

Intestinal Ultrasound in Pediatric Inflammatory Bowel Disease: Promising, but Work in Progress

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Intestinal ultrasound (IUS) is increasingly used and promulgated as a noninvasive monitoring tool for children with inflammatory bowel disease because other diagnostic modalities such as colonoscopy and magnetic resonance imaging cause significant stress in the pediatric population. The most important parameters of inflammation that can be assessed using IUS are bowel wall thickness and hyperemia of the bowel wall. Research has shown that IUS has the potential to be a valuable additional point-of-care tool to guide treatment choice and to monitor and predict treatment response, although evidence of its accuracy and value in clinical practice is still limited. This review gives an update and overview of the current evidence on the use and accuracy of IUS in children with inflammatory bowel disease.

Key Words: intestinal ultrasound, inflammatory bowel disease, pediatrics, disease monitoring, review

Introduction

Inflammatory bowel disease (IBD) is diagnosed during childhood and adolescence in up to 20% of patients. Ileocolonoscopy, upper endoscopy, and small-bowel imaging, most commonly via magnetic resonance enterography (MRE) and sometimes capsule endoscopy (CE), are undertaken at first presentation to assess the baseline location and degree of bowel inflammation.¹ Treatment is aimed not only at controlling symptoms and facilitating normal growth, but also for mucosal and, in the case of Crohn's disease (CD), transmural healing.² Re-evaluation via ileocolonoscopy, MRE, and CE is expensive and may cause significant stress and anxiety in children.^{3,4} Furthermore, in some health care centers endoscopy also requires hospital admission and sedation, and there is a risk of capsule retention with use of CE. Hence, the threshold to perform these examinations during follow-up in children is higher than in adults. Increasingly, noninvasive monitoring is used to verify the resolution of bowel inflammation once clinical remission is achieved, because the adjustment of treatment to achieve mucosal and transmural healing could prevent progression to intestinal complications.² Particularly for children with IBD, it is therefore crucial to improve noninvasive monitoring.

Currently, in addition to monitoring symptoms and linear growth, there are 2 noninvasive methods used to objectively monitor control of inflammation in children with IBD: (1) inflammatory markers in the blood, such as C-reactive protein, leukocyte, and thrombocyte counts, and (2) fecal calprotectin level, which represents intestinal inflammation.

However, all of these tests have limited sensitivity and/or specificity⁵⁻⁷ and provide limited information about disease severity and extent, which are both of importance for choosing the appropriate treatment adjustment. In addition, in recent studies and guidelines, the poor performance in clinical care of the Pediatric Crohn's Disease Activity Index, which includes symptoms, signs, and blood tests, has been emphasized.⁸ The use of intestinal ultrasound (IUS) is increasingly used and promulgated.⁹ As fast, relatively inexpensive noninvasive tool for monitoring disease activity in children with IBD, IUS has the potential to accurately reflect both disease extension and severity. In this review, we give an overview of the current evidence on the use and accuracy of IUS in children with IBD.

How to Assess the Bowel with IUS in Children Parameters of Inflammation

There are several parameters of inflammation that can be measured with IUS (Figs. 1, 2). The parameter that is considered most important is bowel wall thickness (BWT), because swelling of the bowel wall is an important feature of inflammation.¹⁰⁻¹³ Adult guidelines indicate that BWT should be measured from the lumen/mucosa interface to the muscularis/serosa interface, on the anterior side of the bowel.¹¹ In healthy children, the BWT in the small bowel measures approximately 1.0 mm, and colonic BWT measures approximately 1.5 mm, both with a maximum of 1.9 mm.¹⁴ In children with IBD, frequently used cutoff values are 2.5 to 3 mm. However, there is no generally accepted cutoff value yet; in a systematic review

