World Journal of Gastrointestinal Endoscopy

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DOI: 10.4253/wjge.v8.i20.723

World J Gastrointest Endosc 2016 December 16; 8(20): 723-732
ISSN 1948-5190 (online)

REVIEW

Endoscopic evaluation in diagnosis and management of inflammatory bowel disease

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Author contributions: Moran CP and Neary B performed literature review and wrote the paper; Doherty GA contributed critical revision of the manuscript for important intellectual content.

Conflict-of-interest statement: No conflict of interest.

Manuscript source: Invited manuscript

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Received: March 30, 2016
Peer-review started: April 5, 2016
First decision: June 12, 2016
Revised: August 16, 2016
Accepted: September 21, 2016
Article in press: September 22, 2016
Published online: December 16, 2016

Abstract

Endoscopy is a keystone in the management of patients with inflammatory bowel disease (IBD). It is the fundamental diagnostic tool for IBD, and can help discern between ulcerative colitis and Crohn's disease. Endoscopic assessment provides an objective end point in clinical trials, and identifies patients in clinical practice who may benefit from treatment escalation and may assist risk stratification in patients seeking to discontinue therapy. Recent advances in endoscopic assessment of patients with IBD include video capsule endoscopy, and chromoendoscopy. Technological advances enable improved visualization and focused biopsy sampling. Endoscopic resection and close surveillance of dysplastic lesions where feasible is recommended instead of prophylactic colectomy.

Key words: Inflammatory bowel disease; Ulcerative colitis; Crohn's disease; Endoscopy; Capsule endoscopy; Cancer surveillance; Colonoscopy

Core tip: Ileo-colonoscopy remains the most important test in the diagnosis and monitoring of inflammatory bowel disease (IBD). Video capsule endoscopy shows very high sensitivity for small bowel mucosal lesions not accessible to conventional flexible endoscopes. Both techniques facilitate monitoring of response to treatment. Endoscopic activity indices are important for monitoring treatment response and can help identify patients who may benefit from treatment escalation. Colorectal cancer surveillance in patients with IBD is shifting from high frequency random biopsies, to that of high quality visual inspection and targeted biopsies of suspected dysplasia, enabled by technological advances including chromoendoscopy and high-definition endoscopes.

Moran CP, Neary B, Doherty GA. Endoscopic evaluation in diagnosis and management of inflammatory bowel disease. *World J Gastrointest Endosc* 2016; 8(20): 723-732 Available from: URL: http://www.wjgnet.com/1948-5190/full/v8/i20/723.htm DOI: http://dx.doi.org/10.4253/wjge.v8.i20.723

INTRODUCTION

Endoscopy plays an integral role in the diagnosis and management of patients with inflammatory bowel disease (IBD). In patients with lower gastro-intestinal symptoms suggestive of IBD, colonoscopy with intubation, evaluation and biopsies of the terminal ileum enables assessment of disease activity and extent, severity and histological evaluation (Figure 1). Detailed real-time endoscopic examination can help in delineating between ulcerative colitis (UC) and Crohn's disease (CD), and assessing disease behavior in patients with CD. Upper gastrointestinal (GI) endoscopy enables assessment and diagnosis of upper GI CD. The diagnosis of CD can be difficult, small bowel and upper gastrointestinal investigations are recommended after ileo-colonscopy[1]. Video capsule endoscopy (VCE) is useful in the diagnosis and evaluation of patients with IBD, especially non-stricturing small bowel disease.

Endoscopy enables objective measurement of disease response to medical and surgical therapies. Colorectal cancer (CRC) surveillance is imperative in patients with longstanding colonic IBD, except in patients with proctitis or colonic CD limited to only involving one segment of the colorectum[2]. Although essential in the management of patients with IBD, endoscopy is invasive and expensive, placing a burden on patients[3] and healthcare systems. Newer, less invasive tests have not replaced the use of endoscopy in our patients, but rather are used in tandem. Endoscopic ultrasound, and therapeutic endoscopic techniques such as stent placement and balloon dilation are covered elsewhere[4]. This review will focus on paramount roles that endoscopy plays in the management of adults with IBD.

