Ileoscopy reduces the need for small bowel imaging in suspected Crohn's disease

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ABSTRACT

INTRODUCTION: In suspected Crohn's disease (CD), current diagnostic guidelines recommend additional small bowel imaging irrespective of the findings at ileocolonoscopy. Magnetic resonance imaging enterography (MRE) and computed tomography enterography (CTE) are regarded first line imaging techniques and should generally precede capsule endoscopy.

MATERIAL AND METHODS: This article brings together results from a prospective blinded diagnostic study of MRE, CTE, capsule endoscopy and faecal calprotectin (fCal) in 93 patients undergoing their first diagnostic work-up for CD.

RESULTS: In patients with suspected CD, fCal is useful for the identification patients without need for colonoscopy or small bowel imaging. Patients with an elevated fCal should undergo colonoscopy including a persistent attempt to intubate the terminal ileum. CD isolated in the upper small bowel is rare, and in patients with a normal ileocolonoscopy or non-complicated CD in the colon and/or terminal ileum, small bowel imaging provides little extra information compared to ileoscopy alone. Small bowel imaging is primarily indicated if ileoscopy is not achieved and capsule endoscopy is recommended as first line imaging technique. If small bowel stenosis is not ruled out, a preceding test with a patency capsule can be performed to avoid capsule retention. MRE and CTE are complimentary modalities preferably used in patients with stenosis detected at ileocolonoscopy or suspicion of extra-intestinal disease complications.

CONCLUSION: Our results suggest that a diagnostic approach different to that described in the guidelines may be expedient.

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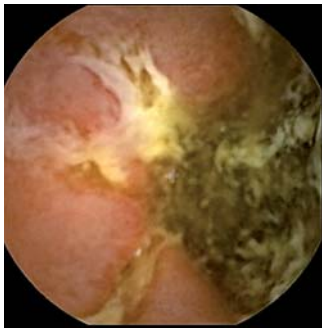
A capsule endoscopy showing longitudinal ulcera in the terminal ileum, which is consistent with Crohn's disease.



ORIGINAL ARTICLE

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There is no single gold standard diagnostic test for Crohn's disease (CD). Even today, CD remains a syndrome diagnosis based on symptoms, physical examination and findings at endoscopy, histology, radiology, biochemical testing and occasionally surgery [1].

CD can affect any region of the gastrointestinal tract – from the mouth to the anus, and often does so discontinuously. At the time of diagnosis, approximately one third of cases have isolated disease in the small intestine, one third colonic disease and one third ileocolonic disease [2, 3]. In approximately 90% of patients, small bowel CD involves the terminal ileum, and CD isolated in the upper small bowel without distal involvement is rare [3]. Ileocolonoscopy is the mainstay for obtaining the diagnosis and an accepted gold standard for assessing ileocolonic CD [1].

In expert hands, ileoscopy is achieved in 85-90% of patients [4]. If the colon is normal and terminal ileum intubation is not achieved during colonoscopy, small bowel imaging plays a central role for obtaining the diagnosis. Conversely, in patients with CD of the colon, the primary purpose of small bowel imaging is to map disease location beyond the reach of the colonoscope.

Current guidelines for diagnosing CD suggest ileocolonoscopy with multiple biopsies from the terminal ileum and each colonic segment as the first diagnostic examination [1]. However, irrespective of the findings at ileocolonoscopy, further investigation is recommended to examine the location and extent of any CD in the upper small bowel (evidence level 5, recommendation grade D). Magnetic resonance imaging enterography (MRE) and computed tomography enterography (CTE) are regarded first line imaging techniques and should generally precede capsule endoscopy [1].

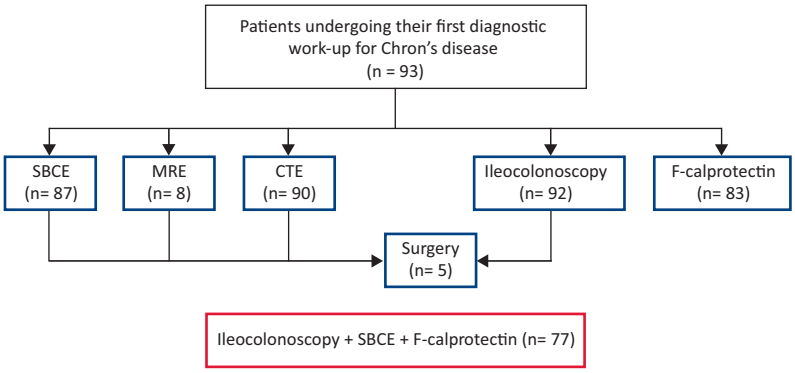
MATERIAL AND METHODS

In this article, we bring together results from a prospective blinded diagnostic study of MRE, CTE, capsule endo-

scopy and faecal calprotectin (fCal) in patients undergoing their first diagnostic work-up for CD [5, 6]. Our data suggest that a diagnostic approach different to that described in the guidelines may be expedient.

