of the studies included in the review.

Nine studies including a total of 1190 patients with suspected CD were identified.^{11–13,15,16,20–23} One study involved a pediatric population.¹⁶ One meta-analysis and 1 systematic review were also considered.^{24,25} The sensitivity of bowel US for the diagnosis of CD calculated from all studies included was 79.7% (95% CI, 71.9%–87.5%). The specificity derived from studies reporting these data was 96.7% (95% CI, 95.1%–98.4%).

Diagnosis of CD was based mainly on the measurement of bowel wall thickness in all studies (Fig. 2A). In the meta-analysis conducted by Fraquelli et al,²⁴ the impact of different cutoff values of bowel wall thickening (BWT: 3 mm versus 4 mm) in determining the presence of CD was evaluated. The authors concluded that, using a cutoff level threshold of 3 mm as normal, sensitivity and specificity were 88% and 93%, respectively. In contrast, when a cutoff level threshold of 4 mm was used, the sensitivity was 75% and specificity 97%.

Established CD

Studies were considered only if they included patients with established CD; when both suspected and established CD were reported, the studies were selected if accuracy results were available for established CD alone (Table 1).

Twelve studies including a total of 845 patients with established CD were identified.^{9–11,14–18,20–23} Only 1 study was performed in a pediatric population.¹⁶ The sensitivity of US for the diagnosis of CD calculated from all studies included was 89% (95% CI, 84.2%–93.8%). The specificity derived from studies reporting these data was 94.3% (95% CI, 84.6%–100%).

Statement 1

1. Bowel US is a useful, noninvasive radiation free imaging technique for the initial diagnostic evaluation of patients with suspected CD (EL 2A, GRB).

Statement 2

1. Bowel US correlates well with endoscopy and cross-sectional imaging techniques at detecting CD lesions (EL 2B, GRB).

Assessment of Disease Location

The accuracy of bowel US in detecting and localizing CD lesions within the bowel has been assessed in several studies. Most of these studies reported the highest sensitivity of bowel US in detecting ileal lesions with lesser sensitivity in detecting lesions located in the upper small bowel and rectum (Table 2).

Ten studies including a total of 925 patients with established CD were identified.^{9–11,14–19,22} Only 1 study was performed in a pediatric population.¹⁶ One systematic review was also considered.²⁵ The sensitivity of bowel US for assessing anatomical lesion of disease calculated from all studies included was 55.6% (95% CI, 36.4%–74.8%) for jejunal lesions, 92.7% (95% CI, 86.7%–98.7) for ileal lesions, and 81.8% (95% CI, 80.2%–83.4) for colonic involvement. The specificity derived from studies reporting these data was 98.5% (95% CI, 96.3%–100%) for jejunal lesions, 88.2% (95% CI, 79.7%–96.6%) for ileal lesions, and 95.3% (95% CI, 88.2%–100%) for colonic involvement.

Statement 3

1. For bowel US, the sensitivity and specificity are highest for anatomical locations (terminal ileum, right and left colon) that are easily accessible (EL 2A, GRB); these are the most frequent sites of involvement by CD.

Assessment of Disease Extent

With regard to assessing the length of small bowel involved, different authors have shown the extent of pathologically thickened bowel wall evaluated by bowel US is significantly correlated with the extent of ileal CD, as measured by radiology and surgery (Table 3).

Nine studies including a total of 1026 patients with established CD were identified.^{10,11,14–19,26} Only 1 study was performed in a pediatric population.¹⁶ The correlation between bowel US and radiological and surgical evaluations for assessing disease extent calculated from all studies included ranged from 0.49 to 0.83. Only 1 study showed a lower correlation ($r = 0.2$) between surgery and bowel US.¹⁵

Statement 4

1. Bowel US correlates with the radiologic and surgical extent of small bowel disease (EL 2B, GRB).

TABLE 1. Accuracy of Bowel US in the Diagnosis of CD (Suspected or Confirmed) Compared with Radiology, Endoscopy or Surgical Findings

| Author | CD Patients, Suspected/ Confirmed | Population | US Technique | Reference Standard | Site Evaluated | Sens, % | Spec, % |
|---------------------------------|---|-------------------------------------|--------------|--|-----------------------|--------------------|--------------------|
| Bringolla et al ⁹ | 0/31 | Adult PC | US | Radiology | Jejunum, ileum, colon | 73 | 93.3 |
| Calabrese et al ¹⁰ | 0/28 | Adult PC | US, SICUS | Radiology | Jejunum, ileum | 96, 100 | NA, NA |
| Castiglione et al ¹¹ | 249/120 | Adult PC | US | Colonoscopy | Distal ileum, colon | 94 | 97 |
| Astegiano et al ¹² | 313/0 | Adult PC | US | Endoscopy, radiology, clinical evaluation | Distal ileum, colon | 74 | 98 |
| Tarjan et al ¹³ | 73/0 | Adult PC | US | Radiology, clinical evaluation | Ileum, colon | 88.4 | 93.3 |
| Macconi et al ¹⁴ | 1/110 | Adult PC | US | Endoscopy, radiology, histology | Ileum, colon | 89.1 | 94 |
| Pallotta et al ¹⁵ | 91/0 | Adult PC | US, SICUS | Endoscopy, radiology, surgery, clinical evaluation | Jejunum, ileum | 57, 94.3 | 100, 98 |
| Pallotta et al ¹⁵ | 0/57 | Adult PC | US, SICUS | Endoscopy, radiology, surgery, clinical evaluation | Jejunum, ileum | 87.3, 98.2 | NA, NA |
| Pallotta et al ¹⁶ | 21/0 | Children PC | US, SICUS | Endoscopy, radiology, clinical evaluation | Jejunum, ileum | 75, 100 | 100, 100 |
| Pallotta et al ¹⁶ | 0/30 | Children PC | US, SICUS | Endoscopy, radiology, clinical evaluation | Jejunum, ileum | 76, 96 | 100, 100 |
| Parente et al ¹⁷ | 0/211 | Adult PC | US | Endoscopy, radiology, surgery | Ileum, colon | 93.4 | 97.3 |
| Parente et al ¹⁸ | 0/102 | Adult PC | US, SICUS | Endoscopy, radiology, surgery | Ileum | 91.4, 96.1 | NA, NA |
| Rispo (2005) ¹⁹ | 84 | Adult PC | US | Endoscopy, radiology | Ileum | 92 | 97 |
| Solvig et al ²⁰ | 59/19 | Adult PC | US | Radiology | Ileum | 95 | 93 |
| Sheridan et al ²¹ | 96 | Adult PC | US | Radiology | Ileum | 75 | 97 |
| Sheridan et al ²¹ | 0/31 | Adult PC | US | Radiology | Ileum | 82 | 57 |
| Pascu 2004 ²² | 61/0 | Adult PC | US | Endoscopy | Terminal ileum, colon | 82 | 97 |
| Pascu et al ²² | 0/37 | Adult PC | US | Endoscopy, radiology, histology, clinical evaluation | Ileum, colon | 74 | 97 |
| Hollerbach et al ²³ | 227/69 | Adult PC | US | — | — | 76/84 | 95/NA |
| Fraquelli et al ²⁴ | Meta-analysis (no. studies = 7) | US | — | — | — | 75–94 | 67–100 |
| Panes et al ²⁵ | 1029 | Systematic review (no. studies = 5) | US | — | — | 85 (95% CI, 83–87) | 98 (95% CI, 95–99) |