ENDOSCOPIC ASSESSMENT OF DISEASE

Ileo-colonoscopy is the gold standard investigation for the diagnosis of UC and ileo-colonic CD. Real time endoscopic assessment can help delineate between CD and UC, although no endoscopic feature is specific for either. The key features that suggest a diagnosis of CD include perianal disease (careful examination of the perianal region at the time of endoscopy, prior to scope insertion, can reveal fistula tract openings, fissures, strictures and tags), skip lesions, cobblestoning, fistula and strictures, as well as isolated ileal disease. A diagnosis of UC is favoured by continuous colonic inflammation in affected bowel, with obvious demarcation between inflamed and non-inflamed bowel[2]. Patients with UC can be mistaken to have CD secondary to backwash ileitis and "skip lesions"; attributed to a caecal patch[5], characterised by localized peri-appendiceal inflammation, and from treatment effect giving the impression of a spared distal colon[6]. To avoid this pitfall, it is recommended to document endoscopic features in each colonic segment and terminal ileum at index ileo-colonoscopy, in addition to taking serial segmental biopsies (from affected mucosa and any raised lesions, and normal appearing mucosa)[2,4]. The presence of fistulae and strictures increase the index of suspicion for CD rather than UC, however these need to fully investigated (to outrule mimics and to ensure that a CRC associated with UC is not dismissed).

In patients with acute severe colitis, a flexible sigmoidoscopy without purgatives is recommended as initial endoscopic investigation[2], to confirm the presence, extent and severity of inflammation, to outrule pseudomembranes (although this may be absent in IBD patients with co-morbid *Clostridium difficile* infection) and obtain tissue for histological analysis (which is useful to outrule cytomegalovirus infection in immune suppressed patients). Early endoscopic assessment can help identify patients at risk of needing rescue medical therapy[7].

One must be aware of conditions that can masquerade as flares of IBD (Table 1)[8-24]. Endoscopic assessment can be useful; however many conditions such as infective colitis, the findings can be non-specific and overlap with features of IBD. The founding tenets of medical practice: History taking (including a careful drug and travel history) and clinical examination are to be used in tandem with other laboratory, endoscopic and histologic assessment.

ENDOSCOPIC SCORING SYSTEMS

Endoscopic evaluation is the gold standard to assess objective signs of mucosal inflammation and healing, frequently used in clinical trials. However, inter-observer variability in the assessment of endoscopic findings in patients with IBD has led to the development of several endoscopic scoring systems for both CD and UC, few of which have been validated. Scoring systems aim to interpret endoscopic disease appearance and translate these findings into a quantified score. Baron *et al*[25] introduced the first scoring system for UC in 1964, they recognised the importance of discontinuous variables in describing endoscopic findings to reduce inter-observer variability[25]. With time numerous other scoring systems[26,27] have been introduced, mainly for use as outcome measures in clinical trials, Table 2 lists some of the commonly used endoscopic indices. Ensuring objective endoscopic evidence of baseline disease activity in clinical trials is associated with reduced placebo remission rates[28,29].

Endoscopic scoring systems can be used in clinical practice to identify patients who may benefit from escalation of medical therapy. In acute severe colitis (ASC), the UCEIS helps predict patient outcomes. Nearly 80% of patients admitted to a single institution with ASC, recording a UCEIS score $\geqslant$ 7 required rescue medical therapy with infliximab or ciclosporine[7]. When UCEIS was $\geqslant$ 5, 33% of patients required colectomy during follow-up, compared with 9% of patients with UCEIS $\leqslant$ 4[7].