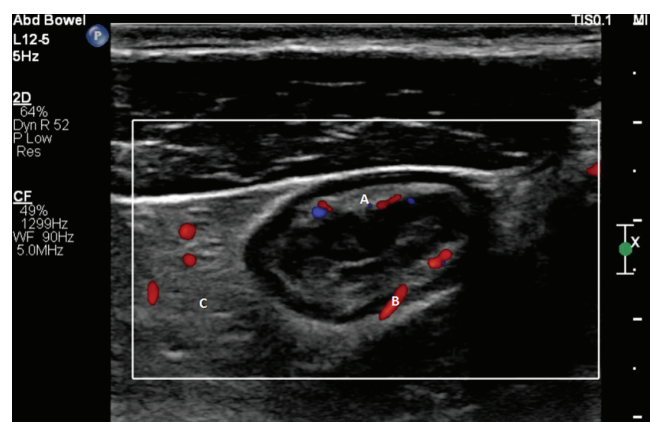
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Table 1. Advantages and Disadvantages of IUS in Children With IBD

Advantages	Disadvantages
Can assess location of disease	Measurement of length of affected segment is less reliable than MRE
Can assess motility	Rectum not always visible
Can assess disease severity and complications	Learning curve
Can assess transmural healing	Operator dependency
Examination is noninvasive and radiation-free	Cutoff values and diagnostic accuracy are not yet established
Low costs	

**Figure 1.** Cross-sectional image of terminal ileum in a patient with CD. A, increased BWT. B, Hyperemia with stretches reaching into mesentery. C, Mesenteric fat proliferation.

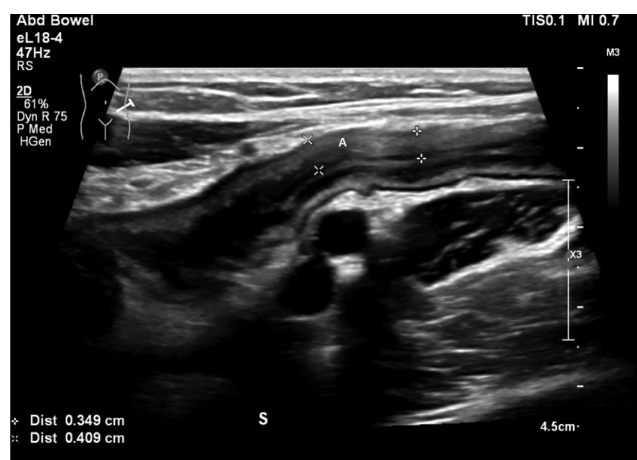
on the diagnostic accuracy of IUS in children with IBD that included 14 studies, cutoff values ranged from 1.5 mm to 4 mm, and some studies used different cutoffs for the small bowel.¹²

The second most often used parameter of inflammation is hyperemia of the bowel wall,¹² which is measured using color Doppler.¹⁵ The presence of hyperemia can be scored dichotomously or semi-quantitatively, using the modified Limberg score.^{16, 17} This score distinguishes 4 grades of hyperemia (no signs of hyperemia, small spots, long stretches, and long stretches into the mesentery) and correlates well to endoscopic and histopathologic disease activity.¹⁸

Other frequently used parameters of inflammation are visibility (stratification) of the bowel wall layers, loss of colonic haustrations, the presence of mesenteric fat proliferation (“creeping fat”), and the presence of enlarged lymph nodes.^{12, 19-21} For patients with CD, it is also possible to assess small-bowel motility and complications such as strictures, abscesses, and fistulas.

CD vs Ulcerative Colitis

Inflammation in ulcerative colitis (UC) is limited to the mucosal layer of the colon, and CD is known for its transmural and panenteric localization. It is possible to discriminate between the 2 types of IBD based on IUS when small-bowel involvement, a patchy distribution of abnormalities in the colon, or complications such as abscesses and fistulas are noted.¹¹ However, the IUS characteristics of both subtypes overlap in the presence of increased BWT and bowel-wall hyperemia. In

**Figure 2.** Longitudinal image of sigmoid colon in a patient with UC. Increased BWT, with loss of haustrations and loss of wall layer stratification.

addition, mesenteric fat proliferation has also been reported in pediatric patients with UC.²² Based on these findings, it is often not possible to distinguish UC from CD using IUS alone.

