

World Journal of *Gastroenterology*

World J Gastroenterol 2023 April 21; 29(15): 2222-2358



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Editorial Board Member of *World Journal of Gastroenterology*, Hirayuki Enomoto, MD, PhD, Associate Professor, Division of Hepatobiliary and Pancreatic Disease, Department of Internal Medicine, Hyogo Medical University, Nishinomiya 663-8501, Hyogo, Japan. enomoto@hyo-med.ac.jp

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INDEXING/ABSTRACTING

The WJG is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports, Index Medicus, MEDLINE, PubMed, PubMed Central, Scopus, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 edition of Journal Citation Reports® cites the 2021 impact factor (IF) for WJG as 5.374; IF without journal self cites: 5.187; 5-year IF: 5.715; Journal Citation Indicator: 0.84; Ranking: 31 among 93 journals in gastroenterology and hepatology; and Quartile category: Q2. The WJG's CiteScore for 2021 is 8.1 and Scopus CiteScore rank 2021: Gastroenterology is 18/149.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Yi-Xuan Cai; **Production Department Director:** Xiang Li; **Editorial Office Director:** Jia-Ru Fan.

NAME OF JOURNAL

World Journal of Gastroenterology

ISSN

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE

October 1, 1995

FREQUENCY

Weekly

EDITORS-IN-CHIEF

Andrzej S Tarnawski

EDITORIAL BOARD MEMBERS

<http://www.wjgnet.com/1007-9327/editorialboard.htm>

PUBLICATION DATE

April 21, 2023

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INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

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<https://www.wjgnet.com/bpg/GerInfo/287>

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<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Intestinal ultrasound as a non-invasive tool to monitor inflammatory bowel disease activity and guide clinical decision making

Michael T Dolinger, Maia Kayal

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Giannetti A, Italy;
Zhou W, China

Received: October 26, 2022

Peer-review started: October 26, 2022

First decision: December 12, 2022

Revised: January 19, 2023

Accepted: March 31, 2023

Article in press: March 31, 2023

Published online: April 21, 2023



Michael T Dolinger, Department of Pediatric Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, NY 10029, United States

Maia Kayal, Department of Medicine, Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, NY 10029, United States

Corresponding author: Maia Kayal, MD, MS, Assistant Professor, Department of Medicine, Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place Box 1069, New York, NY 10029, United States. maia.kayal@mountsinai.org

Abstract

Intestinal ultrasound (IUS) is a non-invasive, real-time, cross-sectional imaging tool that can be used at the point-of-care to assess disease activity in patients with Crohn's disease or ulcerative colitis. IUS promotes quick and impactful treatment decisions that can modify disease progression and enhance patient compliance. This review will summarize the technical aspects of IUS, the evidence to support the use of IUS in disease activity monitoring, the comparison of IUS to current standard of care monitoring modalities such as colonoscopy and calprotectin, and the optimal positioning of IUS in a tight-control monitoring strategy.

Key Words: Crohn's disease; Ulcerative colitis; Disease monitoring; Intestinal ultrasound

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Core Tip: Intestinal ultrasound (IUS) is a non-invasive, real-time, cross-sectional imaging tool that is currently underutilized for direct disease activity monitoring in Crohn's disease (CD) and ulcerative colitis (UC). IUS is the optimal point-of-care method to monitor disease activity in patients with CD or UC with excellent patient compliance and comparison to such traditional monitoring modalities as calprotectin, colonoscopy, and magnetic resonance enterography.

Citation: Dolinger MT, Kayal M. Intestinal ultrasound as a non-invasive tool to monitor inflammatory bowel disease activity and guide clinical decision making. *World J Gastroenterol* 2023; 29(15): 2272-2282

URL: <https://www.wjgnet.com/1007-9327/full/v29/i15/2272.htm>

DOI: <https://dx.doi.org/10.3748/wjg.v29.i15.2272>

INTRODUCTION

The current conventional approach to inflammatory bowel disease (IBD) monitoring in the United States includes routine patient visits to the gastroenterology clinic every 3-6 mo with more urgent or frequent visits based on symptomatology. During these visits, an assessment of the patient's current disease status is undertaken *via* history and physical examination. After the visit, the evaluation typically continues with biomarkers such as C-reactive protein and fecal calprotectin (FC), colonoscopy, and magnetic resonance enterography (MRE) though results are often delayed and compliance rates low. This traditional, fragmented model of IBD monitoring is not well suited to detect subclinical inflammation or prevent disease progression, and has contributed to a therapeutic effectiveness ceiling of 30%[1].