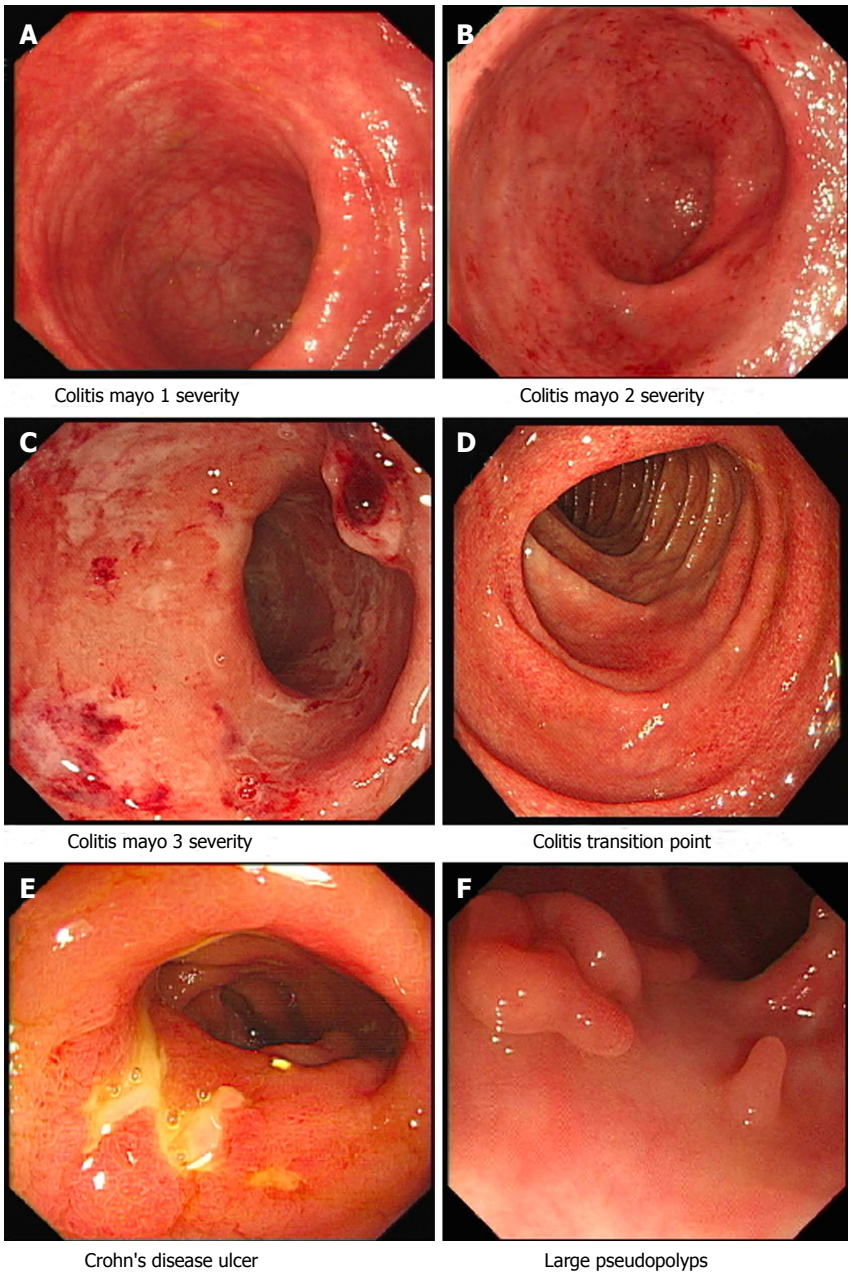

Figure 1 Common endoscopic findings in patients with inflammatory bowel disease.

Early post-operative endoscopic assessment, using the Rutgeert's score, in patients with CD who undergo intestinal resection is useful in predicting the risk of clinical relapse and need for future surgery[30]. Recent data suggest the Rutgeerts score, which quantifies the degree of recurrent mucosal lesions in the pre-anastomotic ileum, can improve selection of patient's who require escalation of treatment to reduce risk of post-operative disease recurrence[31]. A recent study escalated treatment of patients with a Rutgeert's score of i2 or greater, this was associated with significant improvements in mucosal healing and endoscopic recurrence, compared to standard treatment[31]. Prophylactic postoperative Azathioprine use was not superior to endoscopic driven therapy in a study of patients with CD deemed to be high risk for recurrence, in which the primary endpoint was endoscopic remission (i0-i1) at week 102 post-op[32].

Endoscopic response can also help predict patient outcomes. The International Organization for the study of IBD recommends defining endoscopic response as a decrease from baseline in CDEIS or SES-CD score of at least 50%[33]. Mucosal healing and endoscopic response at 26 wk, was predictive of corticosteroid free remission at week 50 in a subgroup analysis of 172 patients from the SONIC trial[34].

