

Monitoring Disease Activity and Progression in Crohn's Disease. A Swiss Perspective on the IBD Ahead 'Optimised Monitoring' Recommendations

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Key Words

Chronic inflammatory bowel disease · Crohn's disease · Disease monitoring · Recommendations · Best-practice guidelines · Endoscopy · Multidetector computed tomography · Calprotectin · Small intestine contrast ultrasonography · Contrast-enhanced ultrasound

Abstract

Background and Aims: The structured IBD Ahead 'Optimised Monitoring' programme was designed to obtain the opinion, insight and advice of gastroenterologists on optimising the monitoring of Crohn's disease activity in four settings: (1) assessment at diagnosis, (2) monitoring in symptomatic patients, (3) monitoring in asymptomatic patients, and (4) the postoperative follow-up. For each of these settings, four monitoring methods were discussed: (a) symptom assessment, (b) endoscopy, (c) laboratory markers, and (d) imaging. Based on literature search and expert opinion compiled during an international consensus meeting, recommendations were given to answer the question 'which diagnostic method, when, and how often'. The International IBD Ahead Expert Panel advised to tailor this guidance to the healthcare system and the

special prerequisites of each country. The IBD Ahead Swiss National Steering Committee proposes best-practice recommendations adapted for Switzerland. **Methods:** The IBD Ahead Steering Committee identified key questions and provided the Swiss Expert Panel with a structured literature research. The expert panel agreed on a set of statements. During an international expert meeting the consolidated outcome of the national meetings was merged into final statements agreed by the participating International and National Steering Committee members – the IBD Ahead 'Optimized Monitoring' Consensus. **Results:** A systematic assessment of symptoms, endoscopy findings, and laboratory markers with special emphasis on faecal calprotectin is deemed necessary even in symptom-free patients. The choice of recommended imaging methods is adapted to the specific situation in Switzerland and highlights the importance of ultrasonography and magnetic resonance imaging besides endoscopy. **Conclusion:** The recommendations stress the importance of monitoring disease activity on a regular basis and by objective parameters, such as faecal calprotectin and endoscopy with detailed documentation of findings. Physicians should not rely on symptoms only and adapt the monitoring schedule and choice of options to individual situations.

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Introduction

Crohn's disease (CD) is a chronic inflammatory disease of the gastrointestinal tract that may lead to irreversible bowel damage such as strictures or fistulae. Despite absence of clinical symptoms, subclinical inflammation often persists and reflects the progression of the disease. Disease progression, frequently resulting in structural gut wall damage, often requires surgical interventions and is frequently associated with some loss of organ function. Therefore, a shift of the therapeutic target has been evolving from symptomatic remission towards mucosal healing to prevent structural gut wall damage. The absence of symptoms and lack of inflammatory markers in association with mucosal healing has also been termed as 'deep remission' which has been suggested as a new treatment target [1, 2]. Along the trajectory towards this target, however, a relevant number of questions remain open. As mucosal healing cannot be expected to occur in all or the vast majority of symptom-free patients, the way of disease monitoring depends on the treatment target. Based on the new treatment targets and subsequent new monitoring challenges, the IBD Ahead programme 2011 identified the most relevant unanswered questions relating to the monitoring of disease activity and progression in CD [3].

By means of a structured consensus-finding process, key clinical data and experience were collected to define the best practice of monitoring in regard to symptom assessment, biological markers, endoscopy, and imaging. These data were consolidated to provide case-based evidence to complement the current ECCO guidelines for the management of CD. Following the international consensus, the programme encourages adaptation according to the situation in the different countries. For Switzerland, several aspects are specific which are not typical for a number of countries involved in the consensus process. First, faecal calprotectin is already a well-established marker to assess the presence or absence (i.e. mucosal healing) of mucosal inflammation, which is readily used in Switzerland but, mainly due to logistical or reimbursement reasons, much less so in many other countries. Second, magnetic resonance imaging (MRI) is accessible for most Swiss patients, whereas in other countries such as the United States or United Kingdom, computed tomography (CT) is easier accessible than MRI. Furthermore, ultrasonography (US), an excellent monitoring tool, is performed by gastroenterologists in Switzerland, which is not the case in many European countries or in the United States.