Intestinal ultrasound (IUS) is a non-invasive, real-time, cross-sectional imaging tool that is currently underutilized for direct disease activity monitoring in Crohn's disease (CD) and ulcerative colitis (UC) [2]. Use of IUS at the point-of-care in a tight monitoring model can add significant value to the routine clinic visit by allowing the treating gastroenterologist to accurately and immediately assess disease activity and treatment responsiveness, something that is sorely lacking in the current traditional IBD care model. Furthermore, IUS allows for the easy assessment of transmural healing (TH), a target beyond simple mucosal healing (MH) that may impact long-term disease outcomes.

In this review, we discuss key concepts to understand how IUS utilization will impact care delivery for patients with IBD and achieve disease modification. We will review the technical aspects of IUS, evidence for detection of disease activity and treatment responsiveness, comparison to current standard of care management tools such as MRE, FC, and ileo colonoscopy, impact on shared understanding and real-time decision making, optimal utilization, and future applications.

TECHNICAL ASPECTS OF IUS

Basic ultrasound machine requirements

Use of IUS as a cross-sectional tool for disease activity monitoring starts with a minimum requirement of a modern ultrasound machine available for regular use. Two probes are needed with ability to assess color Doppler signal (CDS) - a lower-frequency convex array probe (3-5 MHz) for global evaluation of the entire bowel and assessment of complications with ability for deeper penetration, and a higher-frequency linear array probe (5-15 MHz) for visualization of the five bowel wall layers and measurement of bowel wall thickness (BWT) to the level of 0.1 millimeters (mm)[3].

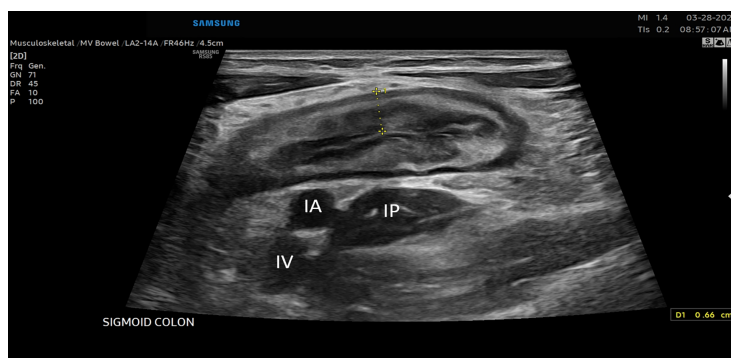
Patient preparation and the role of contrast

Fasting or bowel preparation prior to IUS is unnecessary for optimal visualization of the bowel and the examination can be performed without any prior planning. Intravenous [Contrast Enhanced Ultrasound (CEUS)] or oral contrast [Small Intestinal Contrast Ultrasound (SICUS)] are not beneficial during point-of-care evaluation in IBD activity monitoring and treatment response assessment. The value of CEUS and SICUS, based on local availability and expertise, is in the assessment of suspected complications. CEUS is a valuable tool in the detection of and differentiation of phlegmon and abscesses compared to traditional non-contrast IUS[4]. SICUS adds further value over IUS in the evaluation of proximal small bowel (proximal ileal and jejunal) lesions and detection of stenoses, but the ingestion of oral contrast leads to extended time for completion of the examination that is no longer suitable for use as a point-of-care assessment tool[5,6].

IUS examination

IUS examination should begin with an initial assessment of the distal sigmoid colon using the convex probe beginning in the left lower quadrant of the abdomen or left suprapubic region with identification of the iliac vessels and left iliopsoas muscle, fanning the probe up with the use of graded compression to identify air within the lumen of the distal sigmoid colon and visualization of the subsequent bowel wall layers (Figure 1).

