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REVIEW ARTICLE

Optimising monitoring in the management of Crohn's disease: A physician's perspective

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Abstract

Management of Crohn's disease has traditionally placed high value on subjective symptom assessment; however, it is increasingly appreciated that patient symptoms and objective parameters of inflammation can be disconnected. Therefore, strategies that objectively

Abbreviations: IBD Ahead, Annual excHangE on the ADvances in Inflammatory Bowel Disease; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CDEIS, Crohn's Disease Endoscopic Index of Severity; CRP, C-reactive protein; CT, computed tomography; GI, gastrointestinal; HBI, Harvey–Bradshaw Index; IBD, inflammatory bowel disease; IBDQ, Inflammatory Bowel Disease Questionnaire; ISC, International Steering Committee; MRI, magnetic resonance imaging; QOL, quality of life; SBCE, small-bowel capsule endoscopy; SBFT, small-bowel follow-through; SES-CD, Simple Endoscopic Score for Crohn's Disease; TNF, tumour necrosis factor.

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Endoscopy;
Disease activity index

monitor inflammatory activity should be utilised throughout the disease course to optimise patient management. Initially, a thorough assessment of the severity, location and extent of disease is needed to ensure a correct diagnosis, identify any complications, help assess prognosis and select appropriate therapy. During follow-up, clinical decision-making should be driven by disease activity monitoring, with the aim of optimising treatment for tight disease control. However, few data exist to guide the choice of monitoring tools and the frequency of their use. Furthermore, adaption of monitoring strategies for symptomatic, asymptomatic and post-operative patients has not been well defined. The Annual excHangE on the ADvances in Inflammatory Bowel Disease (IBD Ahead) 2011 educational programme, which included approximately 600 gastroenterologists from 36 countries, has developed practice recommendations for the optimal monitoring of Crohn's disease based on evidence and/or expert opinion. These recommendations address the need to incorporate different modalities of disease assessment (symptom and endoscopic assessment, measurement of biomarkers of inflammatory activity and cross-sectional imaging) into robust monitoring. Furthermore, the importance of measuring and recording parameters in a standardised fashion to enable longitudinal evaluation of disease activity is highlighted.

Contents

1. Introduction

Crohn's disease (CD) is a chronic inflammatory bowel disease (IBD) characterised by periods of symptomatic relapse and remission. Inflammation often persists in the absence of gastrointestinal (GI) symptoms[1] and may lead to progressive bowel damage and complications such as fistulae, abscesses and strictures. In many patients, impaired bowel function ultimately leads to impaired quality of life (QOL) and disability.[2] Therefore, treatment goals in CD are evolving beyond mere control of symptoms towards targeting sustained control of GI inflammation, with the ultimate objectives of preventing bowel damage, reducing long-term disability and maintaining QOL.[3,4] As such, assessment of objective measures of inflammation is an increasingly important part of the management approach in a CD patient. Thorough assessment of disease activity and extent at presentation is needed to ensure a correct diagnosis of IBD (versus non-IBD) and of CD (versus ulcerative colitis), avoid delay in diagnosis, identify complications and help assess prognosis. This information enables appropriate treatment and increases the likelihood of achieving management goals.[5–7] During follow-up, clinical decision-making is increasingly being driven by the findings of continued monitoring (for objective evidence of inflammation), with the aim of optimising treatment for tight disease control.[8]

Despite the potential benefits of longitudinal monitoring in CD, there are several unanswered questions around implementing this model in practice: Which monitoring tools should be used? When should they be used? How should the monitoring strategy differ in different patient scenarios?

Given the uncertainties around these issues, practice recommendations were developed based on the best published evidence available and/or expert opinion as part of the IBD Ahead 2011 educational programme, which involved approximately 600 gastroenterologists from 36 countries (see Appendix A). Here we provide a physician's perspective on a thorough and appropriate baseline assessment, and the

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subsequent optimised monitoring in symptomatic, asymptomatic and post-operative CD patients.

2. Monitoring tools for CD

In CD, disease activity can be evaluated by symptom assessment, endoscopic assessment, measurement of biomarkers and cross-sectional imaging.

2.1. Symptom-based monitoring

Several scoring systems have been developed to evaluate the severity of symptoms in patients with CD (Box 1). The Crohn's Disease Activity Index (CDAI)[9] and the Harvey–Bradshaw Index (HBI)[10] evaluate bowel-related symptoms, complications and general well-being, while the Inflammatory Bowel Disease Questionnaire (IBDQ)[11,12] incorporates social, systemic and emotional symptoms together with bowel-related symptoms. These indices are routinely used in clinical trials to assess drug treatments and are becoming more commonly used in clinical practice, as the threshold for reimbursement for biologic treatment in some countries is assessed using symptom-based scoring. Using indices that are responsive to changes in disease severity has value in allowing consistent longitudinal monitoring of symptoms; however, it must be noted that some items of the CDAI are open to subjective interpretation (e.g. "general well-being" or "severity of abdominal pain").[13] Subjectivity may also impact on the ability of the IBDQ to accurately assess bowel or systemic symptoms[14]; nevertheless, it has shown reliability and validity in assessing QOL domains in CD.[12,15]

2.2. Endoscopy

Mucosal healing has emerged as an important goal in CD management. Several endoscopic scoring systems have been developed to facilitate consistent and reproducible assessment of the severity of mucosal damage at predefined sites (Box 1).[16–18] These instruments assess both disease extent and severity, and are now routinely used in clinical trials. However, lack of a single standardised endoscopy score and broadly accepted or validated thresholds for active disease and endoscopic remission, together with insufficient knowledge of the natural history of different lesions, have precluded their widespread use in routine clinical practice. In addition, endoscopy is invasive, costly, time-consuming and disliked by patients; therefore, it is performed only to inform critical treatment decisions.

2.3. Laboratory-based monitoring

Multiple biomarkers that reflect the presence of active inflammation have been identified; however, very few have proven to be clinically useful in IBD. C-reactive protein (CRP), an acute-phase reactant that correlates moderately well with clinical, endoscopic, histologic, and radiographic disease activity, is inexpensive to measure with a readily available blood test.[19–25] Faecal calprotectin and lactoferrin are heat-stable granulocyte-derived proteins that are relatively inexpensive, non-invasive, and have been studied extensively in IBD.[26–30] Both biomarkers can be assayed directly in stool using ELISA-based testing. They have been shown to correlate significantly with colonic endoscopic score and histology in

Box 1. Symptom-based and endoscopic scoring systems in Crohn's disease.