If applicable, for each item evidence or a recommendation was sought to answer the questions – Which patient? When? How often?

The literature was reviewed to generate evidence-based recommendations. These were discussed and assessed at national meetings in the 36 participating countries. When published evidence was lacking, experts attending the national meetings compiled best-practice recommendations.

At the International IBD Ahead Meeting in September 2011, in Dusseldorf, the consolidated outcome of the literature reviews plus national meetings' outputs were merged into final statements which were agreed upon by the participating International and National Steering Committee members.

Methods

Based on an initial data collection, the International Steering Committee Meeting selected important unanswered questions and areas of uncertainty in the management of CD. The areas of main interest concerning the monitoring of CD activity were condensed into a framework (table 1) comprising four *clinical settings*, namely patients at baseline, symptomatic patients, asymptomatic patients, and postoperative patients, and four *monitoring methods*, symptom assessment, endoscopy, laboratory markers, and imaging.

To ensure tracking disease activity reliably during the course of the disease, a thorough assessment with detailed documentation at diagnosis is important.

Assessment at Diagnosis

Symptom Assessment

Symptom assessment should be used in each patient during each consultation. In clinical practice, gastroenterologists assess symptoms relying on their global clinical judgement. This simple and readily available method seems adequately reproducible. The International Consensus recommends using symptom assessment tools in all patients and during each consultation to establish a baseline value for future comparison (level D). The Crohn's Disease Activity Index (CDAI) [4], the Harvey-Bradshaw Index (HBI) [5], and the Inflammatory Bowel Disease Questionnaire (IBDQ) [6–9] are validated tools for evaluating symptoms before patients enter clinical trials (level A). A benefit of using the CDAI or HBI is their

Table 1. International IBD Ahead Meeting: the underlying framework for monitoring recommendations in CD

	Symptom assessment	Endoscopy	Laboratory markers	Imaging
Assessment at diagnosis				
Monitoring in symptomatic patients				
Monitoring in asymptomatic patients				
Monitoring in post-operative patients				

For each patient scenario and monitoring method, literature findings and summary statements with evidence levels A–D (University of Oxford (UK) Centre for Evidence-Based Medicine, <http://www.cebm.net/index.aspx?o=1025>) are provided.

usefulness for therapeutic decisions at a later time point. They provide semi-objective information facilitating interpretation by colleagues in the same or different institutions. But CDAI and HBI might be too complex to be performed in daily practice, and there is little evidence from literature that using these scores improves outcomes.

Endoscopy

Endoscopy should be performed in all patients at baseline to establish location, extent, and severity of disease (level D). Independently of stage, lesions should be measured and documented carefully. Precise standardized description of endoscopic lesions including type, location, depth, and extent is advocated (level D). This may be achieved by endoscopic scoring tools such as the Crohn's Disease Endoscopy Index of Severity (CDEIS) or the Simple Endoscopic Score for Crohn's Disease (SES-CD).

Ileocolonoscopy, with visualisation of the terminal ileum and all colonic segments, should be performed (level A) [1, 10, 11]; at least two biopsies of every segment and the rectum (in areas that appear both normal and abnormal), should be taken to support diagnosis (level D) [12].

For the detection of upper gastrointestinal involvement, gastroscopy is recommended. Double balloon endoscopy or enteroscopy should be performed in suspected cases of small intestinal involvement (level A) [13–16].

Upper gastrointestinal endoscopy and biopsies are useful, particularly in paediatric patients and in adult patients with upper gastrointestinal symptoms (level D) [17–22].

Small-bowel capsule endoscopy (SBCE) or enteroscopy are recommended to support diagnosis in patients with a high clinical suspicion of CD with inconclusive ileocolonoscopy, gastroscopy and imaging evaluations (level B) [23–35]. Strictures should be excluded previously (level B).

Laboratory Markers – Faecal Markers

Routine laboratory and inflammatory marker assessments as well as faecal calprotectin measurement should be conducted in all patients to establish a baseline value for future comparison [36–46] (level D).

