Development of a predictive model of Crohn's disease proximal small bowel involvement in capsule endoscopy evaluation

Authors   Eduardo Rodrigues-Pinto[1, *], Helder Cardoso[1, *], Bruno Rosa[2], João Santos-Antunes[1], Susana Rodrigues[1], Margarida Marques[1], Susana Lopes[1], Andreia Albuquerque[1], Pedro Carvalho[2], Maria Moreira[2], José Cotter[2], Guilherme Macedo[1]

Institutions   [1] Gastroenterology Department, Centro Hospitalar São João, Porto, Portugal
[2] Gastroenterology Department, Centro Hospitalar do Alto Ave, Guimarães, Portugal

Corresponding author
Eduardo Rodrigues-Pinto, MD
Gastroenterology Department
Centro Hospitalar São João
Porto. Al. Prof. Hernâni
Monteiro 4200 - 319 Porto
Portugal
Phone: +351 919657386
Fax: +351 22 551 3601
edu.gil.pinto@gmail.com

Background and study aims: One of the indications for capsule endoscopy (CE) is the detection of proximal small bowel (SB) involvement in Crohn's disease (CD) patients. Our aim was to assess clinical, laboratory and endoscopic predictors associated with proximal SB involvement in CD patients submitted to CE.
Patients and methods: Retrospective multicenter study in which Lewis score (LS) was systematically determined in 190 CE of patients diagnosed with CD between 2003 and 2014.
Results: Significant inflammatory activity (LS > 135) was present in 23 % of the patients in the first tertile and in 31 % of the patients in the second tertile. Albumin, haemoglobin, and total proteins were significantly lower in patients with a LS > 790 compared to patients with a LS < 135, while white blood cell counts and C-reactive protein were significantly higher. In the univariable analysis, a higher risk for proximal SB involvement at CE was associated with ileal involvement at ileocolonoscopy (OR 2.858, $P = 0.006$), higher platelets levels (OR 1.005, $P = 0.004$) and significant weight loss (OR 2.450, $P = 0.006$). In logistic regression, ileal involvement at ileocolonoscopy (OR 6.817, $P = 0.003$), stricturing behavior (OR 8.653, $P = 0.011$) and significant weight loss (OR 3.629, $P = 0.028$) were independently associated with proximal SB involvement at CE. Considering the ROC curve of this model, a cut-off > 0.249 predicts proximal SB involvement with 90 % sensitivity and 40 % specificity (AUROC 0.732).
Conclusions: One-third of patients had proximal SB involvement. Predictive factors were significant weight loss, stricturing behaviour, and ileal involvement at ileocolonoscopy. These data help to select CD patients that benefit the most from performing a CE.

Introduction

▼

Crohn's disease (CD) is a chronic inflammatory disorder that can affect all or part of the gastrointestinal tract, with heterogeneous manifestations and adverse events. The exact prevalence of small-bowel (SB) involvement in CD has not been well determined, however, according to Western population-based epidemiologic studies, SB involvement is believed to affect as many as 50 % to 80 % of patients [1 – 3]. The ability to accurately assess the SB is crucial for determining optimal patient management. Until a few years ago, a fluoroscopic examination that included SB follow-through (SBFT) was the suggested technique for SB evaluation [4]. In the past 2 decades, advances in cross-sectional image and capsule endoscopy (CE) have led to widespread use of these noninvasive and well-tolerated approaches [4 – 6]. One of the indications for CE is the detection of proximal involvement of SB in CD patients. The role of CE in patients with known CD has been studied in several trials, which have shown superiority of this test over all other modalities in evaluation of disease activity, severity, and extent of disease, particularly for mild lesions and those located in the proximal SB [7 – 10]. However, endoscopic findings are nonspecific and must be carefully interpreted within the proper clinical context [11].
Lewis Score (LS) [12] is a cumulative scoring system based on the characteristics and distribution of villous edema, ulceration and stenosis which has been integrated into the latest software from the PillCam® (Given®, RAPID Reader®). It was developed with the purpose of increasing the objectivity and maximizing inter-observer agreement, when assessing SBCE inflammatory activity. It uses a standard terminology for the description of endoscopic lesions, the CE structured terminology (CEST) [13, 14], and grades the inflammatory activity through a rank of severity, with the pre-