Symptom-based scoring systems

Crohn's Disease Activity Index (CDAI)[9]
- Consists of eight factors, including frequency of soft/liquid stools, severity of abdominal pain, general well-being, presence of extraintestinal manifestations, requirement for antidiarrhoeal medication, presence of an abdominal mass, haematocrit level and percentage deviation from standard body weight.

Harvey–Bradshaw Index (HBI)[10]
- A simple index restricted to clinical parameters of general well-being, abdominal pain, frequency of liquid stools, presence of an abdominal mass and extraintestinal manifestations.

Inflammatory Bowel Disease Questionnaire (IBDQ)[11,12]
- Incorporates social, systemic and emotional symptoms together with bowel-related symptoms into an activity index.
- Shown to be valid and reliable across several different language and culture settings.[110]
- May have a stronger correlation with utility than the CDAI.[111]
- A shortened version of the IBDQ has also been developed and is considered able to detect meaningful clinical changes in health-related quality of life.[112]

Endoscopic scoring systems

Crohn's Disease Endoscopic Index of Severity (CDEIS)[16]
- Five segments are individually scored based on the presence of deep or superficial ulcerations and the extent of surface involved by disease or ulcerations. The presence of stenosis is also scored.
- Scores range from 0–44, with a higher score indicting greater severity.

Simple Endoscopic Score for Crohn's Disease (SES-CD)[17]
- Five segments are individually scored based on the presence and size of ulcers, extent of the ulcerated surface, extent of the affected surface and the presence and type of narrowings.
- Scores range from 0–56, with a higher score indicting greater severity.
- SES-CD has been shown to correlate strongly with the CDEIS and also with symptom-related measures.[113]

Rutgeerts score for post-operative recurrence[18]
- Lesions at the neoterminal ileum and ileocolonic anastomosis are explored and scored on a scale from i0 to i4.
- Score has been shown to predict the duration of symptom-free survival.[18]

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patients with ileocolonic or colonic disease, although not with ileal endoscopic score and histological findings in ileal disease.[31,32] However, there are limitations to using CRP and stool biomarkers to monitor CD activity as they are not specific for IBD. Furthermore, no validated thresholds that define active disease and biochemical remission exist.

2.4. Cross-sectional imaging

Cross-sectional imaging tools are important in CD for establishing disease severity and extent, as well as ruling out complications. As such, they can aid diagnosis and guide therapeutic strategies. Cross-sectional imaging may complement endoscopic assessment by providing additional insight into disease activity, allowing assessment of the entire small bowel and excluding complications such as stenosis or penetrating disease. Various cross-sectional imaging tools are available (Table 1), including magnetic resonance imaging (MRI), ultrasonography and computed tomography (CT). MRI is considered one of the reference standards in the diagnostic assessment of CD.[33] It allows high soft-tissue contrast and has static, dynamic and direct multiplanar imaging capabilities. MRI accuracy is optimised with the use of luminal and intravenous contrast and can be used to evaluate the activity of small- and large-bowel disease and to document complications including stenosis, fistula and abscess. Pelvic MRI is the modality of choice for imaging the pelvis and perianal area. Ultrasonography is a relatively accessible tool for an urgent broad assessment of disease activity and for exclusion of complications, with high reproducibility and low inter-observer variability.[33,34] It is minimally invasive and an ionising radiation-free tool. Contrast-enhanced ultrasonography allows microvascular imaging of the bowel and quantitative differentiation between inflamed and normal bowel segments based on their different diffusion pattern[35]; however, it does not allow differentiation between predominantly inflammatory or fibrotic stenosis.[36] CT enterography combines CT techniques with oral and intravenous contrast.[37] It has similar advantages to MR enterography; however, ionising radiation exposure limits its use to emergency situations.

3. Monitoring in different patient scenarios

Table 2 provides a summary of the final statements from the IBD Ahead 2011 programme. These statements, together with the level of supporting evidence, are provided in Appendix A.

3.1. At diagnosis

Careful evaluation of disease characteristics at baseline is essential for differential diagnosis, establishing the extent, severity and behaviour of disease, objectively evaluating inflammation and ruling out complications. Initial findings inform both prognostic assessment and treatment decisions and also provide a baseline for future follow-up. For these reasons, care should be taken to use standardised tools accurately. It is imperative that a complete assessment be made at diagnosis and, where resources allow, we propose that all four assessment modalities – symptom assessment, endoscopic assessment, laboratory markers and cross-sectional imaging – are used. This will serve as a baseline from which disease evolution and management success can be evaluated.

In clinical practice, gastroenterologists typically rely on their global clinical judgement for symptom evaluation; however, use of a standardised tool (see Box 1) that is responsive to changes in disease severity from diagnosis onwards might allow greater objective and valid assessment. We encourage use of the HBI as it is simple to administer, amenable to same-day clinic visits, relatively well correlated to CDAI scores,[10,38] and has a higher objective component than the IBDQ.

Endoscopy should be performed in all patients with symptoms suggestive of IBD to enable diagnosis and assess the location, extent and severity of mucosal lesions. We strongly suggest using precise and standardised descriptions of endoscopic lesions, including type, location, depth and extent. Scoring of severity may be achieved with the Crohn's Disease Endoscopic Index of Severity (CDEIS)[16] or Simple Endoscopic Score for Crohn's Disease (SES-CD),[17] although use of these tools may not be practical in routine clinical practice. Ileocolonoscopy examining the terminal ileum and all colonic segments, with precise description of lesions, biopsy and subsequent histological examination, is needed to support the diagnosis, as well as to differentiate IBD from other causes of colitis, and CD from ulcerative colitis.[39–41] Biopsies should be taken from endoscopically affected and non-affected areas to histologically document the existence of spare segments between areas of inflammation. When biopsy of abnormal areas is not within the reach of the standard gastroscope or ileocolonoscope, then single- or double-balloon enteroscopy should be considered.[22,23] Upper GI endoscopy/biopsy may be useful, particularly in paediatric patients and in adult patients with upper GI symptoms. In a patient in whom there is high clinical suspicion of CD but inconclusive ileocolonoscopy, gastroscopy, cross-sectional imaging and small-bowel capsule endoscopy (SBCE) may aid diagnosis and should be considered.[42]