The colon should then be tracked proximally visualizing the retroperitoneal descending colon to the left inferior border of the intercostals or just below to denote the splenic flexure, then to identify the transverse colon utilizing the thick wall of the stomach as an anatomical landmark, then to the hepatic flexure, downward toward the right lateral hemiabdomen to visualize the ascending colon, cecum, and



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Figure 1 Inflamed sigmoid colon located super to the iliac vessels and iliopsoas muscle in the left lower quadrant of the abdomen. IA: Iliac artery; IV: Iliac vein; IP: Iliopsoas muscle.

ultimately to the right lower quadrant of the abdomen and/or right suprapubic region to identify the ileocecal valve, and terminal ileum, again using the right lower quadrant iliac vessels and iliopsoas muscle as a landmark for proper identification of the terminal ileum superior. The remainder of the proximal small intestine should be scanned in a “lawn-mower” technique, sweeping up and down over the mid-abdomen, to visualize the remaining proximal small bowel. Differentiation of the large intestine and small intestine from one another during this process is essential and done easily based on the hypermotility and movement of intestinal contents within the small bowel compared to that of the colon. Once the global initial assessment of the bowel is complete with a convex probe, careful repeat assessment of the entire colon and small bowel should be performed for IBD activity assessment with the linear high-frequency probe. Measurements for BWT should be performed for each segment in both longitudinal and transverse planes, with an average of measurements taken at least 1 cm apart denoting the thickness between the lumen-mucosal interface and the muscularis-serosal interface (Figure 2). CDS assessment of the bowel wall for hyperemia should be performed in each segment with use of the modified Limberg score (Figure 3). The other two parameters that should be assessed in each segment are inflammatory fat (iFat) and the presence or loss of bowel wall layer stratification.

Bowel segments for IUS activity monitoring

The primary bowel segments assessed during every IUS examination are the sigmoid colon, descending colon, transverse colon, ascending colon, cecum, and terminal ileum[7]. Visualization of the rectum can be challenging and typically only performed with adequate resolution for disease activity assessment in patients with lower body mass indices and full bladders at the time of examination. Even with visualization of the rectum, normal values are not well defined, thus making it even harder for use at the point-of-care for disease activity assessment without benchmark with another non-invasive biomarker such as FC or a recent endoscopic evaluation. Additionally, the proximal small bowel beyond 30 cm of the ileum remains challenging and even an expert utilizing the proper technique may miss proximal ileal or jejunal inflammation relying on evaluation with IUS alone (Table 1).

MONITORING DISEASE ACTIVITY AND TREATMENT RESPONSE

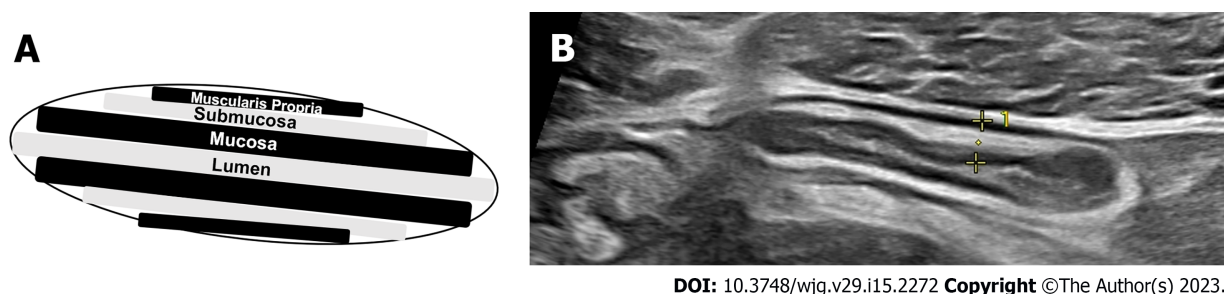
Features of disease activity

IUS assessment of BWT is the primary and most important measure of disease activity in both CD and UC and has been shown to correlate with endoscopic inflammation[8]. In adults, a BWT cut-off > 3 mm in any segment is the most consistent individual IUS parameter that correlates with active endoscopic disease, with a sensitivity and specificity of 88%-89% and 93%-96% respectively[9,10]. When assessing the colonic bowel segments in patients with IBD, the per patient sensitivity and specificity of IUS to detect disease activity is 90% and 96% respectively[11]. UC is a transmural disease and thus IUS is an excellent option to monitor disease activity non-invasively and assess disease extension in patients with ulcerative proctitis[12]. In a retrospective study of patients with UC, BWT alone was shown to correlate with the Mayo endoscopic score[13]. In children, there is no agreed upon cut-off for BWT that correlates with endoscopic activity, however a BWT < 2 mm is almost always normal[14].