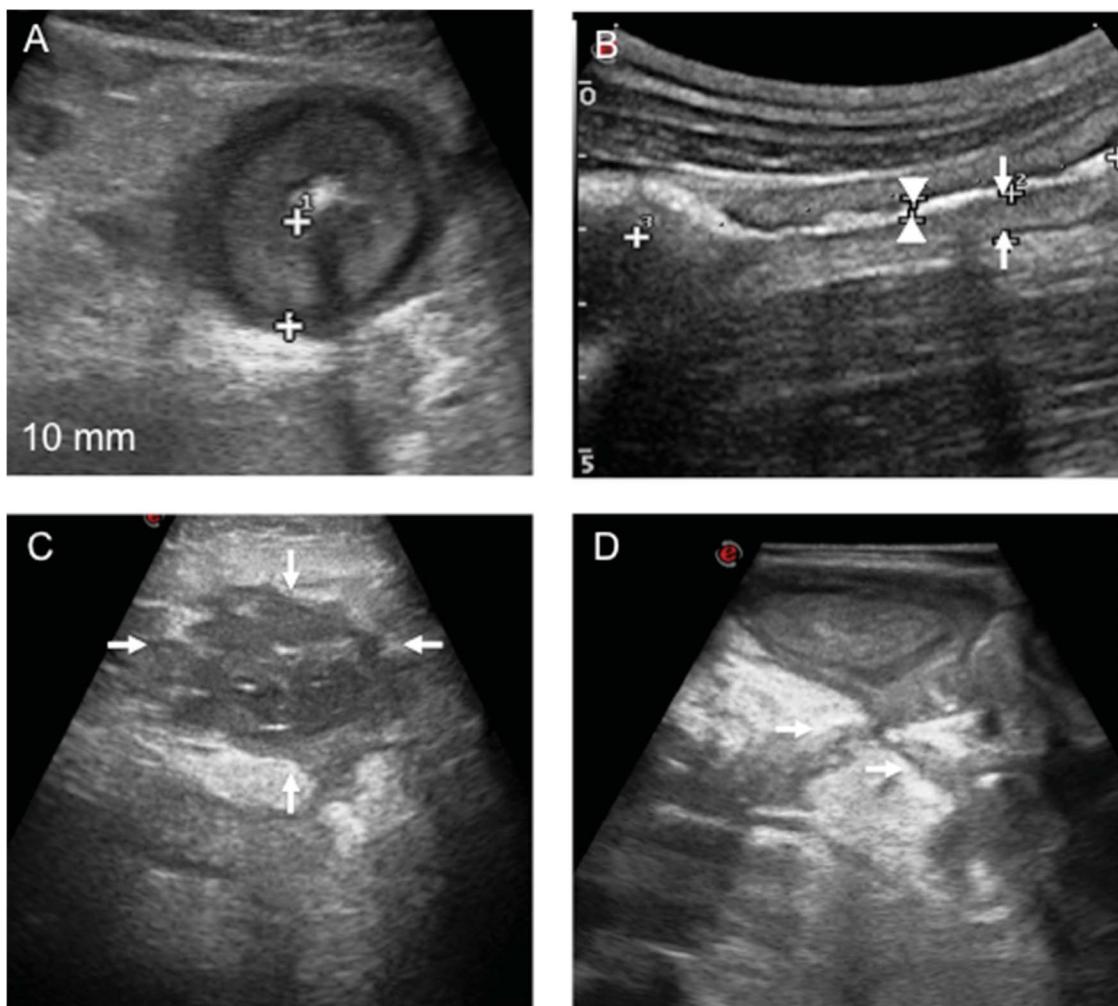


FIGURE 2. BWT of the terminal ileum as assessed by bowel US (A); Stenosis: the white arrows indicate BWT and the arrowheads indicate stenosis of the terminal ileum (B); Abscess (C); Fistulae (D).

Diagnosis of Complications

Detection of Strictures

Bowel stenosis can be revealed by bowel US as thickened walls and narrowed lumen with or without increased lumen diameter of a proximal loop (25–30 mm) (Fig. 2B).^{10,27,28}

Ten studies including a total of 1011 patients with established CD were identified.^{10,11,16–18,27–31} Two studies were performed in pediatric populations.^{16,30} Eight studies used surgical specimens as reference standard.^{17,18,27,29–31} One systematic review was also considered.²⁵ The sensitivity of bowel US for assessing stricturing complications calculated from all studies included was 79.7% (95% CI, 75.2%–84.2%). The specificity derived from studies was 94.7% (95% CI, 89.7%–99.8%) (Table 4).

Sonographic assessment of the echo-pattern of the bowel wall in the strictures may also offer an insight into the histological features, discriminating between fibrotic and inflammatory strictures more accurately than clinical and biochemical markers of

inflammatory activity do³⁴. Loss of stratification of the bowel wall at the level of the stricture suggests its inflammatory nature with a low degree of fibrosis, whereas the presence of stratification suggests a higher degree of fibrosis of the stenosis.³⁴ Findings emerging from preliminary studies showed promising results using elastography in differentiating inflammatory from fibrotic lesions.³⁵

Detection of Abscesses

Abscess can be revealed by bowel US as roundish anechoic lesion, with an irregular wall and a diameter equal or above 2 cm,²⁷ often presenting internal echoes and posterior echo enhancement (Fig. 2C). Bowel US is often considered as a first-level procedure, related to its ease of use in this setting.