In our opinion routine blood tests, (complete blood count, liver profile, albumin, iron studies, renal function, vitamin B12 and assessment of CRP and stool biomarkers) should be conducted in all patients to establish baseline values for future comparison. Initial assessment of CRP has an important diagnostic and prognostic role[19,23,43–45]; however, it should be noted that approximately 20% of patients with active CD may have normal CRP levels.[46] While the sensitivity and specificity of the CRP test are not high enough to allow differentiation from other disorders, thus precluding its use as an IBD screening tool,[47] faecal calprotectin and faecal lactoferrin can help differentiate suspected IBD from IBS or functional disease.[24,28,30,31,48–50] A meta-analysis of 13 studies found that faecal calprotectin had a pooled sensitivity of 93% and pooled specificity of 96% to diagnose IBD in adults; corresponding sensitivity and specificity in children and teenagers were 92% and 76%, respectively.[28] A larger review, including 30 studies, found that faecal calprotectin had a sensitivity of 95% and specificity of 91% for differentiating IBD from non-IBD diagnoses.[30] In addition, the diagnostic precision of faecal calprotectin was greater with a cut-off of 100 μg/g compared with 50 μg/g.

We propose that cross-sectional imaging is needed in all patients at diagnosis to assess the extent and severity of

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Table 1 Pooled analysis of use of ultrasonography, CT and MRI for the diagnosis, assessment of activity and abdominal complications of CT.[51]

	Per-patient sensitivity (95% CI)	Per-patient specificity (95% CI)	Important findings
At diagnosis			
Ultrasonography vs endoscopy	85% (83–87)	98% (95–99)	Factors associated with a diagnosis of CD • Bowel wall thickness ≥4mm • Decreased compressibility of thickened bowel walls, narrowing of the lumen, conglomeration of loops and extramural lesions such as fistulas or abscesses Factors influencing ultrasound accuracy • Disease location and activity (highest sensitivity for anatomic areas easily accessible by ultrasound, such as terminal ileum and left colon) • Differences in ultrasound unit resolution, cut-off unit for bowel wall thickness, experience of ultrasonographers
MRI vs endoscopy	78% (67–84)[114–117]	85% (76–90)	Factors associated with a diagnosis of CD • Bowel wall thickness • Wall enhancement after injection of MRI contrast • Presence of oedema Factors influencing MRI accuracy • Distension of the bowel and use of a luminal contrast may affect accuracy of detecting changes associated with active disease
Assessment of disease extent			
Ultrasonography vs other imaging techniques/endoscopy/surgery	86% (83–88%)	94% (93–95%)	• Bowel hydrosonography increases sensitivity for detection of segments with active disease • Hydrocolonic sonography provides high accuracy for assessing colonic lesions
MRI vs other imaging techniques/ endoscopy/surgery (small bowel)	74% (68–80)	91 (86–95)	• May be more useful than ultrasound for assessment of jejunal and ileal lesions
CT vs ileocolonoscopy/surgery	88%	88%	• Sensitivity for detection of lesions in colonic segments was significantly lower than for the ileum
Assessment of disease activity			
Ultrasonography vs other imaging techniques/endoscopy/surgery	85% (79–89)	91% (87–95)	• Wall thickness and angiographic vascularisation pattern are useful for detection of active disease • Sensitivities and specificities of conventional, Doppler and contrast-enhanced ultrasound are very similar
MRI vs other imaging techniques/ endoscopy/surgery (terminal ileum and/or colon)	80% (77–83)	82% (78–85)	• MRI may achieve a similar sensitivity to ultrasound if adequate luminal distension is achieved
CT vs other imaging techniques/ endoscopy/surgery (terminal ileum)	81% (77–86)	88% (82–91)	

small bowel involvement and to rule out complications such as stenosing or penetrating disease, which may not be detected by symptom assessment or endoscopy alone. A systematic review of published studies calculated the specificity and sensitivity of MRI in the diagnosis of CD to be 78% and 85%, respectively; corresponding values for ultrasonography were 85% and 98%, respectively (Table 1).[51] The accuracy of CT for CD diagnosis has not been robustly evaluated in prospective studies.[51]

A number of findings at MRI have been validated for the diagnosis of active and severe CD, and quantitative indices of activity have been developed to facilitate objective interpretation of MR images.[52,53] MR enterography is our preferred modality for baseline assessment. It is accurate

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Table 2 Summary of recommendations on monitoring for patients with Crohn's disease.

	At diagnosis	Symptomatic patient	Asymptomatic patient	Post-operative patient
Symptoms	Perform in all patients: Use standardised tool (e.g. CDAI or HBI)	Perform 3–6 months after commencing immunosuppressives and 8–12 weeks after commencing biologics: Use standardised tool (e.g. CDAI or HBI)	Perform at each visit as part of global assessment of remission: Use standardised tool (e.g. CDAI or HBI)	Perform 3 months post surgery, every 3 months in the first year following surgery and every 6–12 months thereafter: Use standardised tool (e.g. CDAI or HBI)
Endoscopy	Perform in all patients: Ileocolonoscopy + biopsies; in specific patients, consider upper-GI endoscopy, SBCE or enteroscopy Use precise standardised descriptions of lesions	Perform when therapeutic decisions are required: Extent determined by known sites of involvement and clinical presentation Use precise standardised descriptions of lesions	Perform if concerned about disease progression or when therapeutic decisions are required: Ileocolonoscopy or upper-GI endoscopy as appropriate Use precise standardised descriptions of lesions	Perform 6–12 months post surgery and to confirm post-operative recurrence: Ileocolonoscopy or capsule endoscopy as appropriate Use Rutgeerts score to measure recurrence in neo-terminal ileum
Laboratory parameters	Perform in all patients: Complete blood count, liver profile, albumin, iron studies, renal function, CRP, faecal calprotectin or lactoferrin	Perform when starting or switching therapy and as required thereafter according to disease severity, treatment type and therapeutic response: Complete blood count, liver profile, albumin, iron studies, renal function, CRP, faecal calprotectin or lactoferrin	Perform every 3–12 months as part of the global assessment: Complete blood count, liver profile, albumin, iron studies, renal function, CRP, faecal calprotectin or lactoferrin	Perform 3 months post-surgery, after the first endoscopy, and every 3–6 months thereafter: Complete blood count, liver profile, albumin, iron studies, renal function, vitamin B12, CRP, faecal calprotectin or lactoferrin
Imaging	Perform in all patients: To assess the extend and severity of small bowel involvement and presence of complications Use MR enterography or small bowel ultrasonography	Perform prior to starting therapy, particularly in high-risk patients: To assess the extend and severity of small bowel involvement and presence of complications Use MR enterography or small bowel ultrasonography; limit CT use	Perform if there is concern about disease progression or when new therapeutic modifications are considered: Use MRI or abdominal ultrasonography; limit CT use	Perform when disease activity or structural complications are suspected and endoscopy is inconclusive or not available: Use MR enterography, contrasted-enhanced ultrasonography; limit CT use

