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.

(Inflamm Bowel Dis 2016;0:1–16)

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 trials[1] and increasingly in clinical practice.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.ibdjournal.org).

Received for publication October 7, 2015; Accepted October 13, 2015.

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Supported by an unrestricted educational grant to University of Calgary from Abbvie.

Author disclosures are available in the Acknowledgments.

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DOI 10.1097/MIB.0000000000000706

Published online.

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).

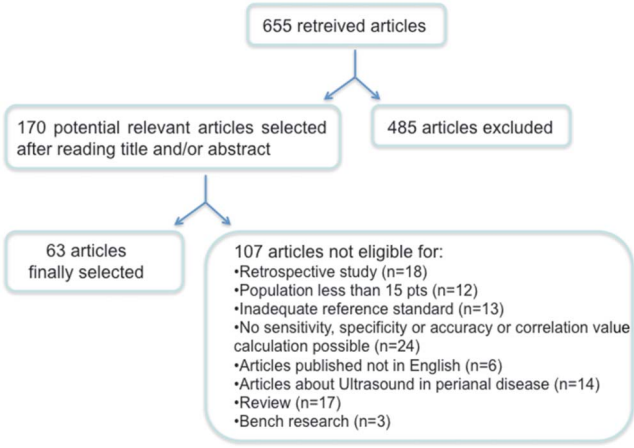

FIGURE 1. Flowchart for the selection of the studies included in the review.

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
Maconi 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)