* These authors contributed equally.

mise that the final numerical score reflects the physician's global assessment of disease. With this scoring system, the SB is evaluated according to the division into equal thirds (tertiles) based on the transit time of the capsule. The LS classifies SB inflammatory activity into three grades of severity of inflammation: 1) normal or clinically insignificant mucosal inflammatory change (score < 135); 2) mild disease (score ≥ 135 < 790); and 3) moderate-to-severe disease (score ≥ 790).

There remains considerable uncertainty regarding when to assess disease activity among patients with known CD, as well as it isn't clear how often proximal SB lesions (first and second tertiles) are found. The aim of the current work was to determine frequency and assess clinical, laboratory and endoscopic predictors of proximal SB involvement in patients with established CD submitted to CE.

Patients and methods
▼

Retrospective and multicenter study based on the records of 190 consecutive patients with known CD subjected to SBCE between 2003 and 2014. Patients were excluded if CE was performed as a part of the initial diagnosis of CD. All patients with CD performed patency capsule prior to CE in order to avoid capsule retention. The diagnosis of CD was made by using widely validated clinical, endoscopic, and histologic criteria [15]. Disease phenotype was determined according to the Montreal classification, based on age at onset, location, and behavior, with perianal and upper gastrointestinal disease as additional modifiers. B1 corresponds to a non-stenosing non-penetrating disease, B2 to a stenosing behaviour, and B3 to a penetrating one. B2 phenotype according to Montreal classification should be defined by the presence of stenosis and clinical symptoms (abdominal pain). Cross-sectional imaging studies were performed in 86 patients prior to CE evaluation (computed tomography enterography [CTE] – 45 patients; magnetic resonance enterography [MRE] – 15 patients; SBFT – 46 patients). All patients had previous ileocolonoscopy and upper endoscopy. Indication for CE was presence of recurrent abdominal pain, diarrhea, significant weight loss, fever, and/or laboratory findings (anemia, thrombocytosis, hypoalbuminemia, increased inflammatory markers) not explained by findings on upper endoscopy and ileocolonoscopy and/or not resolved by an appropriate pharmacological treatment [16]. Significant weight loss was defined as greater than 5% of the original weight.

Gender, age, age at onset, disease location, disease behavior, perianal disease, presence of extra-intestinal manifestations, smoking habits, symptoms and laboratory workup at the date of CE and endoscopic findings closest to the date of CE were thoroughly investigated by reviewing medical records.

To optimize the visualization of the jejunum and ileum with the CE, after an overnight fast, patients ingested 1 L of PEG 4000 oral solution before capsule ingestion. The endoscopic capsules used were the PillCam SB2 and SB3 (Given Imaging, Yokneam, Israel). PillCam SB2 is a fixed frame rate second-generation capsule (2 frames per second over 8 h), while PillCam SB3 is a third-generation capsule with enhanced imaging capabilities with adaptive frame rate. RAPID Reader® was used to review CE images. All capsule registrations previous to RAPID reader availability have been re-read using the new RAPID reader software to calculate the Lewis score. The presence of SB mucosal inflammation on CE was systematically quantified using LS, using the automatic calculator included in the RAPID® software. Normal or clinically insignifi-

cant mucosal inflammatory change was defined as LS < 135, mild inflammation as 135 < LS < 790 and moderate-to-severe disease as LS ≥ 790 [12]. In the appropriate clinical setting, the detection of at least 2 ulcers or 1 stricture were considered specific of small bowel involvement by CD. Capsule readers were blinded to endoscopy and CTE/MRE reports.

Statistics

Categorical variables were described through absolute and relative frequencies and continuous variables were described as mean and standard deviation, median, percentiles, minimum and maximum. Hypotheses were tested about the distribution of continuous variables with non-normal distribution, by using the nonparametric Mann-Whitney and Kruskal-Wallis test, depending on the nature of the hypothesis. Pearson Chi-square and Fisher's exact test were used to test hypotheses about independence of categorical variables, as appropriate.