The recommended panel of markers are complete blood count, liver profile, albumin, iron studies, renal function, vitamin B₁₂, folic acid, and vitamin D (level D).

C-reactive protein (CRP) should be measured to assess the initial inflammatory response (level D) [47–51]; of note, patients with CD may have normal CRP levels despite clinical activity and mucosal inflammation (level A) [52].

Faecal calprotectin should be assessed as a marker of intestinal inflammation (level B); stool analysis and culture, and *Clostridium difficile* toxin testing is also recommended (level D) [43, 44, 53].

Imaging

The international consensus recommends performing baseline imaging 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).

In a patient with complaints suggestive of IBD, US should be the first-choice imaging modality [54–59] (level B). For an acutely ill patient who is admitted to the emergency unit with suspected CD, abdominal multidetector CT (MDCT) scanning is the recommended modality of choice (level B) [60–62].

To evaluate involvement of the small bowel, magnetic resonance enteroclysis or enterography are advised for staging (level A) [63–68]. The same diagnostic accuracy is provided by CT. CD patients usually undergo multiple abdominal imaging during a lifetime. The burden of ionizing radiation using CT scans is significant and should be minimized (level A) [69, 70]. Therefore, in Switzerland

(and also in other Western European countries, depending on availability) MRI is preferred over CT scan for the initial staging [71]. In the United States it was estimated that up to 0.5–2.0% of cancers could be attributed to the radiation of CT scans. The risks in other countries were found to be comparable (Germany 1.5%, United Kingdom 0.6%) [72–74]. The exact cancer risk of recurrent low-dose radiation is difficult to calculate but it is definitely real. IBD patients are exposed to a significant level of diagnostic ionizing radiation over time. The median radiation exposure in patients with CD was found in a retrospective study to accumulate to 26.6 mSv (range 0–279) during a period of 9 years [75].

For detection of stenosing small bowel lesions in patients presenting with symptoms suggestive of stricturing CD, MRI is superior to barium studies (level B) [76]. In bowel distension, CT enteroclysis is superior to CT enterography (although less tolerated by patients), but diagnostic accuracy of both is comparable for the detection of stenotic lesions (level B) [77–80].

In cases of incomplete colonoscopy due to an impassable colonic stricture, colonic inflammatory lesions of the segment not explored by endoscopy can be evaluated by CT colonography (level B). MDCT techniques are highly accurate for the detection of extraintestinal manifestations, especially for abscesses and fistulae (level A) [68, 81]. MRI is the gold standard to image perianal lesions of patients with suspicion of CD (level A) [82–85]. Anorectal US is helpful to evaluate perianal abscesses (level B). Transdermal perineal US might be helpful to evaluate the exact anatomy of perianal complications (level C) [86–92]. In general, MRI is preferred to a CT scan in order to avoid radiation.

Contrast-enhanced ultrasound (CEUS) and small intestine contrast ultrasound (SICUS) play a limited role in baseline assessment due to lack of standardisation and poor accessibility [93–96].

Monitoring in Symptomatic Patients

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).

Symptom Assessment

In each consultation, symptom assessment should be performed. Persisting symptoms must be evaluated clinically, and appropriate guidance is desirable.

In regard to the choice of tools, the same recommendations apply as in baseline assessment. In everyday clinical practice, CDAI or HBI are sometimes used for therapeutic decisions in patients under immunosuppressive or biologic therapy.

Recommended re-evaluation intervals to evaluate the effect of therapeutic options depend on the chosen modality. Symptom evaluation is done (i) 2–4 weeks after initiating corticosteroids, (ii) 3–6 months after initiating immunosuppressive therapy (with earlier evaluation of side effects), and (iii) 8–12 weeks after initiating biologic therapy.

Endoscopy

In patients with unclear clinical presentation, endoscopy and especially colonoscopy should be performed if the result has an impact on treatment decisions, for instance introducing biological therapy (level D). In this case, endoscopic confirmation of disease activity is appropriate unless there is other objective evidence of active disease (level D). Before endoscopy, calprotectin may be used as a surrogate marker for inflammatory activity (level B) [42–44, 97].