FIGURE 1

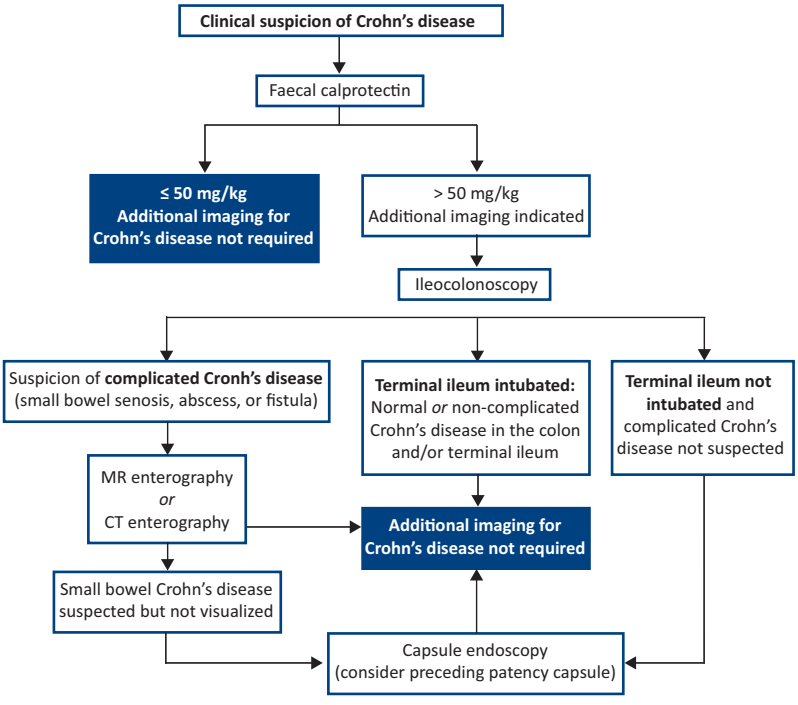
Flow chart showing the number of patients entering the study and completing examinations in accordance with the study protocol. Patient characteristics are described in the original paper [5].



SBCE = small bowel capsule endoscopy; MRE = magnetic resonance enterography; CTE = computed tomography enterography

FIGURE 2

Suggested algorithm for diagnosing Crohn's disease based on results from a prospective study of MR enterography, CT enterography, capsule endoscopy and faecal calprotectin l in 93 patients undergoing their first diagnostic work-up.



CT = computed tomography; MR = magnetic resonance

Trial registration: The study was approved by the Ethics Committee of Southern Denmark (S-20070072) and the Danish Data Protection Agency (journal number: 2007-41-0675). ClinicalTrials.gov identifier: NCT01019460.

RESULTS

Our study population consisted of 93 patients with clinical, endoscopic and/or histological suspicion of CD. Inclusion criteria and patient characteristics are described elsewhere [5, 6]. One study compared sensitivities and specificities of MRE, CTE and capsule endoscopy for detection of CD in the terminal ileum with ileocolonoscopy as gold standard. The other study examined the diagnostic properties of fCal for detection of CD in the same population (only 83 patients provided a stool sample). **Figure 1** shows the number of patients entering the study and completing diagnostic procedures.

Selecting patients for endoscopy

A non-invasive and easily applicable method for selection of patients to invasive procedures is desirable. No clinical index for the diagnosis of CD is available, and biochemical markers of inflammation (C-reactive protein (CRP), orosomucoid, and sedimentation ratio) are limited by inadequate sensitivities [6, 7]. Multiple studies have established fCal as a sensitive marker of intestinal inflammation and a useful tool to discriminate inflammatory bowel diseases from functional disorders [8]. Despite this evidence, fCal has a minor role in the current guidelines for diagnosing CD [1]. In previous studies, fCal was primarily evaluated against colonoscopy, and until recently there has been a lack of evidence regarding the diagnostic performance of fCal in small bowel CD [9, 10]. This aspect is critical because the majority of patients with newly diagnosed CD have small bowel involvement, and the utility of fCal as a screening tool before colonoscopy relies upon equally high sensitivities in all disease locations.