To identify factors predictive of proximal SB involvement at CE, simple and multivariable analysis was performed using logistic regression. To identify independent predictors of proximal SB involvement at CE, all significant variables evaluated in the univariable analysis (ileal lesions at ileocolonoscopy, significant weight loss, platelets) as well as variables previously associated with a poorer prognosis (age at diagnosis, disease location, disease behaviour) were integrated into a multivariable logistic regression using a stepwise method. The results are shown as odds ratio (OR) with 95% confidence intervals (CI). With the values obtained, a logistic function was applied to define a predictive model to our outcome. All the reported P values were two-sided, and P values < 0.05 were considered statistically significant. All data were arranged, processed and analyzed with SPSS ® v.20.0 data (Statistical Package for Social Sciences).

Results
▼

Population

Baseline demographic characteristics of all 190 patients (108 females (57%)) with CD are shown in ◐ Table 1. At diagnosis, most of the patients (n = 139, 75%) were between 17 and 40 years old, 43% (n = 81) had exclusively ileal involvement (L1) and 75% (n = 140) had non-stenosing non-penetrating behavior (B1). Only 16 patients (9%) had gastroduodenal involvement (◐ Table 1). Twenty percent of the patients had perianal disease. Seventy-two percent of the patients (n = 116) had recurrent abdominal pain, 65% (n = 114) had diarrhea, 44% (n = 75) had significant weight loss, 11% (n = 19) had rectal bleeding, and 21% (n = 25) had extra-intestinal manifestations. Twenty-nine patients (20%) were currently smokers and 12 (8%) were former smokers.

After performance of CE, 43% of the patients (n = 81) started corticosteroids, 17% (n = 33) started azathioprine, 11% (n = 21) started biologic therapy and 6% (n = 12) were submitted to surgery.

Capsule endoscopy
▼

At the time of CE performance, median hemoglobin was 13.5 g/dL (6.9 – 17.2), median iron was 65 µg/dL (0 – 231), median ferritin was 23.5 ng/mL (0 – 1727), median white blood cell (WBC) counts were 7.5×10^9 (2.3 – 23), median platelets were 251×10^9 (72 – 849), median total proteins were 71.6 g/dL (47 – 84.5), median albumin was 42.0 g/dL (22 – 53.0), median erythrocyte sedimenta-

Table 1 Baseline characteristic of Crohn's disease (CD) patients regarding gender, Montreal classification and smoking habits.

Characteristics	CD (n = 190)
Female/male (n)	108/82
Montreal classification (n; %)	
Age at diagnosis	
A1	19 (10 %)
A2	139 (75 %)
A3	28 (15 %)
Disease location	
L1	81 (43 %)
L2	17 (9 %)
L3	73 (39 %)
L1 – 4	10 (5 %)
L2 – 4	1 (1 %)
L3 – 4	5 (3 %)
Behaviour	
B1	140 (75 %)
B2	28 (15 %)
B3	19 (10 %)
Perianal disease	24 (20 %)
Smoking habits (n; %)	
Non-smoker	104 (72 %)
Ex-smoker	12 (8 %)
Smoker	20 (20 %)

Table 2 Absolute and relative frequencies for the 1st, 2nd and 3rd tertiles and Lewis score.

Characteristics	CD (n = 190)	
1st tertile score (n; %)		
<135	145	76 %
135 – 790	29	15 %
≥790	16	8 %
2nd tertile score (n; %)		
<135	131	70 %
135 – 790	37	20 %
≥790	20	11 %
3rd tertile score (n; %)		
<135	46	25 %
135 – 790	79	42 %
≥790	61	33 %
Lewis score (n; %)		
<135	38	20 %
135 – 790	81	43 %
≥790	69	37 %

tion rate was 11 mm/h (1 – 89) and median C-reactive protein (CRP) was 3.8 mg/L (0.2 – 209.0).