The diagnostic value of bowel US for diagnosing intra-abdominal abscesses was determined in 6 studies that included a total of 500 patients (Table 4). Four studies provided surgery as reference standard.^{27,28,30–32} One systematic review was also considered.²⁵ The sensitivity of bowel US was 85.6% (95% CI,

TABLE 2. Accuracy of Bowel US in the Assessment of Disease Location in CD

| Author | CS Patients | Population | US Technique | Reference Standard | Site Evaluated | Sens, % | Spec, % |
|---------------------------------|----------------|-------------------------------------|-----------------|---|--|------------------------|----------------------|
| Bringolla et al ⁹ | 31 | Adult PC | US | Radiology | Jejunum, terminal ileum, colon | 60, 70, 82.1 | 96.1, 72.7, 95.4 |
| Calabrese et al ¹⁰ | 28 | Adult PC | US | Radiology | Jejunum, ileum | 0, 100 | NA, NA |
| Calabrese et al ¹⁰ | 28 | Adult PC | SICUS | Radiology | Jejunum, ileum | 100, 100 | NA, NA |
| Castiglione et al ¹¹ | 120 | Adult PC | US | Colonoscopy | Distal ileum, colon | 94, 73 | 97, 92 |
| Maconi et al ¹⁴ | 110 | Adult PC | US | Endoscopy, radiology | Ileum, colon | 93.5, 88.2 | 92.8, 94.2 |
| Pallotta et al ¹⁵ | 57 | Adult PC | US | Endoscopy, radiology, surgery | Jejunum/proximal ileum, terminal ileum | 86.9, 77.8 | NA, NA |
| Pallotta et al ¹⁵ | 57 | Adult PC | SICUS | Endoscopy, radiology, surgery | Jejunum/proximal ileum, terminal ileum | 100, 94.4 | NA, NA |
| Pallotta et al ¹⁶ | 41 | Children PC | US | Endoscopy, radiology, clinical evaluation | Jejunum/proximal ileum, terminal ileum | 50, 83 | 100, 100 |
| Pallotta et al ¹⁶ | 41 | Children PC | SICUS | Endoscopy, radiology, clinical evaluation | Jejunum/proximal ileum, terminal ileum | 93, 97 | 100, 100 |
| Parente et al ¹⁷ | 211 | Adult PC | US | Endoscopy, radiology, surgery | Ileum, colon | 96.7, 90.5 | 90.3, 97.9 |
| Parente et al ¹⁸ | 102 | Adult PC | US | Endoscopy, radiology, surgery | Jejunal ileum | 80, 92 | NA, NA |
| Parente et al ¹⁸ | 102 | Adult PC | SICUS | Endoscopy, radiology, surgery | Jejunal ileum | 100, 98.5 | NA, NA |
| Parente et al ¹⁹ | 188 | Adult PC | US | Endoscopy, radiology | Duodenum/jejunum, ileum, colon, rectum | 33.3, 95.7, 76.5, 18.2 | 98.6, 75, 94.8, 98.3 |
| Pascu et al ²² | 37 | Adult PC | US | Endoscopy | Terminal ileum, colon | 96, 67.5 | 100, 96.5 |
| Panes et al ²⁵ | 939 | Systematic review (no. studies = 5) | US/SICUS | — | — | 86 (95% CI, 83–88) | 94 (95% CI, 93–95) |

83.3%–88%). The specificity derived from studies reporting these data was 94.5% (95% CI, 87.9%–100%). The diagnosis of deep pelvic or retroperitoneal abscesses is more difficult owing to the presence of overlying bowel gas and the difficulty of differentiating an abscess from an intestinal loop with stagnating fluid.

US is a validated technique to guide interventional procedures. Studies demonstrate that percutaneous or transrectal abscess drainage, also in pediatric populations, under sonographic guidance has a high technical success rate of 96%.^{36–38} US drainage of abscess may improve the general status of the patient and allow a less invasive and easier subsequent surgical procedure.³⁷

Detection of Intraabdominal Fistulae

Fistulae are identified as hypoechoic tracts with or without hyperechoic content (Fig. 2D). The diagnostic value of bowel US for diagnosing intraabdominal fistulae was determined in 6 studies

that included a total of 500 patients (Table 4). Four studies provided surgical specimens as reference standard.^{27,28,30–32} One systematic review was also considered.²⁵ The sensitivity of bowel US was 70.1% (95% CI, 59.7%–80.6%). The specificity derived from studies reporting these data was 95.6% (95% CI, 92.5%–98.8%).

Statement 5

1. Bowel US has a high sensitivity and specificity for the diagnosis of CD strictures (EL 2B, GRB).

Statement 6

1. Bowel US has comparable sensitivity and specificity to CT or MRI in the detection of CD abscesses (EL 2B, GRB).

TABLE 3. Accuracy of Bowel US in the Assessment of Disease Extent in CD

| Author | CD Patients | Population | US Technique | Reference Standard | Site Evaluated | Correlation |
|---------------------------------|-------------|-------------|--------------|---|---------------------|--------------------|
| Calabrese et al ¹⁰ | 28 | Adult PC | US | Radiology | Ileum | R = 0.67 |
| Calabrese et al ¹⁰ | 28 | Adult PC | SICUS | Radiology | Jejunum, ileum | NA, R = 0.88 |
| Castiglione et al ¹¹ | 120 | Adult PC | US | MR enterography | Distal ileum, colon | R = 0.69 |
| Maconi et al ¹⁴ | 110 | Adult PC | US | Radiology | Ileum | R = 0.49 |
| Pallotta et al ¹⁵ | 57 | Adult PC | US, SICUS | Radiology | Ileum | R = 0.59, R = 0.88 |
| Pallotta et al ¹⁵ | 57 | Adult PC | US, SICUS | Surgery | Ileum | R = 0.2, R = 0.85 |
| Pallotta et al ¹⁶ | 41 | Children PC | US, SICUS | Endoscopy, radiology, clinical evaluation | Ileum | R = 0.66, R = 0.86 |
| Parente et al ¹⁷ | 211 | Adult PC | US | Radiology | Ileum | R = 0.52 |
| Parente et al ¹⁷ | 85 | Adult PC | US | Surgery | Ileum | R = 0.64 |
| Parente et al ¹⁸ | 102 | Adult PC | US, SICUS | Endoscopy, radiology, surgery | Jejunal, ileum | R = 0.83, R = 0.94 |
| Rispo et al ¹⁹ | 84 | Adult PC | US | Radiology | Ileum | R = 0.67 |
| Parente et al ¹⁹ | 188 | Adult PC | US | Radiology | Ileum | R = 0.73 |