In our population counting 83 patients undergoing their first diagnostic work-up for CD, levels and sensitivities of fCal were equal in colonic and small bowel CD. With a 50 mg/kg cut-off, fCal had a 95% sensitivity for detection of CD and a negative predictive value of 92% (disease prevalence 48%). These performance measures make fCal an effective marker for ruling out CD and for selecting patients for ileocolonoscopy.

Indications for small bowel imaging after ileocolonoscopy

Approximately two thirds of patients with newly diagnosed CD have small bowel involvement [2], but the number of patients with CD isolated to the upper small bowel without distal involvement is low [3]. Hence, it is relevant to question the benefit of additional small

bowel imaging after ileocolonoscopy. A total of 40 patients were diagnosed with CD based on symptoms, clinical and biochemical findings, and the result of ileocolonoscopy with biopsies. Additional imaging yielded the following results (**Table 1**):

- *Normal ileocolonoscopy (n = 43):* A total of three patients (7%; 95% confidence interval (CI): 2-20%) were diagnosed with small bowel CD after additional imaging. However, only one patient (2%; CI: 0.1-14%) had CD located proximal to the terminal ileum and beyond the reach of the colonoscope (i.e. false negative ileocolonoscopy in two patients).
- *CD detected at ileocolonoscopy (n = 31):* A total of 20 patients were diagnosed with CD in the terminal ileum; small bowel imaging confirmed the finding in all patients. Capsule endoscopy (performed in 16/20) suggested disease extension beyond the reach of the colonoscope in 69% (CI: 41-88%). In 11 patients with CD in colon but a normal ileoscopy, CE added no diagnostic information.
- *Colonoscopy without intubation of the terminal ileum (n = 18):* Among patients with a normal colonoscopy or newly diagnosed CD in the colon in whom terminal ileum intubation was not achieved, additional imaging detected small bowel CD in four (22%; CI: 7-48%).

TABLE 1

Results of ileocolonoscopy and small bowel imaging in 93 patients undergoing their first diagnostic work-up for Crohn's disease. The table shows the result of colonoscopy in patients with and without terminal ileum intubation and the number of patients diagnosed with small bowel Crohn's disease after additional imaging. It appears that small bowel imaging is primarily indicated if ileoscopy is not achieved.

Result of colonoscopy	Patients, n	Patients diagnosed with small bowel Crohn's disease after additional imaging, n
Colonoscopy with terminal ileum intubation		
Crohn's disease involving the terminal ileum	20	0
Crohn's disease in the colon and normal terminal ileum	11	0
Normal colon and terminal ileum	43	3
Total	74	
Colonoscopy without terminal ileum intubation		
Crohn's disease in the colon	9	3/9
Normal	9	1/9
Total	18	
Colonoscopy cancelled		
Total	1	

DISCUSSION

These findings suggest that in patients in whom ileocolonoscopy shows a normal terminal ileum, small bowel imaging adds little information irrespective of the colonic findings. In our study, CE added no diagnostic information in patients with CD in the colon and a normal terminal ileum.

In patients with non-complicated CD in the terminal ileum, CE adds no diagnostic information, but can be used to map disease extension beyond the reach of the colonoscope. Furthermore, in the present study, ileoscopy was sufficient to determine the severity of small bowel inflammation. According to current guidelines, extensive small bowel CD should be treated with thiopurines or methotrexate (evidence level 5, recommendation grade D) [11]. To the best of our knowledge, no study has proven that mapping of CD extension at the time of diagnosis – with immunomodulators in extensive disease – benefits clinical outcome compared to ileocolonoscopy alone.

If terminal ileum intubation is not achieved, additional imaging helps diagnose unacknowledged CD located in the small bowel after a normal colonoscopy or map CD in patients with newly diagnosed CD in the colon.

Which small bowel imaging modality?

Previous studies comparing MRE and CTE found similar sensitivities and specificities for detection of small bowel CD [12, 13], and a meta-analysis concluded that the diagnostic yield of capsule endoscopy was significantly higher than that of CTE in patients with suspected CD [14].

No previous studies have compared the diagnostic sensitivity and specificity of MRE, CTE and capsule endoscopy in patients undergoing their first diagnostic work-up for CD. We concluded that the sensitivity and specificity of capsule endoscopy for detection of CD in the terminal ileum is superior to that of cross-sectional imaging. MRE and CTE are complimentary examinations with moderate sensitivities and specificities. The diagnostic yield for CD located proximal to the terminal ileum is significantly higher with capsule endoscopy than with MRE and CTE.