The frequency of endoscopy is directed by clinical symptoms (level D). The type of endoscopic assessment should be determined by known sites of involvement and clinical presentation (level D). Capsule endoscopy or enteroscopy may be considered in patients with negative ileocolonoscopy and imaging evaluations (level D) [24, 98–101].

Laboratory Markers

Laboratory investigations should be conducted in all symptomatic patients (as well as prior to starting therapy) to assess disease activity and exclude intercurrent infection (level D). Blood markers should be used in clinical worsening and in suspicion of disease flare (level B) [102].

CRP is a helpful marker to monitor systemic inflammation in symptomatic patients (level A/Swiss consensus: level B) [102]. Concomitant complete blood count is recommended (level B) [103]. Faecal calprotectin can be used as a surrogate marker for inflammatory activity (level A) [42–44, 97] and to discriminate from functional symptoms (level C). Faecal cultures should be taken to exclude bacterial infections (level D). *C. difficile* infection should be ruled out [104, 105]. Faecal cultures for parasites should be taken three times. Especially in patients under immunosuppressive therapy, biopsies should be taken to search for cytomegalovirus [106, 107].

The frequency of re-assessments will be determined by disease severity, treatment type, and therapeutic response (level D).

Imaging

Small Bowel Symptoms

For small bowel symptoms, MRI enterography is the preferred mode to assess the extent and severity (level A) [63–68]. MRI can detect disease activity at a stricture and differentiate between inflammatory or fibrostenotic stricture, but the diagnostic power to discriminate the two has not been adequately evaluated (level B). MRI is also suitable for monitoring disease activity and evaluating CD preoperatively (level B) [108–110]. Small bowel US might also be useful (level B) [111]. Due to the radiation risks associated with CT enterography and barium techniques (level A), their routine use is not recommended (level D) [112–114].

Complications

CT scans are useful in patients with fulminant symptoms to detect bowel obstruction, perforation, or toxic colon distension (level B) [60–62]. Abdominal MDCT is the modality of choice for an acutely ill CD patient presenting in the emergency room. The MDCT findings correlate well with disease activity (level B) [60–62]. Contrast-enhanced CT of the abdomen/pelvis or US are useful in acutely ill patients to rule out complications such as intra-abdominal abscesses (level B) [61, 68, 115, 116].

In suspected acute complications such as strictures, perforations, abscesses, and obstructions, plain abdominal US (level B) and/or CT scans should be used (level D) [57, 117, 118]. MRI is accurate in imaging extraluminal alterations, too (level A).

Pelvic MRI (level A) and/or transperineal (level C) and rectal US (level B) should be used to assess perianal disease and to rule out perianal abscess. Transdermal perianal US might enhance the diagnostic accuracy regarding perianal fistulae and abscesses (level C) [82–92]. Imaging should be performed in combination with examination under anaesthesia (level D).

Due to radiation risks associated with CT enterography, its use should be limited (level D).

The frequency of conventional radiology and CT are directed by the clinical situation (level D). Acute complications, like abscesses, ileus, or perforation, should be diagnosed immediately (level C).

CEUS and specific components (Doppler flow and bowel wall thickness) of US were observed to be appropriate to monitor the efficacy of the therapy; however, the frequency of the follow-up is not defined (level D). CEUS is not frequently used in clinical practice [93–96].

Monitoring in Asymptomatic Patients

As outlined in the Introduction, there is a discrepancy between symptoms and inflammatory disease activity. The rising importance of new treatment targets such as mucosal healing and deep remission require strategies to monitor disease beyond symptoms which may include laboratory markers, endoscopy, and imaging (level D).

Symptom Assessment

The CDAI or HBI, as well as the IBDQ have been used for verifying remission in CD patients (level A). It is not common clinical practice to measure these indices in asymptomatic patients. Evidence exists that there is a continued impact on quality of life by the disease, even when inactive. Therefore, determination of IBDQ in patients in remission might be of value (level B) [6–9]. Symptom assessment tools should be used during each consultation (level D), the frequency of which depends on the patient's treatment regimen, typically every 3–6 months (level D).