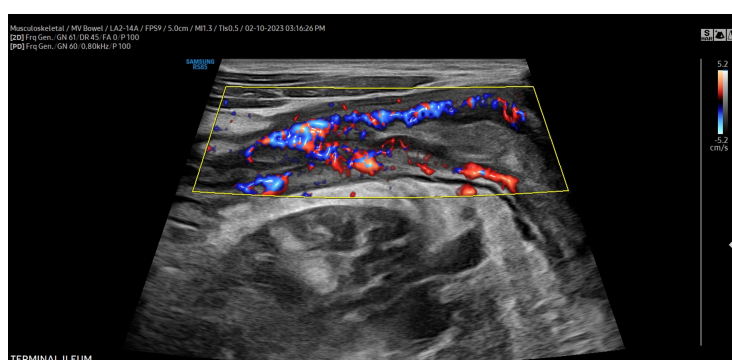
After BWT, hyperemia assessed by CDS is the next most important measure of disease activity. Assessment of CDS alone has been shown to correlate with CD clinical activity[15-17]. When combined with increased BWT, increased hyperemia is almost always representative of active disease. In fact, in development of both CD and UC IUS scores with endoscopy, multivariable analysis demonstrates that often the only independent predictors of endoscopic activity are BWT and hyperemia[18-20]. Additional

Table 1 Optimal and limited bowel segments for intestinal ultrasound disease activity monitoring

Optimal bowel segments	Limited bowel segments
Sigmoid colon	Rectum
Descending colon	Splenic flexure
Transverse colon	Proximal ileum
Ascending colon	Jejunum
Ileocecal valve	
Terminal ileum	



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Figure 2 Measurements for bowel wall thickness. A: Schematic of bowel wall layers; B: Bowel wall thickness measurement in the inflamed terminal ileum, yellow lines indicate the measurement of bowel wall thickness from the lumen-mucosa interface to the muscularis propria-serosal interact.

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Figure 3 Severe hyperemia assessed by color Doppler signal. Color Doppler signal graded by the modified Limberg score. Shown here is a modified Limberg score of 3 in the terminal ileum. A score of 0 = absent signal. A score of 1: Short signals inside the bowel. A score of 2: Long signals inside the bowel, and a score of 3: Long signals inside and outside of the bowel.

characteristics of inflammation in IBD are focal disruption of the bowel wall layers, and hypoechoic or hyperechoic changes in the layers representing a loss of bowel wall stratification. Inflammatory mesenteric fat wrapping is seen, appearing hyperechoic encasing the inflamed bowel.

IUS activity scores

There have been more than twenty IUS activity scores developed for adults with CD and UC, with the most common and important parameters being BWT, followed by both hyperemia and bowel wall stratification[21]. Only a few recently developed IUS scores have been validated with a standardized endoscopic score. They are simple and can be used at the point-of-care for clinical decision making without significant time for calculation (Table 2)[19,20,22-24]. Only two scores specific to children with IBD have been developed, one CD and one UC, and only the UC score is validated with an endoscopic score[24,25]. A novel IUS score recently developed by a group of international experts, the International Bowel Ultrasound Group (IBUS)-SAS (score 0-100), is yet to be validated and is more complex. Although its clinical utility may be limited, it may serve as a novel score for disease monitoring and treatment response in clinical trials[26].

Table 2 Interpretation of validated and simple intestinal ultrasound activity scores for Crohn's disease and ulcerative colitis

IUS scoring system	BWT (mm)	iFAT	Modified LS	LBWS	Other
Crohn's disease indices					
SUS-CD (0-5)[19]	0: < 3.0		0: LS 0		
	1: 3.0-4.9		1: LS 1-2		
	2: 5.0-7.9		2: LS 3		
	3: ≥ 8.0				
Simple US score[20]	0.957 (BWT)		0.859 (LS)		
Ulcerative colitis indices					
MUC[21,24]	1.4 (BWT)		0: LS 0		
			2: LS 1-3		
UC-IUS (0-7)[25]	0: ≤ 2	0: Absent	0: LS 0	0: No loss	
	1: 2.1-3.0	1: Present	1: LS 1	1: Loss is present	
	2: 3.1-4.0		2: LS 2-3		
	3: > 4				
Civitelli UC index (0-4)[26] (pediatric)	0: ≤ 3		0: LS 0	0: No loss	Abnormal haustrations (0: Normal, 1: Abnormal)
	1: > 3		2: LS 1-3	1: Loss is present	

