Endoscopy in Inflammatory Bowel Disease: Indications, Surveillance, and Use in Clinical Practice

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Endoscopy plays an integral role in the diagnosis, management, and surveillance of inflammatory bowel disease (IBD). Because there is no single pathognomonic test that establishes the diagnosis of IBD, endoscopy is useful in establishing the diagnosis, excluding other etiologies, distinguishing Crohn's disease from ulcerative colitis, defining the patterns, extent, and activity of mucosal inflammation, and obtaining mucosal tissue for histologic evaluation. In established IBD, endoscopy helps define the extent and severity of involvement, which in turn influences medical and surgical decisions, aids in targeting medical therapies, and allows for the management of IBD-related complications. Furthermore, endoscopy plays a key role in the surveillance of patients with long-standing colitis who are at increased risk for dysplasia and the development of colorectal cancer.

This review will update the role of endoscopy in IBD, with particular reference to indications, surveillance, and use in clinical research and practice.

Diagnosis of Inflammatory Bowel Disease by Endoscopy

Ulcerative Colitis

None of the endoscopic features of IBD are specific, and the diagnosis should be based on the combination of clinical, endoscopic, and histologic findings. However, the characteristic patterns of inflammation in UC help to differentiate it from that of CD or that of enteric infections. Endoscopically the inflammatory changes begin just above the anorectal junction and spread proximally in a confluent and continuous fashion. The inflammation might be confined to the rectum (proctitis) or extend throughout the entire colon (pancolitis), and there is generally a clear demarcation between involved and normal areas. The earliest endoscopically visualized changes are erythema and vascular congestion of the mucosa. As edema becomes more prominent, small mounds might form, resulting in a fine granular appearance. The mucosa might be friable and bleed with minor contact. As the inflammation become more severe, ulcerations form, and bleeding might occur spontaneously. Coalescence of small ulcers might result in large or linear ulcerations.[2] Because of the characteristics of the inflammation in UC, ulcers always occur surrounded by inflamed and abnormal appearing mucosa.

Biopsy specimens should be taken from areas of inflammation as well as from healthy looking mucosa above the proximal extent of inflammation. A biopsy should be performed on the rectum because a macroscopically and microscopically normal rectum theoretically excludes UC. However, this might not hold true in patients who have initiated treatment with either topical or systemic IBD therapies.[3] Bernstein et al[4] prospectively evaluated 39 patients with treated UC without any features to suggest CD and found 44% to have endoscopic patchiness, including 13% with rectal sparing. Thirty-three percent had histologic patchiness, including 15% with complete rectal sparing. Both endoscopic and histologic patchiness were seen in 23% of patients, leading the authors to conclude that in patients with treated UC, rectal sparing or patchy inflammation does not necessarily imply CD. In addition, patients with distal colitis might have areas of inflammation in more proximal regions such as the periappendiceal region of the cecum.[5] Matsumoto et al[6] compared the clinical course of 23 patients with active distal UC with patchy involvement at the appendiceal orifice to UC patients without periappendiceal involvement. Although patients with periappendiceal involvement had more histologically active disease, their endoscopic remission rate at 12 months was higher (84% vs 40%, $P < .05$), suggesting that periappendiceal involvement might indicate more responsive

Abbreviations used in this paper: ANCA, anti-neutrophil cytoplasmic antibodies; ASCA, anti-Saccharomyces cerevisiae antibodies; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasonography; LGD, low-grade dysplasia; PSC, primary sclerosing cholangitis; TTS, through-the-scope.

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disease. The terminal ileum is characteristically not involved in UC. However, in up to as many as 10% of patients with active pancolitis, "backwash ileitis," nonspecific inflammatory changes without ulceration can extend a few centimeters into the terminal ileum.[2]

Chronic inflammation can result in mucosal atrophy, with loss of the haustral folds and luminal narrowing yielding the "microcolonic" appearance. In addition, mucosal atrophy might leave behind pseudopolyps (inflammatory polyps), swollen islands of edematous granulation tissue that can assume any shape as well as form mucosal bridges. Pseudopolyps are not specific to UC and can also be seen in CD. Although they are believed not to have malignant potential and do not need to be removed, biopsy or polypectomy should be considered if they are atypical in appearance, color, or are bleeding. Because of the potential for intussusception or obstruction, pseudopolyps should also be removed if they are sufficiently large to compromise the lumen.[7]