The mean LS in the first tertile was 146 (±363), in the second tertile was 216 (±513) and in the third tertile was 797 (±1042). Significant inflammatory activity (LS > 135) was present in 23 % of the patients (n = 45) in the first tertile, in 31 % of the patients (n = 57) in the second tertile, and in 36 % of the patients (n = 68) in the first and/or second tertile (○ Table 2). Of the 68 patients with LS > 135 in the first and/or second tertile, 45 had ileal involvement at ileocolonoscopy (32 of 45 in the first tertile and 39 of 57 in the second tertile).

There was no correlation between colonic location activity and LS, in neither of the tertiles.

LS was higher in patients with lower hemoglobin levels (P = 0.006), higher WBC counts (P = 0.032), higher CRPn (P < 0.001), lower total protein levels (P = 0.006) and lower albumin levels (P < 0.001) (○ Table 3).

Clinical factors associated with proximal small-bowel involvement (1st and 2nd tertile) at capsule endoscopy in Crohn's disease patients

In the univariable analysis, a higher risk for proximal SB involvement at CE was associated with ileal involvement at ileocolonoscopy (OR 2.858, 95 % CI [1.346 – 6.068], P = 0.006), higher platelets levels (OR 1.005, 95 % CI [1.002 – 1.009], P = 0.004) and significant weight loss (OR 2.450, 95 % CI [1.293 – 4.642], P = 0.006) (○ Table 4). An older age at diagnosis (>40 years) was associated with a trend toward protection for inflammatory activity at CE (OR 0.3, 95 % CI [0.087 – 1.039], P = 0.057), while lower albumin levels were associated with a trend toward increased risk for inflammatory activity (OR 0.976, 95 % CI [0.951 – 1.001], P = 0.065). In the multivariable logistic regression, ileal involvement at ileocolonoscopy (OR 6.817, 95 % CI [1.895 – 24.525], P = 0.003), stricturing behavior (OR 8.653, 95 % CI [1.629 – 45.972], P = 0.011) and significant weight loss (OR 3.629, 95 % CI [1.138 – 9.391], P = 0.028) were independently associated with proximal SB involvement at CE (AUROC 0.732; 95 % CI [0.648 – 0.817]) (○ Fig. 1).

With the aim of simplifying the application of these results on a daily basis so a likelihood of proximal SB involvement could be achieved, a model was created by applying the following logistic function:

$$\frac{\exp(-2.647+2.158\times B2-0.069\times B3+1.919\times \text{ileal involvement}+1.185\times \text{weight loss})}{1+\exp(-2.647+2.158\times B2-0.069\times B3+1.919\times \text{ileal involvement}+1.185\times \text{weight loss})}$$

Table 3 Comparisons between Lewis score and laboratory work-up at the date of capsule endoscopy (CE) (hemoglobin, leukocytes, total proteins, albumin, C-reactive protein).

	Lewis score			P value*
	<135	135 – 790	≥790	
Hemoglobin at CE (median; IQR$_{25-75}$)	13.9 (13.2 – 15)	13.5 (12.9 – 14.8)	13.1 (11.8 – 14.3)	0.006
White blood cell counts at CE (median; IQR$_{25-75}$)	6.9 (4.9 – 8.5)	7.2 (5.8 – 9.0)	8.2 (6.3 – 9.7)	0.032
Total proteins at CE (median; IQR$_{25-75}$)	74.6 (71.1 – 77.2)	70.9 (61.2 – 75.8)	70.8 (63.9 – 73.1)	0.006
Albumin at CE (median; IQR$_{25-75}$)	45 (42.6 – 47)	41.9 (34.8 – 44.0)	41 (37.7 – 43.0)	<0.001
C-reactive protein at CE (median; IQR$_{25-75}$)	3.4 (1.0 – 6.1)	2.8 (1.2 – 6.3)	7.65 (3.1 – 16.9)	<0.001

* Kruskall-wallis test

Table 4   Clinical factors associated with proximal small-bowel involvement at capsule endoscopy in Crohn's disease patients.

