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Capsule endoscopy in suspected small bowel Crohn's disease — Is it worth repeating a negative study?

Dear Editor,

Crohn's disease (CD) affects the small bowel (SB) in a significant proportion of patients, with approximately 20% having exclusively SB disease [1,2]. Therefore, various modalities have been employed to allow a less invasive assessment/diagnosis when conventional endoscopy has failed. Capsule endoscopy (CE) has a high diagnostic yield (DY) for SB inflammation when compared with alternative SB investigations [3,4]. Therefore, in patients with known CD, the use of CE can positively affect management [5]. However, less information is available for those with ongoing clinical concern of SB CD when the initial CE is negative or inconclusive. Due to patient acceptance and ease of use, repeating CE remains a plausible option. In small series, a repeat CE following an initially negative CE for occult gastrointestinal bleeding (OGIB) has been shown to increase DY, and change management in as many as 39% of patients [6]. During an acute episode, back-to-back CE has also been shown to increase the DY in OGIB [7].

Between March 2005 and March 2018, 2276 SB CE studies were performed at our tertiary centre. During this time period the method of CE video review remained unchanged; CEs were reported based on clinical impression without use of a standardised tool (e.g. Lewis score (LS) or Capsule Endoscopy Crohn's Disease Activity Index (CECDAI)) by one or more of four experienced/experts CE readers. Our prospectively maintained database of CE examinations was used to identify patients undergoing repeat CE for suspected SB CD. Any initial CEs which lead to a diagnosis of CD and those repeated because of incomplete or inadequate recording were excluded. Eventually, a case series of 18 patients was compiled with the aim of assessing the DY of repeating a CE in patients with ongoing clinical suspicion of SB CD and an initial complete negative or inconclusive study. Further clinical data was extracted from the internal hospital records system TrakCare (©Intersystems, Cambridge, MA). The median time between CEs was 598 (48–3123) days and the second CE was carried out with a different capsule model in 12/18 (66.7%) patients. Where the initial capsule video was available this was reviewed prior to writing this letter with a LS assigned retrospectively.

The cohort consisted of 15 women and 3 men, with a median age of 44.4 (15.8–64.0) years at baseline CE. All of these patients had at least one faecal calprotectin (FC) result recorded, with between 1 and 10 (median of 2.5) samples analysed; overall median FC 142.5 (0–1045) μg/g. For the purpose of analysis, FC < 20 μg/g, which is the lower limit of detection by the laboratory (Launch Diagnostic Systems, Longfield, UK), were recorded as 0 μg/g. Median FC results are presented in Table 1 and the FC levels are compared to the CE outcome in Fig. 1.

1. Repeat CE when initial CE is normal or reveals non-IBD diagnosis

Of the five patients with a 'normal' initial CE none had repeat CE suggestive of SB CD (DY: 0%). The median time interval between CEs was 462 (91–1984) days. 4/5 (80%) of the repeats were normal, with 1/5 (20%) showing non-specific SB appearances suggestive of portal hypertensive enteropathy (PHE). The median FC value in this group was 270 (0–667) μg/g. Baseline CE was re-reviewed in 2 of these cases and LS was calculated (both LS = 0); supporting the clinical report for 'normal' issued at the time. Patients with positive initial CE, but non-IBD findings (n = 5), i.e. NSAIDs enteropathy (n = 1; LS = 112), angioectasia (n = 1; LS = 196), appearances suggestive of lymphoproliferative disease (n = 1; LS = 3593) and gastritis (n = 1), had similar findings on repeat CE and one patient with a duodenal ulcer had a normal repeat 3123 days (8.6 years) later; summarised in Table 1. Overall, these patients as a group with a complete initial CE showing no evidence of SB CD had a DY of 0/10 (0%) for SB CD on repeating the CE.

2. Initial CE showing non-specific inflammation

The initial CEs showing inflammation were divided into those which were, on balance felt suggested CD (n = 2), and those which likely did not (n = 6). Of the 2 patients with findings initially suggestive but not specific for SB CD, 1 of the subsequent CEs was again suggestive of CD while the other again only showed non-specific inflammation. They had a median FC of 35 (0–320) μg/g and LSs of 4464 and 1104 on initial CE. These scores would fall in the moderate to severe inflammation category, supporting the clinical impression reported [8]. Six patients had non-specific inflammation, less associated with CD on initial CE. 2/6 (33%) of the repeat

Table 1
Summary of CE findings in patients undergoing repeated capsule endoscopy.