Statement 7

1. Bowel US has comparable sensitivity and specificity at detecting abdominal fistulae to CT and MRI (EL 2B, GRB).

Assessment of Postsurgical Recurrence

Several authors have assessed the role of bowel US in the postoperative follow-up and confirmed the observation of the BWT as an indicator for recurrence (Table 5).

Five studies including a total of 219 patients with a previous ileocolonic resection were identified.^{39,41,42,44} One systematic review was also considered.²⁵ The sensitivity of bowel US was 81.7% (95% CI, 77%–86.3%). The specificity derived from studies reporting these data was 88.3% (95% CI, 83.4%–93.2%).

Statement 8

1. Bowel US is sensitive and specific at detecting postoperative recurrence and correlates well with ileocolonoscopy (EL 2B, GRB).

Assessment of Disease Activity

Direct evaluation of inflammatory activity in CD by bowel US has been suggested but its role remains controversial. Attempts have been made to correlate bowel wall thickness with activity particularly with CD activity index (CDAI) (Table 6).

Eleven studies including a total of 752 patients with established CD were identified.^{9,14,19,22,46,49,52,57,58,61,62} Only 1 study was performed in a pediatric population.⁵² Ten studies considered CDAI as reference standard.^{9,14,22,46,49,52,57,58,61,62} Three

studies used endoscopy as standard for activity.^{19,57,61} One systematic review was also considered.²⁵ Five studies revealed a weak or no correlation between bowel wall thickness and CDAI.^{9,14,49,52,61}

The vascularity of the bowel walls was also assessed using power Doppler US, as a semiquantitative method for determining CD activity. Vascularity within the bowel walls has been evaluated using a subjective scoring system according to the intensity of color signals and/or by the measurement of resistive index obtained from vessels detected within the bowel walls.^{62–68}

Ten studies including a total of 446 patients with established CD were identified^{45,48,53,55–59,61,62} (Table 6). All studies considered CDAI as reference standard and 3 studies used endoscopy as standard for disease activity.^{57,58,61} One systematic review was also considered.²⁵ In most studies, a weak or no correlation between vascularity and clinical activity was observed.^{45,55,57,62}

Statement 9

1. Bowel US can be used to assess disease activity in CD of the small bowel and colon (EL 3B, GRC).

Special Techniques

Small Intestine Contrast Ultrasonography

Over the past few years, the technical evolution of US equipment combined with the use of oral contrast agents such as polyethylene glycol solution, aimed to distend and better characterize the bowel wall, have been used to improve the detection of CD lesions using small intestine contrast ultrasonography (SICUS) (Fig. 3A–B). The use of an oral contrast agent

TABLE 4. Accuracy of Bowel US in the Assessment of Complications in CD

| Author | CD Patients | Population | US Techniques | Reference Standard | Complications | Sens, % | Spec, % | Results |
|---------------------------------|-------------|-------------------|---------------|---|----------------------------|------------------------|-----------------------|---|
| Calabrese et al ¹⁰ | 28 | Adult PC | US, SICUS | Radiology | Stenosis | 76, 94 | — | — |
| Castiglione et al ¹¹ | 120 | Adult PC | US | MR enterography | Stenosis, fistula, abscess | — | — | K = 0.82, P < 0.01; K = 0.67, P, 0.01; K = 0.88, P < 0.01 |
| Gasche et al ²⁷ | 33 | Adult PC | US | Surgery | Stenosis, fistula, abscess | 100, 87, 100 | 91, 90, 92 | — |
| Kohn et al ²⁹ | 44 | Adult PC | US | Radiology, surgery | Stenosis | 82, 75 | 100, 89 | PPV 100%/NPV 75% |
| Maconi et al ¹⁴ | 112 | Adult PC | US | Endoscopy, radiology, CT | Stenosis, fistula, abscess | 74.4, 66.1, 83.3 | 93.1, 95.5, 94.2 | — |
| Maconi et al ³² | 128 | Adult PC | US | Surgery | Fistula, abscess | 71.4, 80.7 | 95.8, 93.1 | PPV 93%/NPV 81%, PPV 75%/NPV 95% |
| Neye et al ³⁰ | 58 | Adult/children PC | US | Clinical, endoscopy, radiology, surgery | Stenosis, fistula, abscess | 86, 78, 90 | 90, 95, 99 | PPV 83%/NPV 92%, PPV 86%/NPV 91%, PPV 90%/NPV 99% |
| Onali et al ³³ | 15 | Adult PC | SICUS | Surgery | Stenosis, fistula, abscess | 92, 60, 100 | —, 88, 80 | PPV 100%, PPV 75%/ NPV 78%, PPV 60%/ NPV 100% |
| Pallotta et al ³¹ | 49 | Adult PC | US/SICUS | Surgery | Stenosis, fistula, abscess | 80/97.5/55.5/96/89/100 | 75/100/100/90.5/95/95 | — |
| Pallotta et al ¹⁶ | 41 | Children PC | US/SICUS | Radiology, endoscopy | Stenosis | 70/94 | 100/100 | — |
| Parente et al ¹⁷ | 296 | Adult PC | US | Radiology, surgery | Stenosis | 79, 90 | 98, 100 | PPV 95%/NPV 89%, PPV 100%/NPV 68% |
| Parente et al ¹⁸ | 102 | Adult PC | US, SICUS | Radiology, endoscopy, surgery | Stenosis | 74, 88.8 | 93.3, 97.3 | PPV 80%/NPV 90.9%, PPV 92.3%/NPV 96% |