IUS: Intestinal ultrasound; BWT: Bowel wall thickness; iFat: Inflammatory fat; LS: Limberg Score; LBWS: Loss of bowel wall stratification; UC: Ulcerative colitis; CD: Crohn's disease.

Monitoring treatment response in CD and UC

IUS is a reliable tool to monitor treatment response in both CD and UC. Improvement in all IUS parameters (BWT, hyperemia, iFat, bowel wall stratification) can be seen within 12 wk of treatment initiation, with faster changes seen in certain patients and in the colon as compared to the ileum. (30) How to interpret these changes, including defining transmural remission, and the timing of repeat IUS assessments remains an evolving concept.

In patients with CD prescribed anti-inflammatory IBD therapy, a large multicenter German study demonstrated that improvement in all IUS measures can be seen at both 3 and 12 mo[27]. TH, defined as a BWT ≤ 3 mm and absent hyperemia by CDS, has been shown to be achievable in approximately 25%-31% of adult patients with CD after 2 years of treatment[28-32]. The STARDUST sub-study recently evaluated the effect of ustekinumab on TH monitored by IUS and demonstrated increasing TH rates to a total of 24.1% by week 48[33]. In 40 adult patients with endoscopically active CD initiating anti-tumor necrosis factor therapy, an 18% decrease in BWT 4-8 wk post-induction predicted endoscopic response [area under the receiver operating characteristic curve (AUROC) = 0.77, odds ratio (OR) = 10.80, $P = 0.012$] and a BWT cut-off of 3.2 mm was accurate to detect endoscopic remission (AUROC = 0.94, OR = 39.42, $P < 0.0001$) at weeks 12-32[34]. Lastly, a recent multicenter Italian study of adult patients with CD treated with various biologic therapies demonstrated higher rates of TH (defined as normalization of all IUS parameters) with improvement in IUS in 53% at 3 mo and 64% by 1 year with a number needed to treat of 3.6 patients in order to achieve TH. Compared to MH alone, TH is associated with improved outcomes and a decreased risk of long-term disease progression[29,30,35,36].

Similarly, there is evidence in patients with UC to support the use of IUS as a monitoring tool of treatment response, and in fact, changes on IUS may be seen quicker in patients with UC compared to those with ileal CD. Evidence comes from a large multicenter German study of patients with UC who experienced clinical relapse and were treated with anti-inflammatory therapies; there was improvement in the colon BWT as early as 2 wk and BWT improvement continued 12 wk after treatment initiation [37]. In a study of 74 patients with UC, those who did not have a significant treatment response on IUS by 3 mo, measured by a significantly increased BWT to > 6 mm and presence of hyperemia, were at increased risk of continued severe endoscopic activity at 15 mo[38]. In 27 patients with UC treated with tofacitinib, BWT correlated with Mayo score ($r = 0.68$, $P < 0.0001$) and UC Endoscopic Index for Severity ($r = 0.73$, $P < 0.0001$) at induction and week 8 after treatment initiation. A decrease in BWT was more pronounced in patients with endoscopic response with a decrease in BWT of 32% from baseline being accurate for endoscopic response (AUROC = 0.87) and a BWT cut-off of 2.8 mm being the most accurate value to detect endoscopic remission (AUROC = 0.87)[39]. Utilizing IUS at baseline in patients with UC can also predict disease course. A Milan Ultrasound Criteria score > 6.2 at baseline in a study of 98

patients with UC was predictive of a negative disease course (need for corticosteroids, change in therapy, hospitalization, or colectomy) at 1.6 years after treatment initiation[40].