In general, physicians should wait 3–6 months before judging efficacy of immunosuppressive therapy and 8–12 weeks before judging biologic efficacy (level D). Side effects need to be evaluated earlier.

Endoscopy

Ileocolonoscopy is recommended in ileocolonic disease; in patients with upper gastrointestinal involvement, upper gastrointestinal endoscopy is recommended (level D). Endoscopy in asymptomatic patients may be appropriate when there is concern about disease progression and when therapeutic modifications are considered (level D). Endoscopic healing is associated with a lower rate of hospitalisation, surgery, steroid- and biological-free remission (level B) [119–124]. There is insufficient evidence to recommend routine endoscopy to assess mucosal healing in all patients, but it is likely to be appropriate within 6 months of starting biological therapy (level D) and is best performed before stopping biological therapy (level C) [125]. Endoscopies without clinical consequence ('routine assessments') should be avoided (level D).

Laboratory Investigations

Laboratory investigations should be part of the global assessment in an asymptomatic patient (level D) at each visit (level D). As a marker of inflammation, CRP and total blood count can be useful to assess inflammation despite absence of clinical symptoms (level B). Calprotectin

can be used as surrogate marker for inflammatory activity (level A).

Routine monitoring of inflammatory markers should be performed on an individual basis and depending on the type of medication (e.g. TNF- α ; level C) every 3–12 months (level D).

Vitamin D and B₁₂ assessments may help to detect disease complications (level B).

Imaging

Imaging in the asymptomatic patient may be appropriate when there is concern about disease progression and when therapeutic modifications are considered (level D). To assess these patients, MRI (enterography, enteroclysis) or abdominal US is preferred (level D). In asymptomatic patients, there is no indication to use conventional radiology or CT (level D). Some clinicians control their symptomless patients with US (level D). US may be helpful to detect inflammation before clinical symptoms occur. The frequency of US examinations should be dependent on the individual risk profile of the patient.

Monitoring in Postoperative Patients

It is acknowledged that disease may recur in the absence of symptoms, and therefore symptoms alone are inadequate when monitoring for postoperative recurrence (level A) [126–128]. A combination of symptom assessment plus endoscopic evidence of recurrence is the present standard of care for assessing outcomes in postoperative CD.

Symptom Assessment

Symptoms should be assessed within 3 months after surgery (level D), followed by regular visits for instance every 3 months in the first year after surgery, then every 6–12 months depending on the risk (level D) as assessed preoperatively.

Endoscopy

Ileocolonoscopy is the gold standard to confirm the diagnosis of postoperative recurrence by defining the presence and severity of morphologic recurrence (level B) and predicting the clinical course (level B) [126, 129–133]. The frequency of further endoscopies depends on the findings of the first endoscopy after surgery, and on the future disease course (level D).

It is recommended to perform ileocolonoscopy between 3 and 6 months postoperatively to check for re-

lapses after surgery (level D) [126, 132, 133]. There is no evidence that performing ileocolonoscopy more than once improves outcomes (level B). Capsule endoscopy is a potential alternative in selected patients (level D). Rutgeerts score should be used to assess recurrence in the neo-terminal ileum (level D).

Laboratory Investigations

Routine laboratory investigations should be conducted (level D), as well as CRP assessments (level C). Calprotectin can indicate disease recurrence after surgery (level C) [134–136]. Determination of vitamin B₁₂ is mandatory after ileocolonic resection (level D) 6 months postoperatively.

Postoperative measurement of faecal markers 6 months after surgery and after first endoscopy is regarded as a suitable non-invasive postsurgery monitoring tool (level D).

There is a disconnection between symptoms and endoscopic disease activity, therefore routine monitoring of inflammatory markers every 3–6 months is recommended (level D). The need for vitamin B₁₂ substitution should be checked regularly (level D).

Imaging

US plays a role in detecting postoperative recurrence in CD. US should be performed 3 months after small bowel resection. In patients at high risk of recurrence, US can be performed regularly even when the index endoscopy 6 months after surgery is normal. SICUS can be a choice to follow-up patients with small bowel resection.