CDAI, Crohn's disease Activity Index; CDEIS, Crohn's Disease Endoscopic Index of Severity; CRP, C-reactive protein, CT, computed tomography; GI, gastrointestinal; HBI, Harvey–Bradshaw Index; IBDQ, Inflammatory Bowel Disease Questionnaire; MR, magnetic resonance; SBCE, small-bowel capsule endoscopy; SES-CD, Simple Endoscopic Score for Crohn's Disease.

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for establishing disease extent and severity,[51,52,54] has been shown to be as effective as endoscopy for diagnosis of CD in some studies,[55,56] and is superior to conventional enteroclysis and small-bowel follow-through (SBFT).[57] Dedicated small-bowel ultrasonography, a standard diagnostic tool in many countries, may also be useful where expertise exists.[33] Small-bowel contrast-enhanced ultrasonography is superior to plain abdominal ultrasound and SBFT in detecting and documenting the extent of small-bowel lesions in CD.[58] Contrast-enhanced pelvic MRI and/or rectal or transperineal ultrasonography are advocated, in combination with examination under anaesthesia, to evaluate the anatomy, extent and severity of perianal disease and detect perianal abscesses needing urgent treatment.[59] MRI can also evaluate fistula anatomy and differentiate between simple and complex fistulas, as well as determine therapeutic effect in fistulising CD patients.[60] Anorectal ultrasound can also detect lesions of the internal and external anal sphincters, evaluate the presence of interspincteric abscess and guide transcutaneous drainage[61]; however, because of the discomfort associated with this procedure, pelvic MRI is favoured where possible.

3.2. Symptomatic patients

Routine monitoring of symptomatic patients is important to optimise therapy and ensure adequate response. We advise that symptoms are assessed at each visit, the frequency of which will depend on disease severity, treatment and response. Again, the consistent use of a standardised tool[9–12] will likely help assessment of response to treatment. We advocate that symptoms be re-evaluated 2–4 weeks after initiating steroids, 3–6 months after initiating immunosuppressive therapy[62] and 8–12 weeks after initiating biological therapy.[63] More frequent visits are recommended in patients with moderate-to-severe disease to rule out deterioration of the clinical condition. If a patient has symptoms that persist despite treatment, further investigations should be performed to rule out complications and reassess disease severity.

Objective evidence of inflammation is of utmost importance in patients being considered for biological therapy. In a post-hoc exploratory analysis of the SONIC study, which compared infliximab monotherapy, azathioprine monotherapy, and the two drugs combined in 508 adults with moderate-to-severe CD who had not undergone previous immunosuppressive or biologic therapy, the effects of infliximab were significantly more pronounced in patients with elevated baseline CRP levels, baseline mucosal lesions, and both elevated baseline CRP levels and mucosal lesions.[64] This underscores the importance of endoscopic exploration or evaluation of inflammatory biomarkers prior to starting treatment. SBCE or enteroscopy may be considered to look for mucosal lesions in patients with negative ileocolonoscopy and imaging evaluations when objectively establishing the presence of disease activity before the initiation of biological therapy.

While mucosal healing has been associated with improved clinical outcomes in CD,[3,65–68] there is a paucity of evidence to guide endoscopic monitoring in symptomatic patients during treatment. A poor correlation exists between endoscopic inflammation and symptom scores after steroid treatment[69]; however, this correlation may be better with biologic treatment.[70] We suggest that endoscopy should be performed to evaluate therapeutic response in patients with persistent or recurrent symptoms despite therapy or more globally when there is a doubt about disease control and concern about disease progression. The extent of endoscopic re-evaluation should be determined based upon known sites of involvement and clinical presentation.

Our recommendation is that performance of a limited number of laboratory investigations has value in the monitoring of symptomatic patients to assess disease activity and exclude intercurrent infection. Prospective studies have established the value of CRP as a marker of the presence and severity of inflammatory activity,[1,19,20,22,45,71–74] although it should be noted that CRP may be normal in patients with active CD.[46] Furthermore, CRP may have a role in evaluating response to therapy. For example, in CD patients treated with anti-tumour necrosis factor (TNF) therapy, an elevated baseline CRP has been shown to correlate with response[75,76] and early normalisation of CRP levels predicts sustained long-term response and mucosal healing.[77] Faecal calprotectin and, to a lesser degree, lactoferrin can be used to differentiate between clinically active and inactive IBD, as well as estimate the degree of mucosal inflammation, as they correlate better with endoscopic inflammation than CRP or white blood cell count.[20,25,32,78–81] Faecal markers may also have a role in the monitoring of therapeutic response: in clinical trials of CD therapies, "normalisation" of faecal markers appeared to be a useful and reliable surrogate for mucosal improvement and healing.[78,79] However, as with CRP, it should be noted that faecal calprotectin and lactoferrin may be normal in patients with clinically and endoscopically active CD, particularly ileal disease.[32] We advise that inflammatory markers should be assessed to confirm active disease before starting or switching therapy,[64] with reassessment at intervals determined by disease severity, treatment type and therapeutic response.