An advantage of MRE and CTE is their ability to visualize the intestinal wall and extra-intestinal surroundings [15]. In our study, cross sectional imaging rarely detected extra-intestinal complications. At the time of diagnosis, intra-abdominal fistulas or abscesses

ABBREVIATIONS

CD = Crohn's disease
CI = 95% confidence interval
CTE = computed tomography enterography
fCal = faecal calprotectin
MRE= magnetic resonance imaging enterography
SBCE = small bowel capsule endoscopy

are uncommon, and the ability to look beyond the mucosa is of little relevance in this group of patients; unless clinical suspicion exists.

Risk of capsule retention

Our data suggest capsule endoscopy as first line diagnostic modality for visualization of the small bowel in patients with suspected CD, but the risk of capsule retention is a concern. However, the reported risk of capsule retention in patients with suspected CD is low (1.4%), and a preceding small bowel radiological assessment does not rule out capsule retention [16].

In our study of MRE, CTE and capsule endoscopy, six out 93 patients were suspected of having a small bowel stenosis [5]. Ileocolonoscopy detected stenosis in the terminal ileum in three patients. None of these were demonstrated with MRE, whereas CTE detected stenosis in all patients. In two additional patients, CTE detected stenosis in the small bowel. Hence, after ileocolonoscopy with a persistent attempt to intubate the terminal ileum, additional stenoses were suspected in only 2% of patients, and it should be emphasized that not all strictures on imaging translate into a mechanically significant obstruction. Sensitivities of conventional small bowel radiography, MRE and CTE for detection of small bowel stenosis are not perfect, and some authors believe that a careful history is perhaps the best single method to determine the risk of capsule retention [17, 18].

In patients with suspected CD, small bowel stenoses are infrequent and capsule endoscopy can be used as first-line modality for detection of small bowel CD beyond the reach of the colonoscope. In selected patients with a clinical suspicion of small bowel stenosis, a preceding test with a patency capsule could be helpful.

Suggested diagnostic algorithm

The above mentioned results suggest a new diagnostic algorithm for diagnosing suspected CD (**Figure 2**). This diagnostic approach is valid for young patients referred to gastroenterology out-patient clinics because of clinical suspicion of CD. It should be emphasized that fCal has a poor sensitivity for detection of colorectal cancer [19] and colonoscopy should be considered in patients > 40 years of age with a recent change in bowel habits.

The diagnostic algorithm yields the following results when applied to our study population of 83 patients examined with fCal, ileocolonoscopy and small bowel imaging:

- fCal was ≤ 50 mg/kg in 26 patients (31%; CI: 22-43%); false negative in two patients.
- fCal was elevated in 57 patients (69%; CI: 57-78%).
  - At subsequent colonoscopy, intubation of the terminal ileum was achieved in 46 patients (ileoscopy rate 81%). CD was diagnosed in 30 patients, and the terminal ileum was involved in 18. Ileoscopy detected a small bowel stenosis in two patients.
  - In 11 patients, ileoscopy was not achieved. Additional imaging revealed small bowel CD in two patients.

In summary, using fCal as a marker to select patients for endoscopy reduces the number of colonoscopies by 31%. With an ileoscopy rate of 81%, additional small bowel imaging is needed in only 13% of patients. Capsule endoscopy can be performed in the majority of these patients. Additional small bowel imaging (or upper endoscopy) may be indicated in few patients with complicated disease or clinical suspicion of CD in the upper gastrointestinal tract without distal involvement.

Limitations

The place of new endoscopic and cross sectional imaging modalities in suspected CD remains to be fully determined. This brief article suggests a new diagnostic algorithm based on evidence provided by a single prospective study of MRE, CTE, capsule endoscopy, and fCal in patients undergoing their first diagnostic work-up for CD. It is not a systematic review of the literature.

Ultrasound is a non-invasive, patient friendly, radiation free and widely available modality for detection of small bowel CD and extra-intestinal complications. Our study did not include ultrasound as a fourth imaging modality. A recent systematic review concluded that ultrasound is an accurate technique for the initial diagnostic workout of patients with suspected CD [20]. Depending on local expertise, ultrasound can substitute MRE or CTE in the suggested diagnostic algorithm. However, the observer variability is significant, and achieving a high accuracy requires experienced radiologists. In patients with a high suspicion of CD, a negative ultrasound should be confirmed with other diagnostic techniques [20].