	Univariate analysis			Multivariate analysis [1]		
	OR[2]	95 % CI	P value [+]	OR[&]	95 % CI	P value [3]
Age at diagnosis (years-old)						
≤17	Ref.					
17 – 40	0.522	0.199 – 1.368	0.186			
>40	0.300	0.087 – 1.039	0.057			
Disease location						
L1 + L1L4	Ref.					
L2 + L2L4	0.184	0.022 – 1.545	0.119			
L3 + L3L4	1.416	0.668 – 3.004	0.364			
Disease behavior						
B1	Ref.			Ref.		
B2	1.560	0.688 – 3.539	0.287	8.653	1.629 – 45.972	0.011
B3	0.831	0.294 – 2.321	0.724	0.933	0.250 – 4.252	0.929
Ileal involvement at ileocolonoscopy						
No	Ref.			Ref.		
Yes	2.858	1.346 – 6.068	0.006	6.817	1.895 – 24.525	0.003
Hemoglobin	0.891	0.740 – 1.073	0.224			
C-reactive protein	1.020	0.997 – 1.045	0.094			
Platelets	1.005	1.002 – 1.009	0.004			
Total proteins	0.990	0.974 – 1.007	0.258			
Albumin	0.976	0.951 – 1.001	0.065			
Weight loss						
No	Ref.			Ref.		
Yes	**2.450**	**1.293 – 4.642**	**0.006**	**3.629**	**1.138 – 9.391**	**0.028**
Abdominal pain						
No	Ref.					
Yes	1.130	0.547 – 2.332	0.741			
Diarrhea						
No	Ref.					
Yes	1.751	0.893 – 3.433	0.103			
Extra-intestinal manifestations						
No	Ref.					
Yes	0.688	0.270 – 1.750	0.432			
Perianal disease						
No	Ref.					
Yes	0.851	0.342 – 2.117	0.729			

[1] independent variables: age at diagnosis, disease location, disease behaviour, ileal lesions at ileocolonoscopy, weight loss, platelets
[2] OR – odds ratio
[3] P value: overall comparison between groups

Assuming a sensitivity of 90 % and a specificity of 40 %, we consider the cut-off of 0.249 as clinically relevant, with a positive predictive value (PPV) of 61 %, a negative predictive value (NPV) of 76 % and an accuracy of 70 %, regarding likelihood of small bowel involvement.

Discussion
▼

Our purpose was to determine which clinical, laboratory and endoscopic factors predict proximal SB involvement in CD patients submitted to CE. One of the indications of CE is the assessment of disease activity and extent in patients with known CD. However, most of previous studies are related to the use of CE in suspected CD with previous negative ileocolonoscopy [16 – 20].
CE findings suggestive of CD involvement can be rather nonspecific and include ulceration, erythema, mucosal oedema and strictures. This presents a significant challenge to the interpreting physician because minor mucosal breaks may occur in 10 % to 15 % of normal individuals while mucosal erosions are present in two-thirds of patients taking nonsteroidal anti-inflammatory drugs [21]. This could explain the variability of the "diagnostic yield" of CE. Also, it must be considered that the "diagnostic yield" is different to either "sensitivity" or "specificity" [22]. Yield of CE varies depending on the type of patient, being lower when performed in patients with only abdominal pain compared with patients with abdominal pain and diarrhea. LS, an inflammation score that is incorporated in Given Imaging Software, is likely to enhance our ability to assess established CD at CE [14].
The largest comparative study of multiple SB imaging modalities involved a comparison of CE, CTE, and MRE performed after ileocolonoscopy. The results reported a significantly superior detection of CD in the proximal SB by CE compared with both CTE and MRE. In suspected or newly diagnosed CD, MRE and CTE have comparable sensitivities and specificities and, in patients without endoscopic or clinical suspicion of stenosis, CE would be the first-line modality for detection of SB CD beyond the reach of the colonoscope. Overall, these comparative studies suggest that CE is more sensitive than SBFT and may be more sensitive than cross-sectional imaging. Several meta-analyses [9, 10, 23, 24] showed
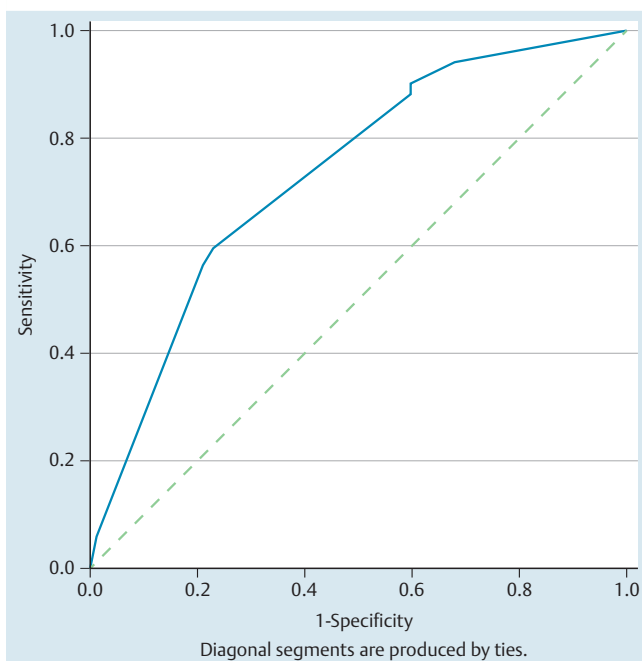
Fig. 1 ROC curve for proximal SB involvement considering CD behavior, ileal involvement at ileocolonoscopy, and weight loss. ROC, Receiver operating characteristic; SB, small-bowel; CD, Crohn's disease