Symptomatic patients with small-bowel disease should have small-bowel cross-sectional imaging prior to starting therapy (and during therapy if they remain symptomatic) to assess the activity of the disease and exclude complications. Currently, the frequency of repeat imaging will depend on the clinical circumstances. The optimum frequency of assessment is unknown. For assessment of complications, plain radiographs are useful in patients with severe or fulminant symptoms for detection of bowel obstruction, perforation or toxic megacolon.[82] Routine use of CT enterography should be avoided because of the radiation risk. However, contrast-enhanced CT of the abdomen/pelvis or ultrasonography is useful and necessary in acutely ill patients to rule out complications, such as intra-abdominal abscess.[83,84] MR enterography should be used to assess the extent and severity of small-bowel disease. MRI parameters have been found to correlate with acute inflammatory score.[85] Small-bowel ultrasonography may also be useful, particularly in patients with disease located in the terminal ileum.[51]

3.3. Asymptomatic patients

In asymptomatic patients, monitoring is needed to ensure sustained control of inflammation beyond symptoms. Patients in remission will typically visit the clinic every 3–6 months, although patients with very indolent and stable disease may only need to be seen every 12 months.

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Symptom assessment forms part of a global approach to assess remission at each visit.[86] At the very least, the HBI or another standardised symptom assessment tool should be used to allow assessments to be longitudinally evaluated using quantitative criteria.[9–12]

Endoscopy is invasive and is not typically used to assess asymptomatic patients, other than when therapy cessation is being considered after a long-term remission or when there is discrepancy between symptoms and objective measures of inflammation (e.g. elevated CRP or faecal calprotectin). Endoscopic remission (CDEIS = 0) was independently associated with a more than two-fold reduction in risk of relapse in a prospective study of infliximab withdrawal in 115 patients with CD who had been treated for at least 1 year with infliximab and an antimetabolite and had been in corticosteroid-free remission for at least 6 months (hazard ratio 2.3; 95% CI 1.1–4.9; p = 0.04).[87] Endoscopy (ileocolonoscopy in ileocolonic disease and upper-GI endoscopy in patients with upper-GI involvement) ought to be considered in asymptomatic patients when there is concern about disease progression and when therapeutic modifications are considered. Precise standardised description of endoscopic lesions including type, location, depth and extent is advocated.

We suggest that laboratory investigations form a routine part of the global assessment at each visit in asymptomatic patients. Complete blood count, liver profile and renal function should be conducted every 3–12 months to monitor treatment side effects. Monitoring CRP and faecal calprotectin is a useful trigger for re-exploration by endoscopy and/or cross-sectional imaging. CRP may be useful in predicting short-term prognosis and relapse.[21,88,89] The prognostic value of stool markers to predict relapse is of major interest in view of their correlation with endoscopic activity in CD,[25,32] and there is evidence to support the use of calprotectin and, to a lesser degree, lactoferrin in this setting. In studies evaluating a single faecal sample, calprotectin was a reliable predictor of relapse in IBD with colonic involvement over a 1-year follow-up period.[26,90–96] However the optimal cut-off threshold has not yet been established and may depend on the clinical situation and the desire to favour high sensitivity over high specificity or vice versa. A continuous comparison between serial CRP values should be performed in individual patients, with any increase above previous values prompting further investigation for possible relapse.

There are very few data evaluating cross-sectional imaging in the asymptomatic CD patient. Our opinion is that cross-sectional imaging may be appropriate in high-risk patients when concern exists about disease progression, there is a discrepancy between symptoms and inflammatory biomarkers and when therapeutic modifications are being considered. In this setting we advocate MR enterography or abdominal ultrasonography, and the avoidance of repeat exposure to ionising radiation.

3.4. Post-operative patients

Recurrence following a resection for CD is common,[18] with a rate of endoscopic recurrence at the anastomosis of 65–90% within 1 year of surgery.[97–99] Monitoring is needed to detect early recurrence and to identify complications. Although the CDAI has been shown to have some value in identifying post-operative recurrence of CD,[100] there are few data to guide symptom assessment in post-operative patients. CD symptoms should be assessed within 3 months of surgery, preferably using the CDAI or HBI. Symptoms should continue to be monitored regularly (e.g. every 3 months) in the first year following surgery, then every 6–12 months thereafter, depending on the risk of recurrence. It is important to note that symptoms may be functionally derived, particularly in the post-operative setting, highlighting the importance of comprehensive monitoring of post-operative patients.

Disease often first recurs in the absence of symptoms,[97,100,101] and symptoms associated with surgery, particularly diarrhoea, may be misinterpreted as a manifestation of disease recurrence. Therefore, the assessment of objective parameters of inflammation is also required to monitor for postoperative recurrence. Endoscopic recurrence precedes clinical recurrence and severe endoscopic appearance predicts a poor prognosis.[18] Ileocolonoscopy should therefore be the gold-standard monitoring tool in this setting to detect and define the presence and severity of morphological recurrence. We consider that capsule endoscopy is a potential alternative in selected patients who have had mid-small bowel resections that are not evaluable by ileocolonoscopy.[42,102,103] The Rutgeerts score was developed for lesions in the neoterminal ileum and at the ileocolonic anastomosis and correlates with future clinical behaviour[18]; we advocate its use for the assessment of recurrence in the neoterminal ileum. Endoscopy should be performed at 6–12 months following surgery, with the frequency of further endoscopies depending on the findings of the first evaluation and on the future disease course.

Very few studies have evaluated the use of biomarkers in the post-operative setting, and there is no good correlation between CRP (or erythrocyte sedimentation rate) and endoscopy score for recurrence at 1 year.[101] We propose routine laboratory investigations during follow up after ileal or colonic resections, including assessment of vitamin B12 levels, and CRP assessment every 3–6 months. Faecal calprotectin and lactoferrin may have a role in predicting early recurrence[104–106]; therefore, we propose that faecal calprotectin is evaluated 3 months post surgery, with consideration of an earlier endoscopy if an increase is seen, and then after the first endoscopy as in the follow-up of asymptomatic patients.

Cross-sectional imaging may be used where disease activity or structural complications are suspected, and where endoscopy is inconclusive. MR enterography,[107] CT enterography[108] and contrast-enhanced ultrasonography[109] may be used, with the frequency of imaging varying on a case-by-case basis, although data are limited.

4. Future directions

The opinions in this article are largely based on clinical experience, given the current lack of integrated evidence to guide optimal monitoring in CD, particularly with respect to the most appropriate time points for using the available tools in different patient scenarios.