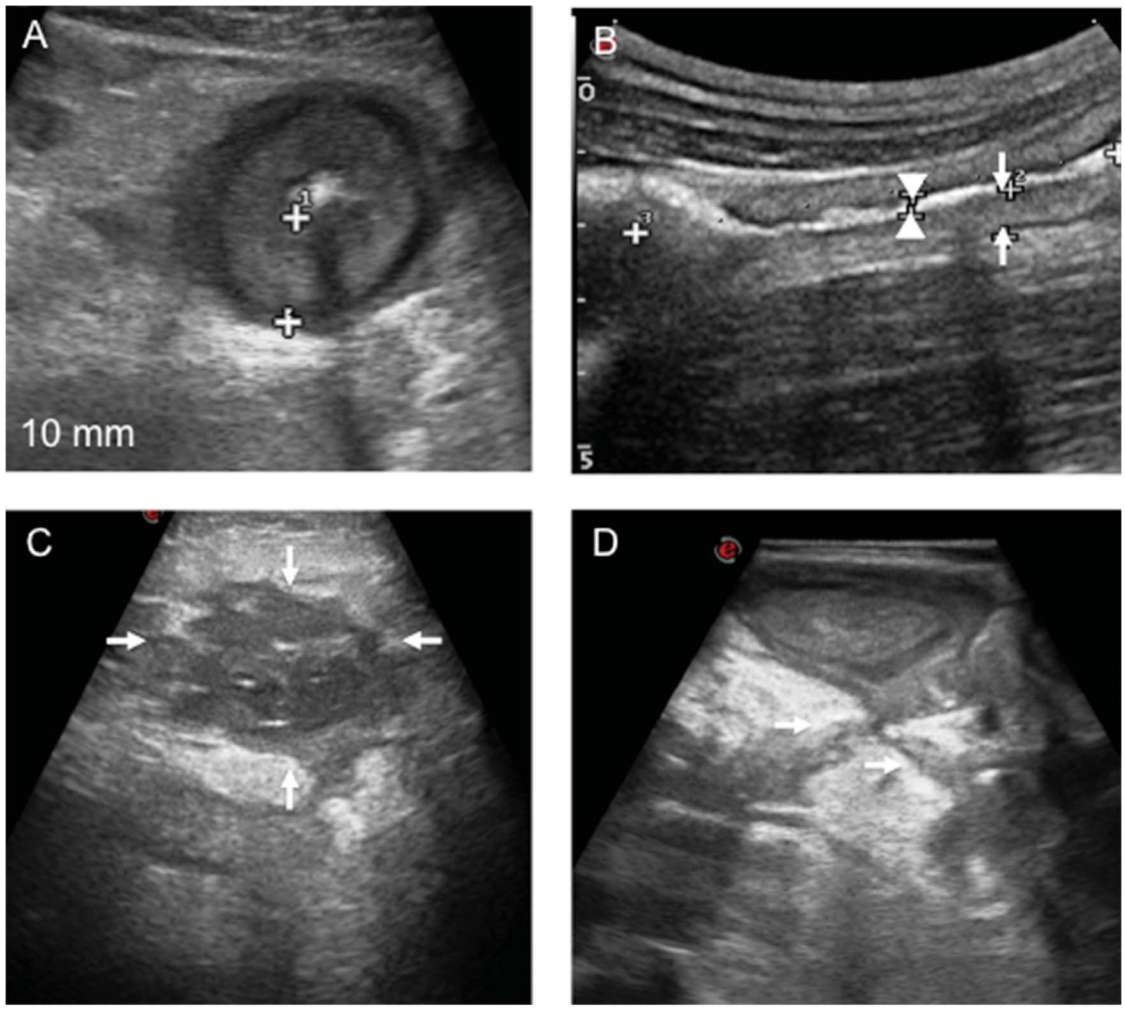

FIGURE 2. BWT of the terminal ileum as assessed by bowel US (A); Stenosis: the white arrows indicate BWT and the arrowheads indicate stenosis of the terminal ileum (B); Abscess (C); Fistulae (D).

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 do[34]. 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	Duodendum/ 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	35.4 (3–105)	Neoterminal ileum	81	86	PPV 96%, NPV 57%
Biancone et al[40]	22	Adult PC	SICUS (BWT > 3 mm)	CE, endoscopy	12	Neoterminal ileum	100, 100	—	—
Castiglione et al[41]	40	Adult PC	US (BWT > 3 mm)	Endoscopy	12	Neoterminal ileum	77	94	PPV 93%, NPV 80%
Castiglione et al[41]	40	Adult PC	SICUS (BWT > 3 mm)	Endoscopy	12	Neoterminal ileum	82	94	PPV 93%, NPV 94%
Onali et al[33]	25	Adult PC	SICUS (BWT > 3 mm)	Endoscopy	12, 36	Neoterminal ileum	100, 100	—	—
Paredes et al[42]	33	Adult PC	US (BWT > 3 mm)	Endoscopy	87.7 (75.4)	Neoterminal ileum	76.9	87	—
Paredes et al[43]	60	Adult PC	US (BWT > 3 mm), CEUS	Endoscopy	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	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 al[41] 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 (Levovist), 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
Kratzer 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
Ripolles 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 al[71] 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 abscesses[74] (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).