that CE has superior diagnostic yields to SB barium studies, ileocolonoscopy, push enteroscopy and CTE in both suspected and established SB CD. CE appears to be better than MRE at identifying SB mucosal lesions, while MRE is more accurate at diagnosing mural, peri-mural and extra-enteric manifestations [25, 26].

Approximately 50 % of patients with symptomatic ileal and/or colonic CD have their proximal SB affected, with most common distributions including the proximal ileum (67 %), jejunum (53 %) and duodenum (32 %) [27]. Recent studies show that proximal involvement is associated with younger age, non-smoking status, co-existence of ileal involvement at ileocolonoscopy, and stenosing pattern [28, 29].

As proposed by the first consensus of the International Conference on Capsule Endoscopy (ICCE), ileocolonoscopy must always be performed prior to CE, considering it for CD diagnosis or exclusion if the patient presents suspicious symptoms (abdominal pain or persistent diarrhea) as well as extraintestinal manifestations, alteration of inflammatory markers, or abnormalities in other imaging tests [30]. The role of CE in patients with established CD has mainly been studied to explain new symptoms and to demonstrate mucosal healing, with no previous reports in the literature regarding predictive factors of SB involvement and which CD patients benefit the most from performing a CE at diagnosis. In this large cohort, it was possible to show that SBCE identifies proximal lesions (first and second tertiles) in 36 % of patients (n = 68) with established CD, when only 9 % were considered to have gastroduodenal involvement at baseline. Even though 34 % of the patients (n = 65) were already known to have poor prognostic factors at baseline (gastroduodenal involvement, perianal disease or extraintestinal manifestations), despite of already being on immunomodulators or biologic therapy at the time of CE performance, they persisted with unexplained symptoms or abnormal laboratory findings. Of the 68 patients with proximal lesions in the SB, 23 did not have ileal involvement at ileocolonoscopy. LS was higher in patients with lower hemoglobin levels, higher WB counts, higher CRP, lower total protein levels, and lower albumin levels.