CAPSULE ENDOSCOPY

When CD is diagnosed at ileo-colonoscopy, it is recom-

Table 1 Mimics of active inflammatory bowel disease

Condition	Comment	Ref.
ITB	Skip lesions, cobblestoning of mucosa, apthous and linear ulcers are found more frequently in patients with CD compared to ITB	[8,9]
	Patulous ileocaecal valve, transverse ulcers more common in ITB	[9,10]
Segmental colitis associated with diverticulosis	Inflammatory changes limited to the segment of bowel containing the diverticula with rectal sparing	[11]
CMV colitis superimposed in IBD	Mucosal bleeding on light contact, wide mucosal defects and punched out ulcers more common in UC complicated by CMV	[12]
	The presence of ulcers helps predict CMV in patients with UC but not CD	[13]
	Other studies could not identify striking differences on endoscopy	[14]
	Biopsies of inflamed mucosa needed assess for inclusion bodies characteristic for CMV colitis	
Clostridium difficile associated disease	Pseudomembranes seldom occur in patients with IBD and *Clostridium difficile* infection	[15]
Campylobacter colitis	Can produce similar appearences to that of UC, detailed endoscopic assessment can help discern from IBD, in addition to stool cultures and biopsies	[16,17]
Ischaemic colitis	Typically a segmental disease, with normal mucosa proximal and distal to affected region of colon	[18]
	Rectum usually spared	[19]
Medication effects	Endoscopic assessment of Ipilimumab induced colitis reveals absent vascular pattern, and erythema in most patients. Variety of endoscopic features described in recent retrospective study	[20]
	NSAID induced colopathy can affect the whole colon, but has a right sided predominance. Colonic findings include ulceration, strictures and diaphragm like strictures	[21]
Solitary rectal ulcer syndrome	Ulcerative lesions (either single or multiple) most common finding, however can present with erythema or polypoid lesions	[22]
Behçet disease	Predilection for ulcers in the ileo-caecal region. Ulcers are typically larger than 1 cm, deep and have discrete margins	[23]
Amebic colitis	Endoscopic findings can vary from procto-sigmoiditis to right colonic involvement, biopsy and microscopic identification of Entamoeba species useful in evaluation of suspected amebiasis	[24]

IBD: Inflammatory bowel disease; ITB: Intestinal tuberculosis; CMV: Cytomegalovirus; CD: Crohn's disease; NSAID: Non-steroidal anti-inflammatory drug.

Table 2 Endoscopic activity indices

Endoscopic score	Comment	Variables	Ref.
Ulcerative colitis endoscopic index of severity	Easy to use. Scoring based on area of bowel most severely affected. Correlates well with patient reported symptoms	Vascular pattern, bleeding, ulcers/erosions	[83-85]
Mayo endoscopic score	Commonly used in clinical practice, four point scale (0-3) (Figure 1)	Vascular pattern, erythema, bleeding, friability, erythema, erosions and ulcers	[86]
Modified mayo endoscopic score	Total endoscopic mucosal activity accounted. Easy to use. Correlates well with clinical and histological activity	Combines disease extent with MES severity	[87]
Ulcerative colitis colonoscopic index of severity	Total score based on parameters throughout the colon. Validated	Vascular pattern, ulceration, granularity, friability/bleeding	[88]
CDEIS	Complex scoring system, time consuming. Validated. Utilised to monitor endoscopic response to treatment	Deep and superficial ulceration, surface of ulcerations, surface of lesions	[33,89]
SES-CD	Correlates well with CDEIS and clinical parameters Utilised to monitor endoscopic response to treatment	Ulcer size, stenosis, ulcerated and affected surfaces	[34,90]
Rutgeerts' score	To assess degree of postoperative recurrence at ileo-colonic anastomosis in Crohn's disease. Easy to use in clinical practice	Apthous ulceration, large ulcers, stenosis, nodularity and ileitis	[30]

SES-CD: Simple endoscopic score for Crohn's disease; CDEIS: Crohn's disease endoscopic index of severity.

mended to assess the extent of small bowel disease. VCE can be useful in the management of patients with known[35,36] or suspected IBD[37], by visualising mucosa not readily accessible by standard endoscopy. VCE is generally safe in patients with CD[35], the main complication of VCE is that of capsule retention. This can be reduced by excluding patients with known or suspected obstruction, and testing with patency capsule (although recent retrospective study of patients with CD capsule retention was not reduced by use of patency capsule in all patients, compared to selective use of patency capsule[38]). Imaging studies or patency capsule is recommended prior to capsule endoscopy in patients with known small bowel CD[4].