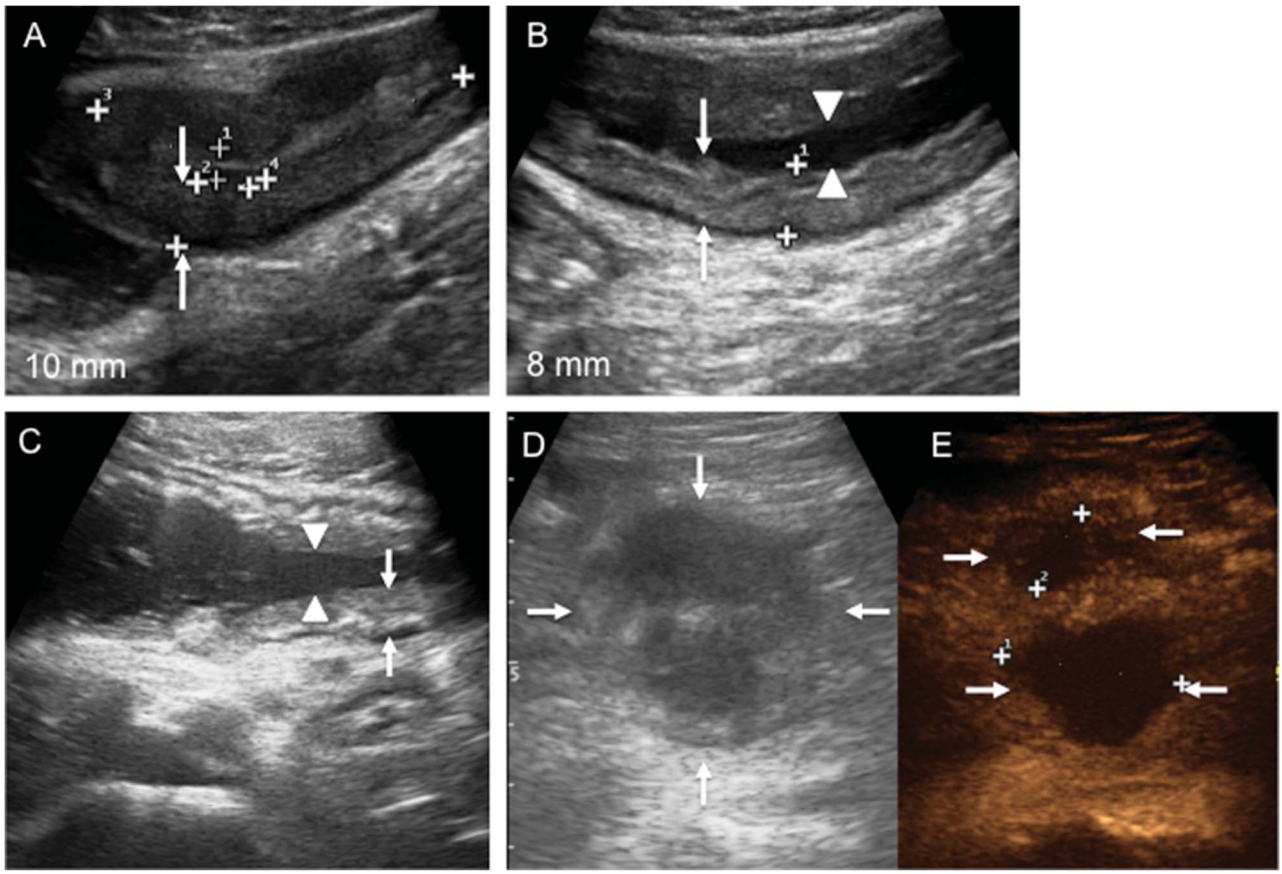

FIGURE 3. Comparison between bowel US (A) and SICUS (B) of a patient with CD. The white arrows indicate BWT of the terminal ileum as assessed by bowel US A, The use of oral contrast agent during assessment allows for the visualization of the lumen (white arrowheads), the better definition of the bowel 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 al[79] developed a semiquantitative score as predictor of short-term surgery risk within 1 month of examination. After this trend, Calabrese et al[46] 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 perintestinal 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 ultrasongraphic 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 periintestinal 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.

ACKNOWLEDGMENTS

Declaration of personal interests: E. Calabrese: None for US equipment. Participated in advisory boards for Abbvie and Mundipharma, received speakers' fees from Abbvie, MSD and Zambon. C. Maaser: None for US equipment. Participated in advisory boards for MSD, received speakers' fees from Abbvie, Falk, MSD, and Shire. F. Zorzi: None for US equipment. Received speakers' fees from Abbvie. K. Kannengiesser: None for US equipment. Received speakers' fees from Abbvie, MSD and Falk Pharma. S. B. Hanauer: Has consulted, participated in advisory boards, received speakers' fees and institutional research support from Abbvie. D. H. Bruining: Participated in advisory board for Bracco. M. Iacucci: None for US equipment. Received research grant from Abbvie and Pentax. G. Maconi: None for US equipment. Received speakers' fees from Sofar. K. L. Novak: Research support Abbvie, advisory boards Abbvie, Janssen, speakers' fees Abbvie. R. Panaccione: None for US equipment. Has consulted, participated in advisory boards, received speakers' fees, research funding and educational support from Abbott Laboratories, Merck, Schering-Plough, Shire, Centocor, Elan Pharmaceuticals, Procter and Gamble, AstraZeneca, Ferring Pharmaceuticals, UCB, GlaxoSmithKline, Bristol-Meyers Squibb, Byk Solvay, Axcan, Janssen, Prometheus, Millennium Pharmaceuticals. D. Strobel: None for US equipment. Received speakers' fees from MSD, Abbvie, Bayer, Bracco, Siemens, Hitachi. S. R. Wilson: Research grants from Abbvie, Janssen Inc., and Lantheus Medical Imaging. Equipment support from Philips and Siemens. Advisory capacity with Lantheus Medical Imaging. M. Watanabe: None for US equipment. Has consulted, participated in advisory boards, received speakers' fees, research funding from Abbvie, Eisai, Ajinomoto, Kyorin, Mitsubishi Tanabe, Takeda, Otsuka, Kyowa Hakko Kirin, Zeria, JIMRO, UCB, Asahi Kasei Medical, Pfizer. F. Pallone: None for US equipment. Received speakers' fees from Abbvie, Takeda and Zambon. S. Ghosh: None for US equipment. Participated in steering committees and advisory boards for Pfizer, Janssen, Abbvie, Ferring, Shire, BMS, Novo Nordisk.

Author contributions: E. Calabrese, C. Maaser, F. Zorzi, and K. Kannengiesser assessed the articles and their relevance to the above topic. All authors participated in the London meeting (July 18th–19th 2014) and were involved in the writing of the article. F. Pallone and S. Ghosh contributed equally to the article.

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