IUS Activity Indices

Several IUS activity indices composed of the aforementioned IUS variables have been developed for the adult population.^{23, 24} However, in the pediatric population research on this topic is limited. One index for pediatric patients with UC was designed by Civitelli et al.²⁵ This index combines BWT, hyperemia, loss of haustrations, and loss of wall layer stratification. In the derivation cohort of 50 children, the index showed good sensitivity and specificity for the detection of severe disease (100% and 93%, respectively; 95% confidence interval [CI] not provided), but it has not been externally validated. A second index, the Simple Pediatric Activity Ultrasound Score, was designed by Kellar et al.²⁶ based on retrospective data in 75 children and can be used for both types of IBD. Parameters used in this index are BWT, hyperemia, and the presence of inflammatory fat. The sensitivity and specificity for this index were 100% (95% CI, 90-100) and 95% (95% CI, 83-99.3), respectively. However, along with its retrospective nature, this study also included patients with a history of resection, possibly affecting the mean BWT, and the baseline endoscopic disease severity was not reported. Therefore, the presence of bias by study sample was unclear and, most important, external validation was lacking. An index for pediatric patients with CD has not been published.

Bowel Preparation

There are no evidence-based guidelines on bowel preparation before an IUS examination in children. Whereas some experts state that a bowel preparation is not needed,¹⁹ the consensus statement of the European Society of Paediatric Radiology and the European Society of Gastrointestinal and Abdominal Radiology—based on expert opinion—states that children should not eat any solid food or drink carbonated fluid or milk for 2 to 6 hours before a bowel ultrasound exam.²⁷ Results of 1 study in healthy adults suggest that the BWT increases by 0.1 to 0.2 mm after eating.²⁸ Although the clinical significance of this small difference may be questionable in daily practice, in research settings it is advisable to standardize bowel preparation protocols.¹⁴

Diagnostic Accuracy and Validity

To date, the diagnostic accuracy of IUS in the pediatric population has not been established; most studies on this topic have important methodological limitations, such as an inefficient time flow between IUS and the reference standard, and unclear blinding procedures. A systematic review on the diagnostic accuracy of IUS in children with IBD showed that different studies on this topic used different criteria to define an IUS as abnormal.¹² In these studies, the sensitivity and specificity of IUS ranged from 39% to 93% and 90% to 100% for diagnosing de novo IBD and from 48% to 93% and 83% to 93% for detecting active disease during follow-up, respectively.

An obvious drawback of IUS could be its reproducibility, in particular interobserver agreement. Three studies have assessed interobserver agreement in children with IBD. The first study, by Dillman, Smith, et al,²⁹ assessed interradiologist agreement in 29 children with small-bowel CD and showed substantial agreement (intraclass correlation coefficient [ICC], 0.63-0.67) for BWT and moderate agreement for hyperemia of the bowel wall (ICC, 0.48-0.58). The second study, by Tsai et al,³⁰ assessed interobserver agreement for terminal ileum images of children suspected to have CD and found moderate agreement for BWT (ICC = 0.64) and good agreement for bowel wall hyperemia (ICC = 0.84). Interobserver agreement for the diagnosis was also good (kappa, 0.6-0.8). The third study assessed interradiologist agreement in 30 children with UC and found excellent agreement for the presence of active disease (ICC = 0.926).³¹ However, these results should be interpreted with caution because the analyses were performed using saved images. No studies have investigated intraobserver agreement.

IUS As Point-Of-Care Tool

Gastroenterologists are increasingly using IUS in clinical practice as a bedside tool during outpatient department visits to guide decision-making.³² In addition to being an additional noninvasive test, an advantage of IUS over other surrogate markers of disease activity is its potential to assess disease location and extension. In addition to weighing in on the decision to upscale or downscale treatment, it can also be used to guide the choice between systemic and local therapy (eg, enemas, budesonide, surgery). Other advantages and disadvantages are displayed in Table 1. In pediatric IBD practices, point-of-care IUS is not yet widely used.³³ Its use in clinical follow-up is propagated in the latest European guidelines on the treatment of pediatric IBD.⁹ However, there are no data on the clinical additional value of IUS when added to regular follow-up. More research is needed to determine for which patients in the outpatient department an IUS is of value.