CONCLUSION

As a first line test in young patients with clinical suspicion of CD, fCal is useful to identify patients without need for colonoscopy or small bowel imaging. Patients with fCal > 50 mg/kg should undergo colonoscopy including a persistent attempt to intubate the terminal ileum, and small bowel imaging is primarily indicated if ileoscopy is not achieved. Capsule endoscopy is superior to MRE and CTE and is therefore recommended as first choice for small bowel imaging in this setting. If stenosis is suspected capsule endoscopy should be preceded by a patency capsule. MRE and CTE are complimentary modalities preferably used in patients with stenosis de-

tected at ileocolonoscopy or suspicion of extra-intestinal disease complications.

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LITERATURE

1. Van Assche G, Dignass A, Panes J et al. The second European evidence-based consensus on the diagnosis and management of Crohn's disease: Definitions and diagnosis. J Crohns Colitis 2010;4:7-27.
2. Vind I, Riis L, Jess T et al. Increasing incidences of inflammatory bowel disease and decreasing surgery rates in Copenhagen City and County, 2003-2005: a population-based study from the Danish Crohn colitis database. Am J Gastroenterol 2006;101:1274-82.
3. Gollop JH, Phillips SF, Melton LJ 3rd et al. Epidemiologic aspects of Crohn's disease: a population based study in Olmsted County, Minnesota, 1943-1982. Gut 1988;29:49-56.
4. Marshall JB, Barthel JS. The frequency of total colonoscopy and terminal ileal intubation in the 1990s. Gastrointest Endosc 1993;39:518-20.
5. Jensen MD, Nathan T, Rafaelsen SR et al. Diagnostic accuracy of capsule endoscopy for small bowel Crohn's disease is superior to that of MR enterography or CT enterography. Clin Gastroenterol Hepatol 2011;9:124-9.
6. Jensen MD, Kjeldsen J, Nathan T. Fecal calprotectin is equally sensitive in Crohn's disease affecting the small bowel and colon. Scand J Gastroenterol 2011;46:694-700.
7. Vermeire S, Van AG, Rutgeerts P. Laboratory markers in IBD: useful, magic, or unnecessary toys? Gut 2006;55:426-31.
8. van Rheenen PF, Van de Vijver E, Fidler V. Faecal calprotectin for screening of patients with suspected inflammatory bowel disease: diagnostic meta-analysis. BMJ 2010;341:c3369.
9. Tibble J, Teahon K, Thjodleifsson B et al. A simple method for assessing intestinal inflammation in Crohn's disease. Gut 2000;47:506-13.
10. Dolwani S, Metzner M, Wassell JJ et al. Diagnostic accuracy of faecal calprotectin estimation in prediction of abnormal small bowel radiology. Aliment Pharmacol Ther 2004;20:615-21.
11. Dignass A, Van Assche G, Lindsay JO et al. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Current management. J Crohns Colitis 2010;4:28-62.
12. Siddiki HA, Fidler JL, Fletcher JG et al. Prospective comparison of state-of-the-art MR enterography and CT enterography in small-bowel Crohn's disease. AJR Am J Roentgenol 2009;193:113-21.
13. Fiorino G, Bonifacio C, Peyrin-Biroulet L et al. Prospective comparison of computed tomography enterography and magnetic resonance enterography for assessment of disease activity and complications in ileocolonic Crohn's disease. Inflamm Bowel Dis 2011;17:1073-80.
14. Dionisio PM, Gurudu SR, Leighton JA et al. Capsule endoscopy has a significantly higher diagnostic yield in patients with suspected and established small-bowel Crohn's disease: a meta-analysis. Am J Gastroenterol 2009;105:1240-8.
15. Jensen MD, Nathan T, Kjeldsen J et al. Incidental findings at MRI-enterography in patients with suspected or known Crohn's disease. World J Gastroenterol 2010;16:76-82.
16. Cave D, Legnani P, De FR et al. ICCE consensus for capsule retention. Endoscopy 2005;37:1065-7.
17. Karagiannis S, Faiss S, Mavrogiannis C. Capsule retention: a feared complication of wireless capsule endoscopy. Scand J Gastroenterol 2009;44:1158-65.
18. Jensen MD, Kjeldsen J, Rafaelsen SR et al. Diagnostic accuracies of MR enterography and CT enterography in symptomatic Crohn's disease. Scand J Gastroenterol 2011;46:1449-57.
19. von Roon AC, Karamountzos L, Purkayastha S et al. Diagnostic precision of fecal calprotectin for inflammatory bowel disease and colorectal malignancy. Am J Gastroenterol 2007;102:803-13.
20. Panes J, Bouzas R, Chaparro M et al. Systematic review: the use of ultrasonography, computed tomography and magnetic resonance imaging for the diagnosis, assessment of activity and abdominal complications of Crohn's disease. Aliment Pharmacol Ther 2011;34:125-45.