In patients with signs and symptoms of UC, a flexible sigmoidoscopy with biopsy and a thorough stool analysis might be sufficient to make the diagnosis. This is particularly true if the scope can be passed beyond the inflamed segments. There are limited data comparing the benefits of initial sigmoidoscopy versus initial colonoscopy. Practice surveys[8] show that the majority of physicians would proceed with colonoscopy if colitis was suggestive of CD in the rectosigmoid area (81%) or if UC extended proximal to the rectosigmoid area (70%). The study concluded that because the majority of physicians chose to establish the extent of disease in both CD and UC at the first endoscopy (index colonoscopy), colonoscopy was more cost-effective. However, when knowledge of disease distribution was not essential for patient care, flexible sigmoidoscopy is associated with substantial cost savings.[8] Although colonoscopy is safe in patients with extensive or severe inflammation, air insufflation should be minimized, and difficulty advancing the scope in a tortuous colon should be avoided to minimize the risk of perforation.[9]

Crohn's Disease

CD can be distinguished from UC at endoscopy by the presence of asymmetrical, heterogeneous patchy inflammation that can occur anywhere throughout the gastrointestinal tract. Areas of inflammation typically are interposed between normal appearing mucosa and are called "skip" lesions. In the setting of colonic disease, the rectum is spared of inflammation in up to 50% of patients. Tiny aphthous erosions are the earliest mucosal changes seen endoscopically.[10] Ulcerations can remain aphthous and superficial or enlarge, becoming deep in appearance. In contrast to UC in which ulcerations occur within inflamed mucosa, the ulcerations in CD commonly occur on a background with a paucity of inflammation. Although the presence of small ulcerations on the ileocecal valve or within the terminal ileum in a symptomatic individual is highly suggestive of CD, incidental ileal ulcers can also be seen in individuals taking NSAIDs[11] as well as those with infections such as yersinia and tuberculosis. Because of the patterns of inflammation, ileocolonoscopy should be standard in any patient with suspected CD.[12] As a result of transmural inflammation, enterocolic (typically ileosigmoid) fistula tract might be seen during endoscopy, albeit infrequently. In patients with chronic disease colonic or ileal strictures might be encountered.

Biopsy specimens should be taken from erosions and ulcerations as well as from normal adjacent areas to establish the presence of lesions occurring on a background of normal mucosa to demonstrate the histologic skip phenomenon. Biopsy specimens taken from the edges of ulcers and aphthous erosions maximize the yield of identifying granulomas, whereas biopsy specimens from cobblestoned mucosa infrequently contain granulomas.[13] Although the incidence of granulomas has been demonstrated in 15%–36% of endoscopic biopsy specimens, they seem to be of little clinical significance except to help confirm the diagnosis.[14] Biopsy specimens should be taken from endoscopically normal rectal mucosa because 13%–37% will display granulomas, which can further help to exclude UC, especially in those patients with disease limited to the colon.[15]

For CD affecting the small bowel, ileocolonoscopy or enteroscopy (for upper gastrointestinal CD) with histology is the gold standard, but only if the lesions are within the reach of the scope. The diagnostic approach to patients with clinical symptoms suggestive of small bowel CD but without specific abnormalities on standard upper endoscopy, ileocolonoscopy, or small bowel contrast imaging (small bowel follow-through or computed tomography) has advanced in recent years. For this subset of patients in whom there is a high clinical suspicion of small bowel CD, push enteroscopy has helped to identify macroscopic and/or microscopic lesions consistent with CD in 50% of patients undergoing the examination.[16] Because of these findings push enteroscopy remains an important diagnostic tool in the evaluation of patients with suspected small bowel CD. However, short of intraoperative enteroscopy there remains a long segment of small bowel that lies beyond our optical reach.