Due to the radiation risks associated with CT enterography, its routine use is not recommended (level D) whereas MRI enterography is a legitimate choice.

Conclusion

Due to good availability of MRI in Switzerland, one of the main characteristics of the country-specific recommendations concerns the reduced use of CT to minimize the radiation burden during the course of the disease. Currently, positron emission tomography does not play a role in the diagnostic management of CD in Switzerland. After establishing a baseline status, endoscopy (in asymptomatic patients) should only be performed if the results trigger a therapeutic consequence. To assess inflammation even in asymptomatic patients, calprotectin can be used as a surrogate marker for inflammatory ac-

tivity in the gastrointestinal tract. Symptom assessment and laboratory evaluation on a regular basis, depending also on the type of therapy, should ensure that the inflammation is continuously inhibited to achieve a sustained remission.

Follow-up of asymptomatic patients by US is an option which is available in Switzerland and that should be used more frequently. Calprotectin is well accepted in Switzerland and should be part of the standard of care in CD as outlined in these recommendations.

In general, Swiss resources for the monitoring of CD patients are excellent. An appropriate use will guarantee optimal care for our patients and will bring us closer to the treatment goal of preventing irreversible bowel wall damage.

Disclosure Statement

Funding: Abbott provided funding for the IBD Ahead programme and for the development of the manuscript. Ulrike S. Novotny (novoMEDtext ag) provided medical writing and editorial support to the authors in the development of the manuscript; financial support for these services was provided by Abbott. The authors maintained complete control over the direction and the content of the paper. Abbott did not review or approve the manuscript content, and had no influence over the manuscript content or the decision to submit for publication.

B.S. has consulted for Abbott/AbbVie Switzerland, Essex/MSD Switzerland, and UCB, and has received speaker's hono-

ria from Abbott, MSD, UCB, and Vifor. C.B. has consulted for Abbott Switzerland, Essex Chemie, MSD Switzerland, Takeda International, UCB, and Vifor Switzerland; has received speaker's honoraria from Abbott, FALK, MSD, UCB, and Vifor, and has received educational grants and research grants from Abbott Switzerland, Essex Chemie, MSD and UCB and Vifor. M.G. has consulted for AbbVie and MSD, and has received speaker's honoraria from AbbVie, UCB and MSD. A.M. has no conflicts of interest to disclose. P.M. has consulted for Abbott Switzerland, AbbVie International, Berlex, Centocor, Delenex, MSD Switzerland and International, UCB, and Vifor Switzerland; has received speaker's honoraria from Abbott, AbbVie, FALK, MSD, UCB, and Vifor, and has received educational grants and research grants from Essex Chemie, MSD, and UCB. A.S. has consulted for AbbVie and MSD, Switzerland; has received speaker's honoraria from AbbVie Switzerland, and MSD Switzerland, and has received research grants from Tillotts Switzerland and MSD Switzerland. F.S. has consulted for Abbott/AbbVie Switzerland, Essex/MSD Switzerland, and UCB; has received speaker's honoraria from Abbott, MSD, UCB, and Vifor, and has received a non-restricted research grant from MSD. S.V. has consulted for Abbott/AbbVie Switzerland, Essex/MSD Switzerland, UCB, Tillotts, Vifor International and Vifor Switzerland; has received speaker's honoraria from Abbott, FALK, MSD, Tillotts, UCB, and Vifor, and has received educational grants and research grants from Abbott, Essex/MSD, UCB. G.R. has consulted for Abbott/AbbVie Switzerland, Abbott International, FALK Germany, Essex/MSD Switzerland, Novartis, Roche, UCB, Tillotts, Vifor International and Vifor Switzerland; has received speaker's honoraria from Abbott, FALK, MSD, Phadia, Tillotts, UCB, and Vifor, and has received educational grants and research grants from Abbot, Ardeypharm, Essex/MSD, FALK, Flamentera, Novartis, Roche, Tillotts, UCB and Zeller.

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