There is a need for simple, reproducible scoring systems and reading methodologies for endoscopy, and for further training in this area. Refinement and validation of endoscopic

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cut-offs is another important area for future research; currently, the level of tolerable mucosal ulceration and the thresholds at which treatment should be intensified for optimal clinical outcomes are unknown. Further validation of non-endoscopic markers of disease activity and treatment response is also awaited, as is the development and validation of new biomarkers and other surrogates of endoscopy. In addition, we need to standardise documentation for patients with CD to allow ease of transfer between healthcare teams and sites.

Available instruments measure disease activity at a fixed point in time. The Lémann score, currently the subject of a cross-sectional validation study, will enable the assessment of cumulative structural damage to the bowel as measured by appropriate imaging modalities and medical history. It has potential for use initially within clinical studies to assess the effect of therapies on the progression of bowel damage.

A number of ongoing clinical studies will provide further data and assess the impact on clinical outcomes of a 'tight control' approach to treatment, based around objective parameters of inflammation. Long-term studies are needed to define and validate the optimal treatment targets in CD. There is much interest currently in the concept of 'deep remission' (defined in the EXTEND study as combined mucosal healing and symptomatic remission[4]) as a potential treatment goal.

5. Conclusions

The IBD Ahead 2011 programme has informed practice guidance for the monitoring of patients with CD to facilitate the achievement of tight disease control through sustained control of inflammation in this progressive condition. Key points include the need to measure and record baseline parameters to enable subsequent tracking of disease activity and progression of lesions; to adopt different approaches in different patient scenarios; to regularly monitor disease activity using objective markers of inflammation, rather than relying on symptomatic assessment; to measure and document precise and standardised descriptions of endoscopic lesions including type, location, depth and extent; and to use cross-sectional imaging for complete assessment of lesions where necessary, and for assessment of stenosing and penetrating complications. We hope that this provides helpful guidance to gastroenterologists in the monitoring of CD within daily clinical practice.

Disclosure

The Annual excHangE on the ADvances in Inflammatory Bowel Disease (IBD Ahead) 2011 educational programme was conducted to develop practice recommendations for the optimal monitoring of Crohn's disease based on evidence and/or expert opinion. The programme involved approximately 600 gastroenterologists from 36 countries, who were selected for participation by AbbVie. This manuscript reports the outcomes from the IBD Ahead 2011 programme. This international survey and discussion programme culminated in the agreement of statements relating to the monitoring of Crohn's disease activity. AbbVie is the sole sponsor for the IBD Ahead programme and provided funding to invited participants, including honoraria for their attendance at the meetings. AbbVie participated in developing the content for the meeting, but was not involved in the development or review of the manuscript with the authors or the vendor. This manuscript reflects the opinions of the authors. The authors determined the final content, and all authors read and approved the final manuscript. No payments were made to the authors for the development of this manuscript.

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Appendix A. IBD Ahead 2011 Statements on the Optimal Monitoring of Crohn's Disease in Clinical Practice

Approximately 600 gastroenterologists from 36 countries participated in the IBD Ahead 2011 programme, which was overseen by an International Steering Committee (ISC) made up of gastroenterology specialists (members are listed in Acknowledgements) and chaired by two authors of this paper, Professor Colombel and Dr Panaccione. In addition, each participating country had its own National Steering Committee.

The programme took place between December 2010 and September 2011 and consisted of several stages. Market research identified key areas of uncertainty in the monitoring of CD in clinical practice. The ISC then reviewed the data collected to develop clinical questions relating to optimal monitoring of CD patients in clinical practice. Feedback was grouped into areas pertaining to: symptom assessment, endoscopic assessment, laboratory markers and cross-sectional imaging. Five researchers (PP, AI, KK, HA and PM) were nominated by the ISC to evaluate published evidence on CD activity monitoring and develop answers to the clinical questions. PubMed, Embase and the Cochrane Library were searched using pre-defined search strings and limits, and additional searches were conducted by hand as required. No time limits were included in the search criteria. Abstracts from the following conferences were searched: European Crohn's and Colitis Organisation Congress 2010, 2011; Digestive Disease Week 2010, 2011; and United European Gastroenterology

Week 2009, 2010. National meetings were held to gather expert opinion on the proposed answers. Where published evidence was not available, experts provided best practice guidance. Consolidated answers were generated and levels of published evidence were assigned to each answer, according to criteria from the University of Oxford Centre for Evidence Based Medicine (http://www.cebm.net/index.aspx?o=1025). An international meeting was then held with experts from each of the 36 participating countries. Participants voted on their level of agreement with each answer using a scale of 1 to 9 (where 1 = strong disagreement and 9 = strong agreement). If ≥75% of participants scored within the 7–9 range, then the answer was deemed to be agreed upon. If <75% of participants scored within this range, the answer was debated and revised, and a second vote was taken. Again, if ≥75% of participants scored within the 7–9 range, the answer was deemed to be agreed upon. If agreement was not reached at this stage, a lack of agreement was noted. The results are noted below.