Pt	M/F	Age (years)	Initial CE findings	Repeat CE findings	Interval between CEs (days)	Median FC result (μg/g)
1	F	28	Normal	Normal	183	300
2	F	55	Normal	Normal	725	270
3	F	62	Normal (poor prep)	Normal	462	439
4	F	59	Normal	?PHE	1984	115
5	F	29	Normal	Normal	91	150
6	F	64	?lymphoproliferative disorder	?inflammatory/infiltrative disorder	377	212
7	F	41	Gastritis	Gastritis	685	135
8	F	36	Duodenal ulcer	Normal	3123	155
9	M	44	NSAID enteropathy	?NSAID ulcer	1063	0
10	F	61	Angioectasia	Angioectasia	538	360
11	M	30	Non-specific (NS) inflammation	Normal	2269	50
12	F	23	NS inflammation	?CD	2066	249
13	F	54	NS inflammation	?CD ?Coeliac	421	105
14	F	57	NS inflammation	NS inflammation	659	395
15	F	15	NS inflammation	Normal	285	27
16	M	53	Mild inflammation at IC valve	Normal	1560	115
17	F	24	?CD	NS inflammation	454	50
18	F	44	?CD	?Gastric CD	48	20

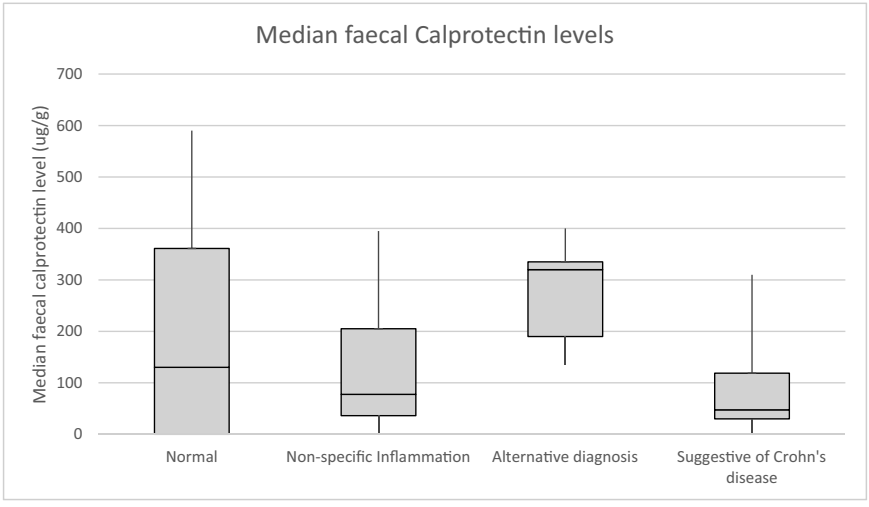

Fig. 1. Median faecal calprotectin level.

CEs were suggestive of SB CD, 3/6 (50%) were normal and 1/6 (17%) again showed non-specific inflammation. One patient with mild terminal ileal (TI) inflammation (LS = 112) on initial capsule had a normal repeat. This group had a median FC of 110 (0–395) μg/g. The 2 patients with findings suggestive of CD on their repeat CE had higher median FC results (117 vs. 82.5) μg/g.

3. Conclusions

In our series, the overall DY of repeating CE in patients with suspected SB CD was 16.7% (3/18). However, in patients with no SB inflammation on the initial CE, none of the repeat CEs showed changes suggestive of CD (DY = 0). In patients with non-specific inflammation, not felt to be suggestive of CD on initial CE, the DY of a repeat CE was 33%. Moreover, patients who had higher FC results were more likely to have evidence supportive of a diagnosis of CD on their repeat CE.

We recognise the small sample of our series. Moreover, the data has been retrospectively drawn and remains heterogenous, with initial capsule video only available for some, so LS could not be calculated for cases. Despite these caveats, our findings would support the hypothesis that repeat CE is useful in equivocal and inconclusive studies where there is clinical suspicion of SB CD. Conversely, in patients whose initial CE showed no evidence or suggestion of SB inflammation, repeating the procedure seems to add little.