Utility for monitoring in pregnancy

While it is critical to control IBD activity during pregnancy, the tools for tight control disease activity monitoring are limited. IUS provides significant value for the precise monitoring of disease activity in the colon throughout all three trimesters and in the terminal ileum during the first two trimesters. In an Australian cohort of 90 pregnant women with IBD, 127 IUS examinations were performed. Adequate ileal views for disease activity assessment were obtained in 93% of patients at less than 20 wk gestational age, but in only 56% of patients at 20-26 wk. In contrast, adequate colonic views were obtained in 91% of all IUS examinations[41]. In this cohort, BWT was compared to FC as the current reference standard for disease activity monitoring during pregnancy and BWT was found to positively correlate with FC ($r = 0.26$, $P = 0.03$) and had a sensitivity of 74%, specificity of 83% and negative predictive value of 90%. Similarly, in a small Dutch cohort of 38 pregnant women with IBD, 27 of whom were followed with serial IUS examinations during pregnancy, feasibility to assess the terminal ileum significantly decreased from 91.3% in the first trimester to 21.7% in the third trimester ($P < 0.0001$). When compared to FC and clinical activity combined, IUS was able to distinguish active from quiescent disease with 84% sensitivity and 98% specificity[42].

Utility for monitoring in pediatrics

In children, use of IUS as a non-invasive tool to monitor disease activity is of even more importance than in adults, as younger children often require sedation for MRE and there is a need to reduce the risk of radiation exposure from repeated CT scans. As previously stated, there is a clear consensus that a cut-off value for normal BWT in children is not 3 mm, but more likely to be in the range of 2-2.5 mm[14]. Similar to adults, IUS can be used to monitor treatment response in children with CD treated with infliximab. In a study of 28 children with newly diagnosed ileal CD, BWT, hyperemia and involved segment length all significantly decreased as early as 2 wk after infliximab initiation and there was a strong correlation between CDS and FC ($r = 0.71$, $P < 0.0001$). Linear mixed models from this study demonstrated that BWT, hyperemia, and involved segment length continue to decrease over the course of 6 mo after infliximab initiation[43]. In a small pilot study of 13 children with small bowel CD undergoing infliximab induction, bowel wall hyperemia decreased in all but one patient post-induction ($P = 0.01$), indicating that hyperemia assessed by CDS may be the earliest IUS measure to normalize post-induction[44].

Utility for monitoring postoperative CD recurrence

IUS is an accurate tool for monitoring postoperative CD recurrence in the neo-terminal ileum after ileocolic resection. BWT greater than 3-3.5 mm is accurate to detect recurrence based on ileocolonoscopy with a sensitivity of 90%-100%[45]. In a study using both traditional IUS and CEUS to assess CD recurrence, 90 patients, 62 of which had severe recurrence (Rutgeerts score i3 or i4), underwent IUS, CEUS, and endoscopy. A BWT > 5 mm, without any additional parameters, demonstrated 100% specificity to detect recurrence and a BWT > 6 mm was 95.7% specific to detect severe recurrence. The addition of bowel wall contrast enhancement $\geq 70\%$ to either BWT ≥ 5 or 6 mm was the most accurate to the Rutgeerts score with an AUROC of 0.89 for detecting recurrence[46].

COMPARISON WITH OTHER CROSS-SECTIONAL IMAGING MODALITIES

Overall IUS, MRE, and CTE have similar accuracy for the diagnosis of CD complications such as strictures, abscesses, and fistulae[47]. In the largest study to date, the prospective multi-center METRIC trial included 284 patients, 233 of which had small bowel CD, and demonstrated that IUS and MRE are comparable for detection of disease in the terminal ileum. IUS had a sensitivity and specificity of 92% and 84% while MRE had a sensitivity and specificity of 97% and 96%. MRE was superior to IUS for the detection of small bowel disease extent with a sensitivity of 80% compared to 70% for IUS. Similarly, in a multicenter Italian study of 234 adult patients with CD, IUS and MRE had comparable accuracy with a sensitivity and specificity to detect inflammation of 96% and 97% for IUS and 96% and 94% for MRE. MRE was more accurate than IUS to define small bowel disease extension ($r = 0.69$) and detect fistulae ($k = 0.67$), but comparable for detection of strictures ($k = 0.82$) and abscesses ($k = 0.88$)[48]. As such, the updated guidelines from the European Crohn's and Colitis Organization (ECCO)-European Society for Gastrointestinal and Abdominal Radiology and ECCO-European Society for Pediatric Gastroenterology, Hepatology, and Nutrition now propose the use of IUS in the diagnostic evaluation for adult and pediatric CD[49,50].