TABLE 5. Accuracy of Bowel US in the Assessment of Postsurgical Recurrence in CD

| Author | CD Patients | Population | US Technique | Reference | Standard | Time Evaluation, mo | Site Evaluated | Sens, % | Spec, % | Results |
|---------------------------------|-------------|------------|-----------------------|-----------|---------------|---------------------|-------------------|----------|------------|--------------------------------------|
| Andreoli et al ³⁹ | 41 | Adult PC | US (BWT > 5 mm) | Endoscopy | CE, endoscopy | 35.4 (3–105) | Neoterminal ileum | 81 | 86 | PPV 96%, NPV 57% |
| Biancone et al ⁴⁰ | 22 | Adult PC | SICUS (BWT > 3 mm) | Endoscopy | CE, endoscopy | 12 | Neoterminal ileum | 100, 100 | — | PPV 93%, NPV 80% |
| Castiglione et al ⁴¹ | 40 | Adult PC | US (BWT > 3 mm) | Endoscopy | CE, endoscopy | 12 | Neoterminal ileum | 77 | 94 | PPV 93%, NPV 94% |
| Castiglione et al ⁴¹ | 40 | Adult PC | SICUS (BWT > 3 mm) | Endoscopy | CE, endoscopy | 12 | Neoterminal ileum | 82 | 94 | — |
| Onali et al ³³ | 25 | Adult PC | SICUS (BWT > 3 mm) | Endoscopy | CE, endoscopy | 12, 36 | Neoterminal ileum | 100, 100 | — | — |
| Paredes et al ⁴² | 33 | Adult PC | US (BWT > 3 mm) | Endoscopy | CEUS | 87.7 (75.4) | Neoterminal ileum | 76.9 | 87 | — |
| Paredes et al ⁴³ | 60 | Adult PC | US (BWT > 3 mm), CEUS | Endoscopy | CEUS | 60 | Neoterminal ileum | 89.8, 98 | 81.8, 81.8 | PPV 97.5%/NPV 64.3%, PPV 96%/NPV 90% |
| Rispo et al ⁴⁴ | 45 | Adult PC | US (BWT > 3 mm) | Endoscopy | CEUS | 12 | Neoterminal ileum | 79 | 95 | PPV 95%, NPV 80% |

does not alter the procedure greatly; the same equipment is used with the addition of 375 to 800 mL of oral contrast fluid, however, the procedure duration increases ranging from 25 to 60 minutes.⁶⁹ This technique and its evidence are still currently limited to Italy, although the accuracy in detecting lesions in CD is indisputable.^{10,15,16,18,31,33,40,41,70,71} Two studies including a total of 112 patients with suspected CD were identified^{15,16} (Table 1). One study was performed in a pediatric population.¹⁶ The sensitivity of SICUS for CD diagnosis was 95.4% (95% CI, 89.9%–100%) and the specificity was 98.4% (95% CI, 96.4%–100%). Four studies including a total of 217 patients with established CD were identified^{10,15,16,18} (Table 1). The sensitivity of SICUS was 97.1% (95% CI, 95.2%–99%) and the specificity was 100%.

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; 4 studies including a total of 228 patients with established CD were identified^{10,15,16,18} (Table 2). The sensitivity of SICUS for assessing anatomical 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. The correlation between SICUS and radiological/surgical evaluations for assessing disease extent calculated from all studies included ranged from 0.85 to 0.94 (Table 3). These findings suggest that SICUS may be used as an alternative technique to invasive procedures to assess small bowel lesions and monitor CD extent changes over time.

The use of oral contrast agents also leads to a significantly greater accuracy in detecting the presence and number of stenoses (Fig. 3C). SICUS detected at least 1 or 2 stenoses in >10% and >20% more patients, respectively, in comparison with bowel US without oral contrast agent. Five studies including a total of 235 patients with established CD were identified^{10,16,18,31,33} (Table 4). The sensitivity of SICUS was 92.3% (95% CI, 89.5%–95.1%) and the specificity was 92.1% (95% CI, 90.3%–93.9%). Using SICUS, the sensitivity and specificity for detection of abscesses was 100% and 91.5% (95% CI, 76.8–100), respectively.^{31,33} The sensitivity and specificity for detection of fistula was 87.6% (95% CI, 52.2–100) and 89.9% (95% CI, 87.4–92.4), respectively.^{31,33}

Using SICUS, 3 studies including a total of 87 patients in the postoperative setting were identified^{40,41,70} (Table 5). The sensitivity of SICUS was 91.7% (95% CI, 80%–100%) and the specificity was 94%. In relation to the grading of endoscopic postoperative recurrence, Castiglione et al⁴¹ analyzed the best cutoff value of BWT for differentiating the severity of CD recurrence using bowel US and SICUS. In this study based on the receiver operating characteristic curve, a BWT = 5 mm showed sensitivity, specificity, positive, and negative predictive values of 93%, 96%, 88%, and 97%, respectively, for the diagnosis of severe postoperative recurrence at bowel US, whereas a BWT = 4 mm was the best cutoff value differentiating mild from severe CD recurrence using SICUS with a sensitivity, specificity, positive, and negative predictive values of 86%, 96%, 97%, and 79%, respectively.⁴¹ Furthermore, a study demonstrated that in patients with a Rutgeerts' score ≥ 3 , a significantly higher median BWT,