Statements on optimal monitoring of Crohn's disease in clinical practice

1. Which assessments should be used at diagnosis?
   - 1.a. Symptom monitoring
     - 1.a.1. The CDAI and HBI, as well as the IBDQ, are validated tools for evaluating symptoms before patients enter clinical trials[9–12] (Level A) — 92% agreed.
     - 1.a.2. In clinical practice, gastroenterologists rely on their global clinical judgement when assessing symptoms; assessments may be more comparable longitudinally if the CDAI or HBI is used (Level D) — 90% agreed.
     - 1.a.3 Symptom assessment tools should be used in all patients to establish a baseline value for future comparison (Level D) — 85% agreed.
   - 1.b Endoscopy
     - 1.b.1 Ileocolonoscopy, with visualisation [precise description of lesions], of the terminal ileum and all colonic segments should be performed[39–41] (Level A); at least two biopsies of every segment and the rectum, including areas that appear normal and abnormal, should be taken to support diagnosis (Level D) — 85% agreed.
     - 1.b.2. Upper GI endoscopy and biopsies are useful, particularly in paediatric patients and in adult patients with upper GI symptoms (Level D) — 90% agreed.
     - 1.b.3. SBCE is recommended to support diagnosis in patients with a high clinical suspicion of CD with inconclusive ileocolonoscopy, gastroscopy and imaging evaluations[42,102] (Level B) — 88% agreed.
     - 1.b.4. Enteroscopy is recommended when abnormalities exist only in areas where traditional endoscopic procedures for tissue biopsy are not possible (Level D) — 87% agreed.
     - 1.b.5. Precise standardised description of endoscopic lesions including type, location, depth and extent is advocated (Level D). This may be achieved by utilising endoscopic scoring tools such as the CDEIS or the SES-CD — 86% agreed.
     - 1.b.6. Endoscopy should be performed in all patients at baseline to establish location, extent and severity of disease (Level D) — 96% agreed.
   - 1.c Laboratory-based monitoring
     - 1.c.1. Routine laboratory investigations should be conducted, including complete blood count, liver profile, albumin, iron studies, renal function and vitamin B12 (Level D) — 83% agreed.
     - 1.c.2. CRP should be assessed as a marker of inflammation (Level D); patients with CD may have normal CRP levels — 95% agreed.
     - 1.c.3. Faecal calprotectin, and to a lesser degree lactoferrin, can be assessed as a marker of intestinal inflammation (Level B)[17,21–24] to differentiate between intestinal inflammation and IBS (Level B)[24,28,30,31,48–50]; stool analysis and culture, and *C. difficile* toxin testing is also recommended (Level D) — 90% agreed.
     - 1.c.4. Routine laboratory and inflammatory marker assessments should be conducted in all patients, where available, to establish a baseline value for future comparison (Level D) — 94% agreed.
   - 1.d. Cross-sectional imaging
     - 1.d.1. MR enterography, where available, or CT if not, is the recommended modality for baseline assessment and should be used to assess the extent and severity of disease (Level B)[51,52,54–57,118–120]; dedicated small bowel ultrasonography may also be useful where expertise exists (Level B)[33,58]; barium SBFT or enteroclysis should be replaced by the above modalities where available (Level D) — 86% agreed.
     - 1.d.2. MRI, CT and/or ultrasound should be used to detect and rule out disease complications[49–53,55–60] (Level B) — 88% agreed.
     - 1.d.3. Baseline imaging should be performed in all patients to assess the extent and severity of small bowel involvement and to rule out complications such as fibrostenosing or penetrating disease (Level D); the choice of modality may be influenced by availability, which could vary between countries (Level D) — 94% agreed.
2. Which assessments should be used in the symptomatic patient and when should they be used?
2. Routine monitoring of patients through symptom assessment, endoscopic evaluation, laboratory markers and imaging, is important to ensure adequate response to therapeutic interventions and to optimise therapy (Level D) — 94% agreed.
   - 2.a. Symptom monitoring
     - 2.a.1 The CDAI and HBI, as well as the IBDQ, are commonly used in clinical trials, especially for establishing the efficacy of pharmaceutical agents under investigation[6,64,121] (Level A) — 90% agreed.
     - 2.a.2. In clinical practice, gastroenterologists rely on their global clinical judgement when assessing symptoms; assessments may be more comparable longitudinally if the CDAI or HBI is used (Level D) — 93% agreed.
     - 2.a.3. In general, physicians should re-evaluate symptoms 2–4 weeks after initiating corticosteroids, 3–6 months after initiating immunosuppressive therapy, and 8–12 weeks after initiating biologic therapy to establish therapeutic response (Level D) — 89% agreed.
     - 2.a.4. Symptoms that persist despite therapeutic intervention should prompt further investigations to rule out complications and reassess disease severity (Level D) — 99% agreed.
     - 2.a.5. Symptoms should be assessed at each visit, the frequency of which will be determined by disease severity, treatment type and therapeutic response (Level D) — 99% agreed.
   - 2.b. Endoscopy
     - 2.b.1 Mucosal healing has become an important therapeutic goal (Level D) — 92% agreed.
     - 2.b.2. Extent of endoscopic assessment should be determined by known sites of involvement and clinical presentation (Level D) — 85% agreed.

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2.b.3. Capsule endoscopy or enteroscopy may be considered in patients with negative ileocolonoscopy and imaging evaluations (Level D) — 84% agreed.
2.b.4. Precise standardised description of endoscopic lesions including type, location, depth and extent is advocated (Level D). This may be achieved by utilising endoscopic scoring tools such as the CDEIS and SES-CD — 94% agreed.
2.b.5. Endoscopic evaluation should be performed to assess ongoing disease activity, especially when other objective evidence of active disease is absent, or to evaluate therapeutic response in patients with persistent or recurrent symptoms despite therapy (Level D) — 94% agreed.
2.b.6. There is insufficient evidence to recommend routine repeat endoscopy in symptomatic patients; it should be considered in patients in whom it will affect further therapeutic decisions (Level D) — 96% agreed.

2.c. Laboratory-based monitoring
2.c.1. Laboratory investigations should be conducted in all symptomatic patients to assess disease activity and exclude intercurrent infection (Level D) — 95% agreed.
2.c.2. CRP should be assessed as a marker of inflammation in all symptomatic patients[1,19,20,22,45,71–74] (Level A) — 94% agreed.
2.c.3. Faecal calprotectin, and to a lesser degree lactoferrin, can be used as a marker of intestinal inflammation in symptomatic patients[17,21,63–67] (Level B) — 90% strongly agreed.
2.c.4. Inflammatory markers should be assessed to confirm disease activity prior to starting or switching therapy (Level D) — 95% agreed.
2.c.5. The frequency of reassessment of inflammatory markers will be determined by disease severity, treatment type and therapeutic response (Level D) — 96% strongly agreed.

2.d. Cross-sectional imaging
2.d.1 MR enterography is the preferred mode to assess the extent and severity of small bowel disease (Level A)[51,85]; small bowel ultrasonography may also be useful (Level B).[51] Due to the radiation risks associated with CT enterography, routine use is not recommended (Level D) — 84% agreed.
2.d.2. A plain radiograph is useful in patients with severe symptoms for the detection of bowel obstruction, perforation or toxic colon distension (Level B)[82] — 86% strongly agreed.
2.d.3. Contrast-enhanced CT of the abdomen/pelvis or ultrasonography is useful in acutely ill patients to rule out complications such as intra-abdominal abscess[83,84] (Level B) — 91% agreed.
2.d.4. Pelvic MRI (Level A) and/or transperineal (Level C)[60,122,123] and rectal ultrasonography (Level B)[61] should be used to assess perianal disease and rule out perianal abscess; imaging should be performed in combination with examination under anaesthesia (Level D) — 85% agreed.
2.d.5. Small-bowel imaging is recommended in symptomatic patients with small bowel disease prior to starting therapy, especially in high-risk patients where it can be used to monitor disease extent and severity and therapeutic response (Level D) — 81% agreed.
2.d.6. The frequency of imaging should be based on the clinical situation; due to the radiation risks associated with CT enterography, its use should be limited (Level D) — 99% agreed.