In the multivariable analysis, significant weight loss, stricturing behavior and ileal involvement at ileocolonoscopy were predictive factors of SB involvement. Considering the ROC curve of the model, a cut-off higher than 0.249 predicts proximal SB involvement with 90 % sensitivity and 40 % specificity. Even though the specificity of the ROC model is low, it has a high sensitivity and a moderately high NPV (76 %). This cut-off helps to select which patients may benefit the most from performing CE, once it would detect 90 % of the patients with lesions in the proximal SB, inaccessible to conventional endoscopy/ileocolonoscopy; Likewise, patients with a cut-off lower than 0.249 are less likely to benefit from performing CE, once 76 % of them won't have proximal SB involvement. CE should be considered when a change in disease management is foreseen [22]. As previously reported [29], the prevalence of jejunal lesions is higher when the terminal ileum is involved and associated with an increased risk of further clinical relapse; it may be regarded as a factor of severity. Our results reinforce this point. Furthermore, given CE high diagnostic yield for established disease, its findings may influence management changes and clinical monitoring. It is well known that the presence of SB involvement is associated with an increased risk of further clinical relapse [28] and therefore an early and rapid diagnosis is necessary. Therefore, in the presence of symptoms or signs unexplained by previous exams, particularly significant weight loss, stricturing behavior or ileal involvement at colonoscopy, CE may detect lesions accounting for manifestations beyond the duodenum and terminal ileum, otherwise inaccessible to conventional endoscopy. Once CE is superior to cross sectional imaging for the detection of proximal lesions, CE could be a better exam to be performed, in patients with unexplained symptoms and a location of the disease in the terminal ileum previously seen at ileocolonoscopy. Even though the findings obtained by our model are of undoubted interest, they require validation, in order to help selecting the CD patients that benefit the most from performing a CE at diagnosis.

Competing interests: None

References

1 *Annese V, Daperno M, Rutter MD* et al. European Crohn's and Colitis Organisation. European evidence based consensus for endoscopy in inflammatory bowel disease. J Crohns Colitis 2013; 7: 982 – 1018

2 *Gower-Rousseau C, Vasseur F, Fumery M* et al. Epidemiology of inflammatory bowel diseases: new insights from a French population-based registry (EPIMAD). Dig Liver Dis 2013; 45: 89 – 94

3 *Nuij VJ, Zelinkova Z, Rijk MC* et al. Dutch Delta IBD Group. Phenotype of inflammatory bowel disease at diagnosis in the Netherlands: a population-based inception cohort study (the Delta Cohort). Inflamm Bowel Dis 2013; 19: 2215 – 2222

4 *Stuart S, Conner T, Ahmed A* et al. The smaller bowel: imaging the small bowel in paediatric Crohn's disease. Postgrad Med J 2011; 87: 288 – 297

5 *Di Nardo G, Aloi M, Oliva S* et al. Investigation of small bowel in pediatric Crohn's disease. Inflamm Bowel Dis 2012; 18: 1760 – 1776

6 *Fletcher JG, Fidler JL, Bruining DH* et al. New concepts in intestinal imaging for inflammatory bowel diseases. Gastroenterology 2011; 140: 1795 – 1806

7 *Leighton JA, Legnani P, Seidman EG.* Role of capsule endoscopy in inflammatory bowel disease: where we are and where we are going. Inflamm Bowel Dis 2007; 13: 331 – 337

8 *Marmo R, Rotondano G, Piscopo R* et al. Meta-analysis: capsule enteroscopy vs. conventional modalities in diagnosis of small bowel diseases. Aliment Pharmacol Ther 2005; 22: 595 – 604

9 *Triester SL*, *Leighton JA*, *Leontiadis GI* et al. A meta-analysis of the yield of capsule endoscopy compared to other diagnostic modalities in patients with non-stricturing small bowel Crohn's disease. Am J Gastroenterol 2006; 101: 954 – 964

10 *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 2010; 105: 1240 – 1248; quiz 1249

11 *Solem CA*, *Loftus EVJr*, *Fletcher JG* et al. Small-bowel imaging in Crohn's disease: a prospective, blinded, 4-way comparison trial. Gastrointest Endosc 2008; 68: 255 – 266

12 *Gralnek IM*, *Defranchis R*, *Seidman E* et al. Development of a capsule endoscopy scoring index for small bowel mucosal inflammatory change. Aliment Pharmacol Ther 2008; 27: 146 – 154

13 *Korman LY*. Standard terminology for capsule endoscopy. Gastrointest Endosc Clin N Am 2004; 14: 33 – 41