TABLE 6. Accuracy of Bowel US in the Assessment of Disease Activity in CD

| Author | CD Patients, Total/Active | Population | US Activity Evaluation | Reference Standard | Site Evaluated | Sens, % | Spec, % | Results |
|---------------------------------|---------------------------|------------|--|--|-----------------------|--------------|--------------|---|
| Bolondi et al ⁴⁵ | 22/11 | Adult CC | V mean portal flow, RI of SMA | CDAI | — | NA | NA | R = 0.427, — |
| Brignola et al ⁹ | 31/17 | Adult PC | BWT | CDAI, CRP, ¹¹¹ In scan | Ileum, colon | NA | NA | R = NS, P < 0.05, R = 0.75 |
| Calabrese et al ⁴⁶ | 110/30 | Adult PC | Sonographic lesion index for CD | CDAI, CRP | Ileum, colon | NA | NA | P = 0.05, P = 0.03 |
| De Franco et al ⁴⁷ | 54/36 | Adult PC | CEUS (β coeff/MPI) (Sonovue-QLAB) | CICDA, CDAI | Terminal ileum | 86/97, 94/94 | 83/83, 54/59 | AUC 0.89/0.92, AUC 0.69/0.73 |
| Di Sabatino et al ⁴⁸ | 31/18 | Adult CC | CEUS (Levodist), color Doppler US | CDAI | Ileum | 74.1, 45.1 | 100, 100 | — |
| Futagami et al ⁴⁹ | 55/30 | Adult CC | UICD (BWT) | CDAI, CRP | Ileum, colon | NA | NA | R = 0.281, R = 0.163 |
| Girlich et al ⁵⁰ | 41/NA | Adult CC | CEUS (Sonovue-Qontrast) | HBI | — | NA | NA | R = 0.645 |
| Goertz et al ⁵¹ | 45/22 | Adult CC | CEUS (Sonovue-Qontrast) | HBI | — | NA | NA | P = NS |
| Haber et al ⁵² | 23/NA | Adult PC | BWT | PCDAI | Ileum, colon | NA | NA | R = 0.573 |
| Karoui et al ⁵³ | 40/17 | Adult CC | RI of SMA | CDAI | — | 35.5 | 95.7 | NS |
| Kratzner et al ⁵⁴ | 21/5 | Adult PC | CEUS (Sonovue, HDI-Lab) | CDAI | Terminal ileum | NA | NA | NS |
| Maconi et al ¹⁴ | 110/NA | Adult PC | BWT | CDAI, CRP | Ileum, colon | NA | NA | R = 0.22, R = 0.22 |
| Maconi et al ⁵⁵ | 31/15 | Adult CC | V mean portal flow, RI of SMA | CDAI | Ileum, colon | NA | NA | NS |
| Maconi et al ⁵⁶ | 76/47 | Adult CC | V mean portal flow, RI of SMA | CDAI, CRP | Ileum, colon | NA | NA | NS |
| Miao et al ⁵⁷ | 30/23 | Adult PC | BWT, RI of SMA | CDAI and one or more of endoscopy, radiology, or surgery | — | NA | NA | P < 0.001, P = NS |
| Migaleddu et al ⁵⁸ | 47/30 | Adult PC | BWT, color Doppler US, CEUS (Sonovue) | Endoscopy + histology, CDAI | Terminal ileum, colon | 90, 90, 93 | 93, 93, 94 | Linear correlation coefficient for CEUS, BWT, and color Doppler US versus CDAI 0.74, 0.68, and 0.73, respectively |
| Parente et al ¹⁹ | 188/NA | Adult PC | BWT | CDAI, CRP | Ileum, colon | NA | NA | R = 0.25, R = 0.17 |
| Pascu (2004) ⁵⁹ | 37/NA | Adult PC | US score (BWT, color Doppler) | Endoscopy, CDAI | Terminal ileum, colon | NA | NA | R = 0.83, R = NS |

TABLE 6 (Continued)

| Author | CD Patients, Total/Active | Population | US Activity Evaluation | Reference Standard | Site Evaluated | Sens, % | Spec, % | Results |
|-------------------------------|---------------------------|-------------------------------------|--|-----------------------------------|-----------------------|--------------------|--------------------|---------------------------------|
| Rapaccini et al ⁵⁹ | 48/22 | Adult PC | RI of SMA, color Doppler US, CEUS (Levovist) | Clinical laboratory and radiology | Ileum, colon | 52.4, 45.5, 97.8 | 88.5, 80.8, 68.5 | — |
| Wong et al ⁶⁰ | 30/27 | Adult PC | CEUS | Endoscopy (CDEIS) | Terminal ileum, colon | NA | NA | P = NS |
| Ripollés et al ⁶¹ | 61/46 | Adult PC | BWT, color Doppler US, CEUS (SonoVue) | Endoscopy | Small bowel, colon | NA | NA | P = 0.019, P = 0.002, P < 0.001 |
| Heyne (2002) ⁵⁷ | 60/36 | Adult CC | BWT, Doppler US | CDAI | — | NA | NA | P < 0.05, P = NS |
| Panes 2011 ²⁵ | 207 | Systematic review (no. studies = 6) | Doppler US, CEUS | — | — | 91 (95% CI, 79-89) | 91 (95% CI, 87-95) | — |

extent of the lesions, and prestenotic dilation were observed in comparison with patients with an endoscopic score ≤ 2 . Accordingly, the lumen diameter was significantly lower in patients with a Rutgeerts' score ≥ 3 .⁷² In this setting, the use of oral contrast agent has been proved to be of value in accurately defining the site and evaluation of the anastomosis. Using a receiver operating characteristic curve analysis, Pallotta et al⁷¹ demonstrated that combining BWT of ileocolonic anastomosis and the extent of intramural lesions of neoterminal ileum, SICUS discriminated patients with or without endoscopic lesions (0.95).

Direct comparison between bowel US and SICUS in determining CD lesions were evaluated in 9 studies.^{10,15,16,18,31,41,48,58,61} Six studies including a total of 419 patients with established CD were identified^{10,15,16,18,31,41} (see Table 7, Supplemental Digital Content 1, <http://links.lww.com/IBD/B234>). Only 1 study was performed in a pediatric population.¹⁶ SICUS showed a gained value in identifying jejunal lesions with a sensitivity ranging from 13% to 43%, ileal lesions ranging from 0% to 17%, strictures from 14.4% to 24%, fistulas 41%, and abscess 11%. SICUS showed a better correlation with radiological evaluation in term of extent ranging from 0.88 to 0.94 than bowel US (0.53–0.83).

Contrast-enhanced Ultrasound

To increase the sensitivity of Doppler US in detecting vascularity of the diseased bowel wall as a marker of activity, US intravenous contrast agents have been introduced. The second generation echo-signal enhancer SonoVue is injected as a bolus in units of 1.2 to 4.5 mL into an antecubital vein, immediately followed by injection of 10 mL of normal saline solution flush (0.9% NaCl). For each examination, a recording is begun a few seconds before the intravenous administration of the agent, and continuous imaging is performed for 40 seconds.⁷³

The effectiveness of contrast-enhanced ultrasound (CEUS) in assessing activity of CD, despite some positive findings, remains to be established. Nine studies including a total of 382 patients with established CD were identified^{47,48,50,51,54,58-61} (Table 6). Six studies considered clinical indexes (CDAI or Harvey-Bradshaw index) as reference standards^{47,48,50,51,54,59} and 3 used endoscopy as standard for activity.^{58,60,61} One systematic review was also considered.²⁵ In most studies, a weak or no correlation between vascularity assessed by CEUS and clinical activity was observed.^{51,54}

The detection of vascular signals by power Doppler US around but not within the lesions may help to differentiate intraabdominal abscesses from inflammatory masses. Findings emerging from preliminary studies show that the assessment of vascularity using intravenous SonoVue allows for the differentiation between inflammatory masses and abscesses⁷⁴ (Fig. 3D-E).