3. Which assessments should be used in the asymptomatic patient and when should they be used?
3. It is acknowledged that there is a disconnect between symptoms and inflammatory disease activity; therefore, a strategy to monitor disease beyond symptoms should be adopted, and may include laboratory markers, endoscopy and imaging (Level D) — 98% agreed.

3.a. Symptom monitoring
3.a.1. The CDAI and HBI, as well as the IBDQ, are used for monitoring patients participating in clinical trials, who achieve remission (Level A)[6,64,124] — 96% agreed.
3.a.2. In clinical practice, gastroenterologists rely on their global clinical judgement when assessing symptoms; assessments may be more comparable longitudinally if the CDAI or HBI is used (Level D) — 97% agreed.
3.a.3. Symptom assessment is part of a global approach to assess remission at each visit[86] (Level B) — 94% agreed.
3.a.4. Symptoms should be assessed at each visit, the frequency of which is dependent on the patient's treatment regimen, but typically every 3–6 months (Level D) — 82% agreed. [Note added in manuscript development: Patients in remission will typically visit the clinic every 3–6 months, although patients with very indolent and stable disease may only need to be seen every 12 months.]

3.b. Endoscopy
3.b.1 Ileocolonoscopy is recommended in ileocolonic disease; in patients with upper GI involvement, upper GI endoscopy is recommended (Level D) — 89% agreed.
3.b.2. Precise standardised description of endoscopic lesions including type, location, depth and extent is advocated (Level D). This may be achieved by utilising endoscopic scoring tools such as the CDEIS and SES-CD — 90% agreed.
3.b.3. Endoscopy in asymptomatic patients may be appropriate when there is concern about disease progression and when therapeutic modifications are considered (Level D) — 88% agreed.

3.c. Laboratory-based monitoring
3.c.1. Laboratory investigations should be part of the global assessment in an asymptomatic patient (Level D) — 94% agreed.
3.c.2. CRP should be assessed as a marker of inflammation[21,88,89] (Level A) — 97% agreed.
3.c.3. Faecal calprotectin (Level B) and lactoferrin (Level C) can be assessed as markers of intestinal inflammation (Level B)[25,73–79] — 96% agreed.
3.c.4. Inflammatory markers should be assessed at each visit (Level D) — 78% agreed.
3.c.5. Routine monitoring of inflammatory markers should be performed on an individual basis and performed every 3–12 months (Level D) — 94% agreed.

3.d. Cross-sectional imaging
3.d.1. MRI/enterography/enteroclysis or abdominal ultrasonography are preferred (Level D); repeated exposure to ionising radiation should be avoided (Level D) — 94% agreed. [Note added in manuscript development: the authors concluded that MR enteroclysis should not be advocated.]
3.d.2. Imaging in the asymptomatic patient may be appropriate when there is concern about disease progression and when therapeutic modifications are considered (Level D) — 94% agreed.

4. Which assessments should be used in the post-operative patient and when should they be used?

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4.a. Symptom monitoring
- 4.a.1. It is acknowledged that disease may recur in the absence of symptoms, and therefore symptoms alone are inadequate when monitoring for post-operative recurrence[97,100,101] (Level A) — 97% agreed.
- 4.a.2. In clinical practice, gastroenterologists rely on their global clinical judgement when assessing symptoms; assessments may be more comparable longitudinally if the CDAI or HBI is used (Level D) — 88% agreed.
- 4.a.3. Symptoms should be assessed within 3 months post surgery (Level D) — 78% agreed.
- 4.a.4. Symptoms should be assessed regularly (for instance every 3 months) in the first year after surgery, and then every 6–12 months depending on the risk (Level D) — 88% agreed.

4.b. Endoscopy
- 4.b.1. Ileocolonoscopy should be the standard-of-care monitoring tool (Level B)[39–41]; capsule endoscopy is a potential alternative in selected patients (Level D) — 80% agreed.
- 4.b.2. Rutgeerts score should be used to assess recurrence in the neo-terminal ileum (Level D) — 88% agreed.
- 4.b.3. Endoscopy should be performed 6–12 months after surgery (Level D) — 89% agreed.
- 4.b.4. Endoscopy may be used to confirm the diagnosis of post-operative recurrence by defining the presence and severity of morphologic recurrence (Level B)[18] — 93% agreed.
- 4.b.5. The frequency of further endoscopies depends on the findings of the first endoscopy after surgery, and on future disease course (Level D) — 91% agreed.

4.c. Laboratory-based markers
- 4.c.1. Routine laboratory investigations, including vitamin B12 levels, should be conducted (Level D) — 91% agreed.
- 4.c.2. CRP assessment should be conducted[101] (Level C) — 87% agreed.
- 4.c.3. Faecal calprotectin and lactoferrin assessments may be conducted[104–106] (Level C) — 88% agreed.
- 4.c.4. Faecal calprotectin may identify patients with early recurrence[104–106] (Level C). This may be done at 3 months post surgery and after first endoscopy. CRP may be measured at regular visits (Level D) — 96% agreed.
- 4.c.5. As there is a disconnect between symptoms and endoscopic disease activity, routine monitoring of inflammatory markers every 3–6 months is recommended (Level D) — 87% agreed.

4.d. Cross-sectional imaging
- 4.d.1. MR enterography(Level C), CT enterography (Level C) and contrast-enhanced ultrasonography (Level C) may be used[49–53,55–60] — 87% agreed.
- 4.d.2. Imaging may be used when disease activity or structural complications are suspected, and endoscopy is inconclusive (Level D) — 93% agreed. [Note added in manuscript development: the authors further refined this statement to: Cross-sectional imaging may be used when disease activity or structural complications are suspected, and endoscopy is inconclusive.]
- 4.d.3. The frequency of cross-sectional imaging should be based on individual cases; due to the radiation risks associated with CT enterography, routine use is not recommended (Level D) — 97% agreed.

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