14 *Korman LY*, *Delvaux M*, *Gay G* et al. Capsule endoscopy structured terminology (CEST): proposal of a standardized and structured terminology for reporting capsule endoscopy procedures. Endoscopy 2005; 37: 951 – 959

15 *Dignass A*, *Van Assche G*, *Lindsay JO* et al. European Crohn's and Colitis Organisation (ECCO). The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Current management. J Crohns Colitis 2010; 4: 28 – 62

16 *Valle J*, *Alcántara M*, *Pérez-Grueso MJ* et al. Clinical features of patients with negative results from traditional diagnostic work-up and Crohn's disease findings from capsule endoscopy. J Clin Gastroenterol 2006; 40: 692 – 696

17 *Herrerías JM*, *Caunedo A*, *Rodríguez-Téllez M* et al. Capsule endoscopy in patients with suspected Crohn's disease and negative endoscopy. Endoscopy 2003; 35: 564 – 568

18 *Fireman Z*, *Mahajna E*, *Broide E* et al. Diagnosing small bowel Crohn's disease with wireless capsule endoscopy. Gut 2003; 52: 390 – 392

19 *Girelli CM*, *Porta P*, *Malacrida V* et al. Clinical outcome of patients examined by capsule endoscopy for suspected small bowel Crohn's disease. Dig Liver Dis 2007; 39: 148 – 154

20 *Fireman Z*, *Eliakim R*, *Adler S* et al. Capsule endoscopy in real life: a four-centre experience of 160 consecutive patients in Israel. Eur J Gastroenterol Hepatol 2004; 16: 927 – 931

21 *Sidhu R*, *Brunt LK*, *Morley SR* et al. Undisclosed use of nonsteroidal anti-inflammatory drugs may underlie small-bowel injury observed by capsule endoscopy. Clin Gastroenterol Hepatol 2010; 8: 992 – 995

22 *Bourreille A*, *Ignjatovic A*, *Aabakken L* et al. World Organisation of Digestive Endoscopy (OMED) and the European Crohn's and Colitis Organisation (ECCO). Role of small-bowel endoscopy in the management of patients with inflammatory bowel disease: an international OMED-ECCO consensus . Endoscopy 2009; 41: 618 – 637

23 *Pasha SF*, *Leighton JA*, *Das A* et al. Double-balloon enteroscopy and capsule endoscopy have comparable diagnostic yield in small-bowel disease: a meta-analysis. Clin Gastroenterol Hepatol 2008; 6: 671 – 676

24 *Chen X*, *Ran ZH*, *Tong JL*. A meta-analysis of the yield of capsule endoscopy compared to double-balloon enteroscopy in patients with small bowel diseases. World J Gastroenterol 2007; 13: 4372 – 4378

25 *Crook DW*, *Knuesel PR*, *Froehlich JM* et al. Comparison of magnetic resonance enterography and video capsule endoscopy in evaluating small bowel disease. Eur J Gastroenterol Hepatol 2009; 21: 54 – 65

26 *Tillack C*, *Seiderer J*, *Brand S* et al. Correlation of magnetic resonance enteroclysis (MRE) and wireless capsule endoscopy (CE) in the diagnosis of small bowel lesions in Crohn's disease. Inflamm Bowel Dis 2008; 14: 1219 – 1928

27 *Petruzziello C*, *Onali S*, *Calabrese E* et al. Wireless capsule endoscopy and proximal small bowel lesions in Crohn's disease. World J Gastroenterol 2010; 16: 3299 – 3304

28 *Lazarev M*, *Huang C*, *Bitton A* et al. Relationship between proximal Crohn's disease location and disease behavior and surgery: a cross-sectional study of the IBD Genetics Consortium. Am J Gastroenterol 2013; 108: 106 – 112

29 *Flamant M*, *Trang C*, *Maillard O* et al. The prevalence and outcome of jejunal lesions visualized by small bowel capsule endoscopy in Crohn's disease. Inflamm Bowel Dis 2013; 19: 1390 – 1396

30 *Lewis BS*. Expanding role of capsule endoscopy in inflammatory bowel disease. World J Gastroenterol 2008; 14: 4137 – 4141