A prospective, multi-centered, blinded cohort study of patients with suspected CD found that VCE is equivalent

to ileo-colonoscopy in detecting ileo-caecal inflammation, and is superior to small bowel follow through studies[37]. In patients with suspected inflammatory phenotype CD, VCE is safe and can confirm diagnosis of CD in the presence of a normal ileo-colonoscopy[37]. VCE was superior to MRE and CTE in detecting mucosal lesions proximal to the terminal ileum, in a blinded prospective study of patients with suspected or newly diagnosed CD[39]. However, some authors have suggested that there is a trade-off between sensitivity and specificity with VCE. In particular, while VCE has greater sensitivity for small bowel mucosal lesions in individuals with suspected CD, there is a risk that presence of minor mucosal erosions can give rise to "false positive" diagnosis[40]. This underlines the importance of use of a scoring system (the Lewis index[41], is validated[42] and is comprised of three parameters: stenosis, ulceration and mucosal oedema).

A recent retrospective study of CD patients with isolated small bowel disease, undergoing VCE at diagnosis, found that moderate to severe disease as defined by the Lewis Score[41]; was associated with need for hospitalisation and corticosteroid use after 12 mo follow-up[43]. Conversely a retrospective study of patients with suspected CD, a low Lewis score (defined as < 135) is associated with a low probability CD diagnosis being confirmed on follow-up[44]. VCE also enables assessment of mucosal healing after initiating immunomodulator or biological therapy[45].

VCE may be contraindicated in patients with stricturing CD. MRE and CTE are utilized inpatients with complicated phenotype CD requiring small bowel evaluation, although their use can be limited by patient factors and local availability. Recently the magnetic resonance index of activity has been shown to correlate well with the SES-CD in the assessment of ileal lesions[46].

CRC SURVEILLANCE

Following index endoscopy, endoscopic re-evaluation to guide treatment is typically repeated every few years. Endoscopic surveillance is recommended to commence after 8[2,4,47] to 10[48] years from initial symptoms in patients with colonic disease, as some patients are at increased risk of developing CRC[49]. Patients with extensive colonic disease, concomitant PSC[50], young age at diagnosis, history of sporadic CRC in first degree relative, advanced age[51], severe inflammation[52] and longer duration of disease are at increased risk of developing CRC[53,54]. The optimal surveillance interval is uncertain, the major gastrointestinal societies have differing recommendations[2,4,47,48] but most now increasingly recognize that surveillance efforts are best focused on those at highest risk.

The goal of surveillance is to reduce CRC related mortality and morbidity, by detecting asymptomatic CRC and premalignant lesions. The risk of CRC in patients with IBD is less than previously reported (meta-analysis of population based studies described a pooled standardized incidence ratio of 1.7[53]), and is not increased in all patients. The incidence of CRC in patients with UC has decreased in the last few decades[55]. A nationwide Danish cohort found that patients diagnosed with UC in the 1980s were at increased risk of CRC, however that excessive risk of CRC has declined and no longer exceeds that of the general population[54]. CRC pathogenesis in patients with IBD is thought to occur mainly from dysplasia rather than adenoma to CRC sequence. Patients with colonic CD (3.9%) and UC (6.3%) were found to have reduced risk of developing sporadic adenomatous polyps compared to control population (25.9%)[56]. Interestingly patients with small bowel CD had similar rate of adenomas as control population[56].

The development of flat dysplasia in patients with colonic IBD makes endoscopic surveillance challenging. Traditionally surveillance consisted of numerous random biopsies (4 quadrant biopsies every 10 cm, minimum of 32 biopsies[47]), in addition to any suspicious lesions. The aim of random biopsy sampling is to detect dysplasia, often without visible mucosal abnormalities, before to progresses to CRC. However the principle that dysplasia in patients with IBD occurs usually occurs without visible mucosal abnormalities, has been challenged[57,58].