Wireless capsule endoscopy now provides us with a tool to evaluate patients with suspected small bowel CD

who have undergone unrevealing endoscopic (enteroscopy and ileocolonoscopy) and radiologic evaluations. Herrerias et al[17] with wireless capsule endoscopy studied 21 patients in whom there was a clinical suspicion of small bowel CD that could not be confirmed by using traditional techniques. Nine patients (43%) had lesions supporting the diagnosis of CD. Furthermore, in 3 of 4 patients (75%) in whom ileoscopy was not technically possible, capsule endoscopy identified lesions deemed to be compatible with CD. In 6 of 9 (66%) patients with a normal ileoscopy, findings suggestive of CD were observed, leading the authors to conclude the capsule identified CD in more proximal parts of the ileum. The most frequently identified lesions were aphthous erosions, linear and serpiginous ulcers, and fissures located in the distal ileum.[17] Although recent studies show capsule endoscopy to be a valuable diagnostic tool, some hesitancy must be used in interpreting the findings as conclusive because capsule technology lacks the ability to obtain histologic confirmation. Although wireless capsule endoscopy is noninvasive, does not require sedation, and allows study of the entire small bowel, capsule endoscopy does carry the risk of being retained proximal to a small bowel stricture, precipitating a small bowel obstruction. It our current practice to exclude small bowel strictures with a barium small bowel study before capsule endoscopy. To date there have been a number of reports of capsule retention and small bowel obstruction in patients with CD requiring either endoscopic or surgical intervention.[18] Although the experience with capsule endoscopy in IBD is still in its early stages, there seems to be a definite role in patients in whom there is a clinical suspicion of small bowel CD, and upper endoscopy, ileoscopy, enteroscopy, and small bowel x-ray or computed tomographic enterography have been unrevealing or are not technically possible.

Role of Endoscopy in Distinguishing Inflammatory Bowel Disease From Other Disorders

Endoscopy with biopsy plays an important adjunct to the clinical and radiographic findings in distinguishing IBD from enteric infections, mesenteric ischemia, neoplasia, diverticulitis, radiation colitis, drug-induced colitis, and other etiologies. In a prospective study of patients presenting with acute mucoid bloody diarrhea with suspected IBD, up to one third were found to have an infectious etiology.[19] However, complicating this picture is the propensity for patients with IBD to be superinfected with bacterial pathogens.[20] Distinguishing acute self-limited colitis, which most commonly is due to an infectious etiology, from IBD requires a careful clinical evaluation and stool analysis. Endoscopy with biopsy might be required if stool analysis is negative and the patient has persistent symptoms. In most patients a flexible sigmoidoscopy is sufficient; however, if the history, examination, or imaging studies suggest right-sided colitis, or if CD is suspected, ileocolonoscopy is more definitive.

The mucosal response to an infectious agent and therefore the endoscopic appearance can vary with the virulence, duration of the infection, status of the host immune system, as well as history of recent antimicrobial therapy. The endoscopic features common in enteric infections and uncommon to IBD are the presence of purulent exudates or pseudomembranes completely or partially covering the mucosa. The erythema, edema, granularity, and patchy inflammation of the mucosa seen in enteric infections can appear indistinguishable from IBD.[19] Histologic examination of mucosal biopsy specimens can be helpful in distinguishing IBD from infectious diseases. Pseudomembranes, viral inclusion bodies, or amebic trophozoites might help to identify infections, whereas granulomas might help support a diagnosis of CD once other infectious processes have been ruled out.[21] Cultures of material in which biopsy was performed might increase the yield over stool cultures in identifying infectious pathogens.[22]

Apart from the history, one of the most significant tools in helping to differentiate IBD from acute self-limited colitis are the chronic histologic changes associated with IBD and not acute self-limited colitis. Features of chronicity such as distorted crypt architecture, increased cellularity of the lamina propria, a villous surface, epithelioid granulomas, crypt atrophy, basal lymphoid aggregates, and basally located isolated giant cells have been identified as having a high predictive value (87%–100%) for IBD.[23] The absence of any these features in addition to the absence of Paneth's cell metaplasia virtually excludes IBD.[24] Unfortunately even with these endoscopic and histologic differences, in some cases it can be difficult to distinguish enteric infection from IBD. Table 1 lists the more common infections of the colon and the endoscopic findings that can mimic CD and UC.