Assessing and Predicting Therapeutic Response

In addition to using IUS to assess disease activity at 1 time point, IUS can also be used to monitor response to treatment. This functionality is illustrated by 2 longitudinal studies in children with CD starting on infliximab; BWT, hyperemia of the bowel wall, and length of disease involvement decreased over time, reflecting a response to treatment.^{34,35} In addition, Scarallo et al²² performed a retrospective study in 52 children with acute severe colitis. In this study, an IUS was performed at day 3 of admission, and both BWT (>3.4 mm) and loss of

colonic haustrations were significantly associated with steroid treatment failure, suggesting a role for IUS as a prediction tool for therapeutic response in children with acute severe colitis. However, additional prospective studies correlating changes in IUS parameters with relevant disease outcomes while also including existing noninvasive markers are needed to determine its utility as a predictor of the disease course in children.

Advanced Ultrasound

Contrast-Enhanced Ultrasound

Contrast-enhanced ultrasound (CEUS) can be used to identify inflamed bowel loops with more precision. With CEUS, a contrast fluid with microbubbles is injected intravenously. Subsequently, these microbubbles can be visualized upon their contact with the ultrasound soundwaves, using specialized software.³⁶ Because of safety concerns, contrast use has been limited to the adult population for a long time. However—although safety data are limited and usage is off-label—according to the European Federation of Societies for Ultrasound in Medicine and Biology, CEUS is safe to use in children.³⁷ Nevertheless, evidence for its utility in children with IBD is still scarce: 1 case series has been published, in which CEUS provided useful clinical information on the degree of inflammation,³⁸ and a pilot study in 20 children and adolescents with CD showed a sensitivity of 100% with magnetic resonance imaging as the reference standard, without reporting the specificity and the 95% CI.³⁹ In all, the advantage of CEUS in the pediatric population remains to be proven. Because CEUS requires intravenous access, the acceptability for children is a concern.

Small-Intestine Contrast Ultrasound

Small-intestine contrast ultrasound (SICUS) is another advanced ultrasound technique. With SICUS, proximal small bowel loops can be identified with more precision by administering a nonabsorbable oral contrast solution, such as polyethylene glycol. This fluid is anechoic (ie, it is black on ultrasound imaging) and can be followed with the ultrasound probe while it moves through the proximal bowel loops. A meta-analysis comparing SICUS to MRE and CE in adults and children with CD showed a similar diagnostic yield of the 3 imaging tools.⁴⁰ In addition, 2 studies in children with CD or a suspicion of CD suggested a better diagnostic accuracy of SICUS, compared to standard IUS.^{41,42} The limitations of SICUS are its long duration of approximately 40 minutes, compared to 10 to 20 minutes for standard IUS,⁴¹ making it less suitable as a point-of-care tool.

Elastography

Shear-wave elastography is an emerging advanced ultrasound technique that can be used in patients with IBD to differentiate between fibrotic and inflammatory strictures.⁴³ This technique quantifies tissue stiffness by measuring the propagation through the tissue of a high-intensity pulse (shear waves) and has been approved for use in children by the U.S. Food & Drug Administration.⁴⁴ Evidence for use in children with IBD is limited; 1 case series in adolescents aged 16 to 20 years has been published. In this descriptive study, some additional information obtained by elastography compared to CEUS on tissue stiffness of strictures is described.³⁸ In addition, 1 pilot study in 14 children with CD showed a correlation between elastography and other IUS markers (BWT, hyperemia,

wall layer stratification) and biochemical markers (C-reactive protein, erythrocyte sedimentation rate) for disease activity.⁴⁵

Training

For IUS in adults, a training curriculum was designed by a group of international experts from the International Bowel Ultrasound Group.⁴⁶ However, there is no evidence or consensus on how to train pediatricians and pediatric gastroenterologists for IUS in children, and no specific training curriculum exists that is focused on children.

Conclusions

Research has shown that IUS is potentially a valuable additional tool for monitoring disease activity, monitoring and predicting response to therapy, and guiding treatment choice. However, scientific evidence on IUS in the pediatric population regarding its diagnostic accuracy and reproducibility, its added value in current clinical practice, and its training requirements is limited. Until these data become available, guiding clinical decisions with IUS should be done with prudence.

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