Only 1 study considered CEUS in the postoperative recurrence setting. The sensitivity and the specificity were 98% and 81.8%, respectively.⁴³

Direct comparison between Doppler US and CEUS in assessing activity was evaluated in 3 studies including a total of 139 patients with established CD^{48,58,61} (see Table 8, Supplemental Digital Content 2, <http://links.lww.com/IBD/B235>).

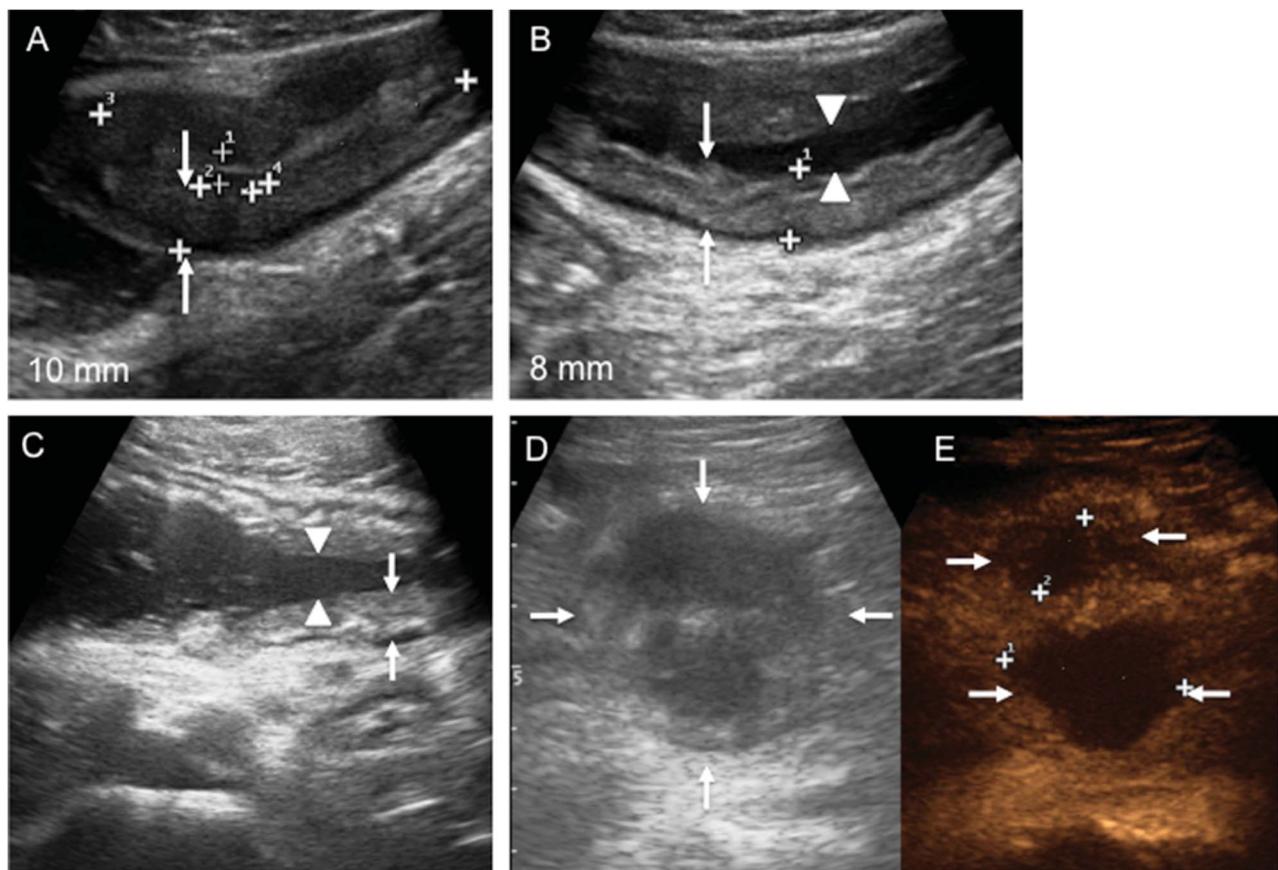


FIGURE 3. Comparison between bowel US (A) and SICUS (B) of a patient with CD. The white arrows indicate BWT of the terminal ileum as assessed by bowel US A, The use of oral contrast agent during assessment allows for the visualization of the lumen (white arrowheads), the better definition of the bowel walls and the echopattern (white arrows) (B). Stenosis assessed by SICUS: the white arrows indicate BWT and the arrowheads exactly indicate narrowed lumen diameter of the terminal ileum (C). Abscess assessed by bowel US (D), and CEUS (E). In panel E, the white arrows indicate no vascular lesions representing abscesses as assessed by CEUS.

Interobserver Agreement, Training and Learning Curve

Interobserver agreement between operators with various degrees of experience in bowel US, and its learning curve, needs to be investigated further^{18,60,75} (see Table 9, Supplemental Digital Content 3, <http://links.lww.com/IBD/B236>). Preliminary results from an Italian study evaluated that bowel US signs used in CD can be standardized and showed a fair to a good reproducibility among 6 operators (interobserver agreement was calculated using kappa statistics for qualitative variables). In particular, BWT showed an excellent reproducibility.⁷⁵

Statement 10

1. The use of intraluminal orally administered contrast agents, such as isoosmolar polyethylene glycol solution, improves the overall accuracy in diagnosing small bowel CD (EL 2B, GRB).