Follow-up analysis from the METRIC trial for observer agreement demonstrated that IUS and MRE are similar, with IUS performing slightly better than MRE numerically. Interobserver agreement for MRE was modest for new diagnosis [68% ($k = 0.36$)] and relapsed patients [78% ($k = 0.56$)] and only slight for colonic assessment for new diagnosis [61% ($k = 0.21$)] and relapsed patients [60% ($k = 0.20$)]

[51]. Interobserver agreement for IUS was higher than MRE in the small bowel for new diagnosis [82% ($k = 0.64$)] and for relapsed patients [81% ($k = 0.63$)] and in the colon for new diagnosis [64% ($k = 0.27$)] and relapsed patients [78% ($k = 0.56$)] [52]. Furthermore, a retrospective study in children with IBD demonstrated that MRE is not accurate for the assessment of colonic disease, with the simplified Magnetic Resonance Index of Activity unable to identify severe lesions in colonic segments [53].

IMPACT ON PATIENT MANAGEMENT AND SHARED DECISION MAKING

When determining the optimal tight control monitoring tool, perhaps the most important aspect to consider is patient preference and compliance. IUS is one of the most preferred monitoring tool by patients with IBD. In a survey of 121 Australian patients with a formal diagnosis of IBD, IUS scored highly acceptable for disease activity monitoring (mean 9.20 ± 1.37) compared to colonoscopy (7.94 ± 2.30), FC (8.17 ± 1.96), serum sampling (8.87 ± 1.62) and alternative forms of cross-sectional imaging (8.67 ± 1.60) [54].

Beyond preference, use of IUS for IBD monitoring enhances shared understanding and increases the ability of providers to make major treatment decisions during routine clinic visits. In a study of patients randomized to ultrasound-driven IBD care *vs* non-ultrasound driven IBD care, patients who underwent IUS reported better understanding of all aspects of their disease and symptoms, and were more confident in their ability to make informed decisions about managing their disease [55]. Furthermore, gastroenterologists altered management by changing medications in 47% of patients in the ultrasound group compared to just 22% in the non-ultrasound group ($P = 0.002$). Based on disease activity, providers were more likely to change therapy when patients had an IUS compared to when they did not ($P = 0.024$).

POSITIONING ALGORITHM AT THE POINT OF CARE IN THE CLINIC

Debate over the timing and utilization of IUS for tight control monitoring, as well as the definition of treatment response and remission, is ongoing. Multiple studies demonstrate a decrease in BWT by week 4 after therapy initiation, but the longitudinal effect of response reassessment at this early timepoint is still unclear [43,56]. A panel of gastroenterologists from the IBUS developed an expert consensus statement and defined: (1) IUS response as a decrease in BWT by 25% from baseline or 2.0 mm, or greater than 1.0 mm with a decrease in CDS by the modified Limberg score of one grade; and (2) IUS remission as a BWT ≤ 3 mm and normal CDS or absence of hyperemia [57].

Here we propose a practical tight control monitoring algorithm based on IUS (Figure 4). IUS should be repeated post-induction at week eight, regardless of biologic therapy, to assess change in BWT and hyperemia by CDS. If there is no change or an increase in BWT and/or hyperemia, optimization of therapy (dose or interval escalation) should be considered. Repeat IUS should then occur again in eight weeks to reassess response. If again there is no change or worsening, repeat ileocolonoscopy assessment and subsequent therapy discontinuation and switch should be considered. If there is IUS response (as defined above), then the interval to repeat IUS should be extended to 12 wk. Repeat IUS should be performed then every 12 wk until one year and if complete IUS transmural remission is achieved, then IUS can be performed every 6 mo for subsequent monitoring and confirmation of sustained transmural remission.