Conflict of interest
None declared.

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Not all NAFLD patients are the same: We need to find a personalized therapeutic approach

Dear Editor,

In the clinical practice, any decision should include considerations regarding the clinical and physical circumstances of any patient, in order to establish what is wrong and what treatment options are available and adequate [1]. In addition, these clinical decisions should be strengthened by research evidence regarding the efficacy, effectiveness, and efficiency of the therapeutic approaches [1]. Lastly, clinical expertise is required to carry any consideration jointly and recommend the treatment that the patient is well-disposed to accept [1].

To date, although there are no approved pharmacological treatments for NAFLD (and its advanced forms), the NAFLD management essentially focuses on four key goals: (a) lifestyle change in order to effect weight loss and reduce obesity, (b) control of the main cardiometabolic risk factors, theoretically using agents with potential beneficial liver effects; (c) correction of all modifiable factors that lead the development and progression of liver fibrosis, given that hepatic fibrosis seems to be the strongest predictor of poor long-term outcomes; and (d) prevention of hepatic and extra-hepatic complications [2–4]. Of these, interventions addressing obesity and the features of metabolic syndrome (such as dyslipidemia, hypertension, and impaired fasting glucose) may exert advantageous effects on the risk of NAFLD-related complications, including cardiovascular disease [2–4]. However, by way of illustration, it is important to remember that, once cardiac dysfunction has progressed to clinically symptomatic heart failure (e.g., NYHA class III and IV), a paradoxical relationship between body mass index and survival outcomes occurs [5]; in other words, patients with advanced heart failure and higher body mass index tend to have better risk adjusted survival when compared to those with lower body mass index [5]. Such paradox may indirectly suggest that caution should be applied when trying to effect weight loss in patients with advanced cardiac dysfunction [3].

Extending the clinical meaning of this paradox to other cardiometabolic risk factors, it is possible to speculate that carefulness may be exerted when we comply with the achievement of stringent cardiometabolic goals in NAFLD patients with serious complications. On the basis of this background, although there are no specific studies and most experts [4,6–8] suggest the need for obtaining tight cardiometabolic targets in (all) NAFLD patients, I believe that, for instance, a blood pressure <130/80 mmHg and a glycemic target with a hemoglobin A1c <48 mmol/mol [4,6] (as it is often suggested) may be not adequate for all NAFLD patients, in particular for those with important and serious comorbidities. A stringent target range of systolic blood pressure (i.e., 110–130 mmHg) or a less stringent range (i.e., 120–140 mmHg) may be preferred in NAFLD patients according to the presence or absence of several relevant factors, including hepatic, macrovascular and microvascular complications, postural hypotension, falls risk, cognitive impairment, polypharmacy, presence of resources and support systems. Similar considerations may be adopted for glucose (i.e., HbA1c <48 mmol/mol as stringent target and <58 mmol/mol as less stringent goal) or lipid (i.e., LDL-cholesterol <70 mg/dl as stringent target and <100 mg/dl as less stringent goal) targets, with the only difference that for these goals we would presumably consider target levels rather than target ranges. Despite the fact that the inclusion of the aforementioned factors is mostly based on clinical experience of each physician, they may, however, represent an important early starting point, waiting for an improvement in our knowledge based on future clinical studies. Since NAFLD is a multi-systemic disease and NAFLD patients are at a high risk of developing several hepatic and extra-hepatic complications [2,3,6–9], a careful cardiometabolic evaluation should be always implemented in these patients before submitting them to any (vigorous) therapeutic efforts or achieving any stringent clinical goals. In a forthcoming personalized medicine era, any cardiometabolic target should be individualized and customized on the basis of the clinical history and the comorbidities of patients, always keeping in mind the concept that the heterogeneity of NAFLD and its complications may display variability in exposure to metabolic stress, differences in fat accumulation in the liver and other vital organs and alterations in repair mechanisms [10,11]. In this context, interestingly, emerging evidence seems to suggest a potential use of several novel individual non-invasive biomarkers (such as inflammation-associated proteome, lipidome, and metabolome) for accurately distinguishing NAFLD groups with high and low levels of myocardial, epicardial, pericardial, and liver fat depots in order to better differentiate their cardiometabolic risk [11,12]. Doubtless, these new and emerging data (essentially based on molecular diagnostics and