2. The addition of oral contrast agent improves the accuracy of detecting small bowel lesions along the entire length of the small bowel and the correlation with radiologic and surgical extent of small bowel disease (EL 2B GRB).
3. The use of oral contrast agents improves the accuracy of detecting CD stricturing and penetrating complications (EL 2B, GRB). Oral contrast agent improves the accuracy of detecting postoperative recurrence of inflammation in CD (EL 2B, GRB).
4. Increased bowel wall thickness in the neoterminal ileum seems to be the most sensitive parameter for determining postoperative recurrence severity (EL 2B, GRB).

Statement 11

1. Further prospective studies in larger series of patients are needed to assess CD activity using CEUS in comparison with other ultrasonographic techniques (EL 3B, GRC).

Statement 12

1. Interobserver agreement seems good for bowel wall thickness but the evidence is limited (EL 3B, GRC).

Prognostic Factor

Bowel US may also be of use for predicting course and prognosis in CD^{46,76–79} (see Table 10, Supplemental Digital Content 10, <http://links.lww.com/IBD/B237>). Bowel wall thickness was shown to be higher in patients who were resected over a short period after bowel US assessment than in those not operated suggesting that BWT (7 mm, odds ratio = 19.521, 95% CI, 5.362–71.065) may independently be associated with the risk of surgery.⁷⁶

Bowel wall pattern and thickness assessed by bowel US were independently and significantly associated with surgery regardless of the presence of intestinal complications or disease activity. Rigazio et al⁷⁹ developed a semiquantitative score as predictor of short-term surgery risk within 1 month of examination. After this trend, Calabrese et al⁴⁶ tried to develop a numerical index quantitating small bowel damage as detected by SICUS in patients with an established diagnosis of CD. The aim was to try to convert qualitative sonographic images into a numerical index for CD (sonographic lesion index for CD). Patients having higher lesion indices at SICUS underwent operation more frequently than lower indices after 1-year follow-up. Hence, sonographic lesion index for CD may offer the potential for predicting the progression of the small bowel disease over a period through serial assessments as a monitoring tool.⁴⁶

Regarding extraintestinal structures as a marker of peri-intestinal inflammatory reaction in active CD, mesenteric fat hypertrophy correlated with biochemical and clinical activity and with internal fistulas and increased BWT.⁷⁸ In quiescent CD, mesenteric hypertrophy does not seem to be a risk factor for relapse.⁷⁸

Statement 13

1. Bowel US (with or without oral/intravenous contrast) may be a tool for predicting the risk of surgery (EL4).

Monitoring Therapeutic Responses

Because it is not yet clear how mucosal healing corresponds to healing of the bowel wall layers, transmural healing has been explored in patients with CD treated with immunosuppressants and/or anti-tumor necrosis factor drugs using bowel US. The definition of transmural healing is an evolving concept.

Nine studies including 265 patients with CD, have explored the evolution of sonographic parameters of inflammation over time during medical therapy^{80–88} (see Table 11, Supplemental Digital Content 5, <http://links.lww.com/IBD/B238>). The utility of bowel US for assessing drug response has been compared with

ileocolonoscopy only in 3 studies in which concordance was high (weighted κ between 0.63 and 0.76).^{80,82,86} Two studies showed no changes in ultrasonographic parameters before and after therapy.^{81,87} One study demonstrated variations of a combination of sonographic parameters (sonographic lesion index for CD) only in patients with clinical response to anti-tumor necrosis factor α treatments induction.⁸⁸

Statement 14

1. Bowel US (with or without oral/intravenous contrast) can be used for assessing and monitoring inflammatory changes in patients with CD during treatments (EL 3B, GRB).

DISCUSSION

The management of CD has evolved over the last decades with a better understanding of disease progression and the clear recognition that there remains a disconnect between activity as defined by persistent inflammation and symptoms experienced by the patient. It is believed that unrecognized or uncontrolled inflammation can lead to progressive damage and complications requiring operation. Therefore, it is desirable to define suitable monitoring strategies that are acceptable to patients, physicians, and society. Ideally, this would involve modalities that are safe, noninvasive, and can be delivered at a reasonable cost repeatedly. Bowel US constitutes an attractive first-choice imaging modality because it meets all the criteria mentioned. Bowel US can be repeated frequently to assess and monitor lesions over time. Our review indicates that the diagnostic value of bowel US in patients with CD has been evaluated in several studies, which have shown a high accuracy for detecting lesions and complications, for assessing postoperative recurrence, for evaluating activity, and monitoring therapeutic responses. The limitations of this study should be considered. Thickening of the intestinal walls is not specific for CD, also being present in infectious, neoplastic, and other inflammatory diseases. Therefore, when used as a first imaging diagnostic procedure, differential diagnosis by US relies on an analysis of the site, extent, and US characteristics of the BWT. The most useful US findings in CD are terminal ileal wall thickening and segmental thickening, as well as the presence of concomitant perientestinal lesions such as abscesses or fistulae.

Moderate heterogeneity of studies in terms of patient numbers and disease severity, timing, and type of reference tests, technical considerations around bowel US procedures, and the quality of the data, made the analysis problematic in the opinion of all authors. The accuracy of bowel US in detection of complications could be overestimated by a selection bias related to disease severity of the patients enrolled. None of the studies analyzed the influence of concomitant medications as a covariate in the models to correlate radiological findings and activity or in evaluating postoperative recurrence. Another possible limitation might be that bowel US is performed by clinicians and not by radiologists in most studies.

Despite these limitations, the recent availability of new sonographic techniques and contrast agents with a good accuracy in comparison with other radiologic and endoscopic assessments increases the usefulness of bowel US in all CD indications and its role should be greater than that defined in the guidelines.⁶ Elastography is a new imaging modality that can differentiate inflammatory from fibrotic intestine in rat models of IBD and can differentiate between fibrotic and unaffected intestine in a pilot study in humans with CD. Prospective clinical studies are needed.³⁵

Successful evaluation of the bowel using US depends on the skill and experience of operators that makes this technique available in routine clinical practice. There are no published learning curve studies that define expertise in this technique, but Italian authors estimate that approximately 6 months and 100 examinations are needed to gain proficiency.⁸¹ The German Society of US in Medicine has proposed a dedicated upgrade trainee including high-frequency bowel US after basic US.^{82,83} Prospective studies and multispecialty consensuses need to investigate how different specialties and different geographical jurisdictions could have converging competencies to define bowel US training routes.

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