Endoscopic Differentiation of Ulcerative Disease and Crohn's Disease

The differentiation of CD and UC has important medical, surgical, and prognostic ramifications. Although ileocolonoscopy can differentiate the characteristic appearances of inflammation of CD and UC in the

Table 1. Infectious Colitis Pathogens Mimicking IBD

Infectious agent	Clinical and/or endoscopic features	Mimics		Diagnostic test
		UC	CD	
Bacterial pathogens				
Salmonella	Friable mucosa with petechia, might be segmental	+	+	Stool culture
Shigella	Patchy, intense magenta-colored erythema, rectal sparing rare	+	−	Stool culture
Campylobacter	Abdominal pain worse than endoscopic findings, acute like CD/chronic like UC	+	+	Stool culture
Escherichia coli 0157:H7	Range from nonbloody diarrhea to fulminant colitis, R>L	+	++	Stool culture or biopsy
Yersinia	Patchy, R>L, ileal aphthoid ulcers	+	++	Stool culture or serology
Clostridium difficile	Prior antibiotics, pseudomembranes, L>R, rectal sparing in 30%	+	+	Stool toxins
Klebsiella oxytoca	Hemorrhagic colitis in association with antibiotics	+	−	Withdraw antibiotics
Tuberculosis	Transverse/circumferential ulcers, cecal narrowing, no rectal/perianal lesions	−	++	Ziehl-Neelsen stain of rectal biopsy
Gonorrhea	Anal intercourse, proctitis, perianal friability and ulcerations	+	−	Culture (rectal swab)
Chlamydia	Anal intercourse, lymphogranuloma venereum, perianal stricture, abscess, fistula	+	−	Serology, Frei test
Syphilis	Anal intercourse, proctitis; perianal vesicles and low rectal ulcers	+	+	Serology, silver stain of rectal biopsy
Parasitic pathogens				
Schistosomiasis	Travel, extensive colitis, segmental lesions including large proliferative polyps	+	−	Stool examination, rectal biopsy
Amebiasis	Travel, immigrants, men who have sex with men, acute like UC/chronic like CD	+	+	Fresh stool for trophozoites, serology, or rectal biopsy
Viral pathogens				
Herpes simplex	Anal intercourse, painful proctitis, perianal vesicles, deep ulcers in lower rectum	+	+	Biopsy
Cytomegalovirus	Immunocompromised, fulminant R>L colitis, discrete punched-out shallow ulcers	+	+	Biopsy ulcer edge for viral inclusion bodies, serology
Fungal pathogens				
Candida	Immunocompromised, neutropenic and AIDS, esophageal > colon	−	+	Biopsy evidence of invasion
Aspergillus	Immunocompromised, neutropenic and AIDS, bleeding ulcers	−	+	Biopsy evidence of invasion
Histoplasmosis	Immunocompromised, midwestern USA, pulmonary > GI symptoms, R>L	−	+	Special stains, culture

AIDS, acquired immunodeficiency syndrome.
Adapted and reprinted with permission from Farrell and Peppercorn.[89]

majority of cases, 10% of patients have "indeterminate" colitis. In a prospective series of more than 350 IBD patients followed for more than 22 months, index colonoscopy and biopsy were accurate in distinguishing UC and CD in 89% of cases, the IBD diagnosis was revised in 4% of cases, and the diagnosis of indeterminate colitis remained in 7% of patients. Although the differentiation was more difficult in the presence of severe inflammation, the most useful discriminatory features for CD were the presence of discontinuous inflammation, anal lesions, and cobblestoning. Erosions or microulcerations occurring within a granular mucosa were found to be specific for UC.[25] A large population study of 791 patients with IBD found that after 1–2 years of follow-up, 10% of patients were reclassified. Eighty-eight percent of the patients with UC and 91% of patients with CD had their initial diagnosis confirmed, whereas 33% of patients with indeterminate colitis were reclassified as UC and 17% as CD.[26] This study points out the importance of reevaluation after an initial diagnosis not only in patients with indeterminate colitis, but also in patients with UC and CD.

In addition to ileocolonoscopy with biopsy, radiology, and serologic testing (anti-neutrophil cytoplasmic antibodies [ANCA] and anti-Saccharomyces cerevisiae antibodies [ASCA]) some authors have recommended upper endoscopy in patients with indeterminate colitis with either targeted or random biopsies to evaluate for granulomas of the upper gastrointestinal tract.[27] The utility of wireless capsule endoscopy has also been studied in a series of 31 patients with indeterminate colitis, of whom 23 had known antineutrophil cytoplasmic antibody and ASCA serologies. Capsule studies showed small bowel findings in 52% of patients. The small bowel findings were found in equal frequencies in patients with both UC-like and CD-like serologic patterns.[28] This lends