In patients with UC diagnosed with LGD, risk factors for progression to HGD or CRC include lesions greater than 1 cm, and lesions invisible on endoscopy[59]. Patients with UC were found to have a low risk of progression to CRC after resection of polypoid dysplasia, in a meta-analysis not including any studies using chromoendoscopy[60]. This finding supports current practice of resection and surveillance of raised lesions with dysplasia[49] (although non-adenoma like raised lesions with dysplasia are usually difficult to resect by polypectomy). In a prospective study of patients with undergoing surveillance colonoscopy, CE was superior to random biopsy or WLE in detecting dysplasia[61]. These findings contrast with a large retrospective study, which found no difference between CE and WLE with random and targeted biopsies, in detection rates for dysplasia[62]. Narrow band imaging has not been shown to be superior to white light endoscopy for detecting dysplasia in patients with IBD[63,64]. CE with targeted biopsies are more cost effective than traditional WLE endoscopy with random biopsies[65], and are recommended as preferred method of surveillance in recent guidelines[2,4,48].

The incidence of CRC amongst patients with IBD enrolled in regular surveillance appears to be lower than previously reported[52,66], likely reflecting improvements in medical care and quality of endoscopies performed; with both of this factors benefiting from technological advances. In patients with IBD who develop CRC, those involved in surveillance programmes have better survival rates than those not enrolled in regular surveillance[67].

MUCOSAL HEALING

Clinical remission and endoscopic remission correlate poorly[68], especially in CD. VCE reveals that in patients with small bowel CD in clinical remission, mucosal healing (defined as a Lewis score < 135) is rare[69]. Mucosal healing has become an important treatment target in managing patients with IBD, and is associated with improved outcomes[70,71]. A recent meta-analysis found that mucosa healing was associated with long-term clinical remission, corticosteroid free remission and avoidance of colectomy[71]. Mucosal healing at 26 wk was predictive of corticosteroid free remission at week 50 in a subgroup analysis of 172 patients from the SONIC trial[34]. Considerations influencing the choice of modality to assess mucosal healing are discussed in a recent review[72], colonoscopy is the gold standard in ileo-colonic disease. Faecal calprotectin has been proposed as a surrogate non-invasive marker for mucosal healing, which may rationalize the use of endoscopy in assessing mucosal healing[73]. Faecal markers may not, however, have adequate negative predictive value in all patients, especially those with limited, small bowel disease.

There is a discrepancy between the endoscopic and histological assessment in UC[74], especially mild disease[75]. Endoscopic mucosal healing or inactivity, does not always equate to quiescent microscopic disease[76]. Histological remission is not yet a routinely sought objective in the management of IBD[77], however histological remission better predicts need for hospitisation and corticosteroid use in patients with UC compared to endoscopic remission[78]. A recent prospective study of 179 patients with UC in clinical remission, revealed an association between baseline histology grade and risk of clinical relapse[79]. Patients with an elevated histological grade (Geboes[80] grade $\geqslant$ 3.1) at baseline had a relative risk of clinical relapse, over 12 mo follow-up, of 3.5 (95%CI: 1.9-6.4, P < 0.0001)[79]. To aid assessment of histological disease activity in patients with IBD, there needs to be close co-operation between endoscopists and histopathologists[81].

Confocal laser endomicroscopy has the potential to provide real-time microscopic assessment ("endopathology"), which can help predict disease relapse in patients with endoscopic and clinical remission[82].

CONCLUSION

Endoscopy remains integral in the diagnosis and management of IBD, endoscopic disease assessment is essential for objective monitoring of treatment response. Endoscopic severity scores facilitate monitoring of endoscopic response to treatment, and help identify patients who may benefit from escalation of therapy.

The paradigm of CRC surveillance in patients with IBD is shifting from high frequency random biopsies, to that of high quality visual inspection and targeted biopsies of suspected dysplasia, enabled by technological advances including CE and high-definition endoscopes. Current practice in the management of dysplasia entails resection of dysplastic lesions where possible, rather than colectomy.

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P- Reviewer: Actis GC, Wenzl HH, Yildiz K **S- Editor**: Qiu S
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