FUTURE APPLICATIONS

Eventually, the use of IUS at the point-of-care may be able to quantify the proportion of active *vs* chronic inflammation in patients with IBD. This will aid in treatment decision making, guiding choices toward either an anti-inflammatory or anti-fibrotic therapy, with or without surgery. In a study of 35 CD patients who underwent shear wave elastography (SWE) within 1 wk of surgical resection, a cut-off value of 22.5 kPa was 69.6% sensitive and 91.7% specific with an AUROC of 0.82 to discriminate between mild/moderate and severe fibrosis based on histopathology [58]. Future studies validating cut-offs to discriminate degrees of fibrosis and active inflammation are still needed, but in the future provides will be able to personalize management for patients based on where they fall on the active inflammation *vs* fibrosis pathway utilizing SWE [59,60]. Additionally, use of hand-held IUS in combination with artificial intelligence will be able to help patients monitor both their active inflammation and fibrosis remotely for further tight control in the future [61].

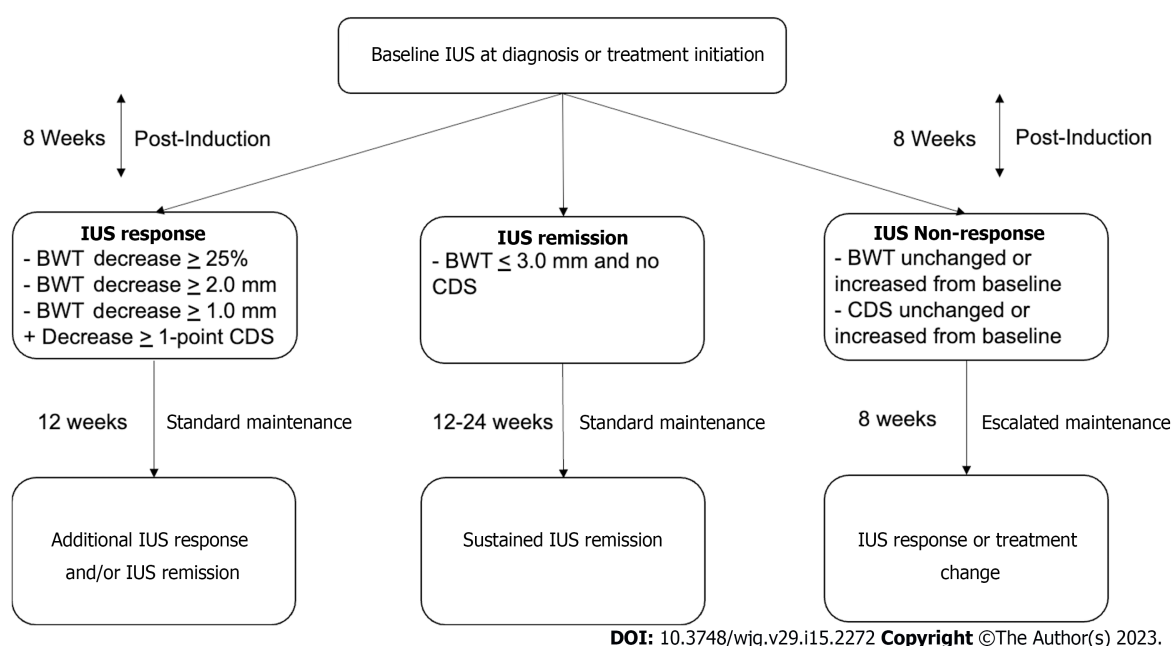


Figure 4 Intestinal ultrasound-based tight control monitoring algorithm. IUS: Intestinal ultrasound; BWT: Bowel wall thickness; CDS: Color Doppler signal.

CONCLUSION

IUS is an accurate, non-invasive cross-sectional imaging tool to assess IBD activity in real time. Incorporation of IUS into a tight control monitoring strategy promotes quick and impactful treatment decisions that can modify disease progression and enhance patient compliance. Specific populations of patients with IBD, especially children and pregnant women, would benefit significantly from the increased use of IUS for disease monitoring. Continued advances in technology will likely allow for enhanced stratification of active *vs* chronic inflammation at the point-of-care and enable remote monitoring for even tighter control. Ultimately, an IUS-based tight control monitoring algorithm and prediction tool may be used for early treatment decisions to achieve sustained deep remission and disease modification.

FOOTNOTES

Author contributions: Dolinger MT and Kayal M contributed to the conception of the manuscript, Dolinger MT drafted manuscript; Kayal M edited the manuscript.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

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Country/Territory of origin: United States

ORCID number: Maia Kayal 0000-0002-9640-950X.

S-Editor: Wang JJ

L-Editor: A

P-Editor: Cai YX

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