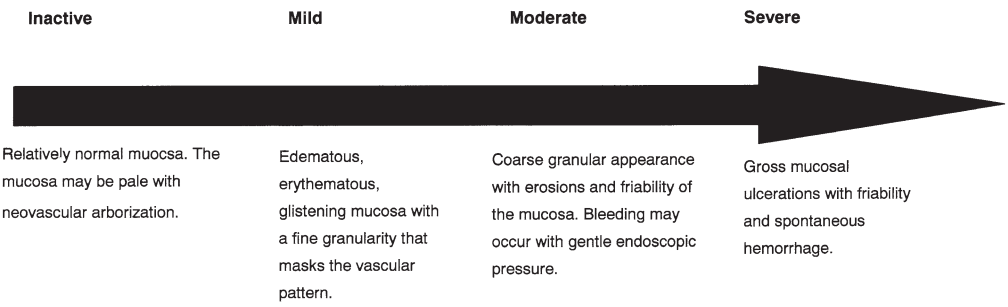

Figure 1. Spectrum of endoscopic findings in UC.[35]

further support that the diagnosis of CD or UC cannot be made with a single test, but it requires the integration of the clinical, serologic, endoscopic, histologic, and radiographic information. Endoscopic ultrasonography (EUS) has been used in small series to differentiate CD from UC on the basis of the transmural nature of CD; however, its role has remained limited.[29] As targeted cytokine therapies diverge in the treatment of CD and UC, new diagnostic technologies will need to be developed to better classify indeterminate colitis.

Endoscopic Assessment of Extent and Severity of Disease

Ulcerative Colitis

Localization of disease aids in determining prognosis and appropriateness of medical therapies, helps to stratify risk of colon cancer, and can help decision making in those undergoing surgical therapy. Colonoscopy with mucosal biopsy is significantly more sensitive than barium contrast studies in defining the extent of disease.[30] However, the endoscopic appearance alone tends to underestimate the extent when compared to histologic involvement.[31] A recent study comparing chromoendoscopy to conventional colonoscopy in chronic UC found a significantly better correlation between chromoendoscopy and extent of disease defined by histology (89%) as compared to conventional colonoscopy (52%). Conventional colonoscopy underestimated extent of disease by 16 cm compared to 2 cm by chromoendoscopy when compared to histology.[32] Consequently, biopsy specimens should be taken from beyond the most proximal extent of endoscopic inflammation by using the histologic involvement to define the proximal extent of disease. In clinical practice, identifying patients with disease limited to the rectum or left colon allows for targeted topical therapies in the form of medicated suppositories or enemas, whereas patients with more extensive disease might be better served with oral or combination therapy.

The extent of mucosal involvement in IBD is not static but can regress or progress over time. Studies have identified that up to one third of patients initially diagnosed with disease limited to the rectum will have proximal extension.[33] In a large series of UC patients the probability for further progression of proctosigmoiditis, evaluated by sigmoidoscopy and radiology, was 53% after 25 years.[34] Because the risk of developing colorectal cancer relates to the extent of mucosal involvement, periodic restaging of extent of disease is important in patients with long-standing colitis.

Although the role of direct endoscopic assessment in patients with mild to moderate symptoms remains controversial, endoscopy plays an important role in patients with severe clinical or steroid refractory disease. Flexible sigmoidoscopy with limited insufflation is sufficient in most patients because the most severe disease is typically encountered distally. Several UC studies have shown that the endoscopic severity correlates with severity of symptoms and can predict the need for intensive medical or surgical therapy. Numerous assessment scores have been developed, but many are complex and time-consuming, and their use is limited to clinical trials. In clinical practice discriminating the endoscopic severity of disease along a spectrum (inactive, mild, moderate, and severe disease) is usually sufficient to make decisions regarding medical management. Patients with inactive disease might have a relatively normal appearing mucosa with a distorted vascular pattern but without friability. Mild disease might appear edematous and granular with distortion of the vascular markings. Moderate endoscopic disease is defined by the presence of a coarse granular appearance with erosions and friability of the mucosa that might bleed with endoscopic pressure. Severe disease might display gross ulcerations as well as areas that bleed spontaneously.[35] Figure 1 depicts the spectrum of the endoscopic findings in UC.

The presence of severe, deep colonic ulcerations down to the level of the muscularis mucosa has been associated with a disease that is refractory to medical therapy with an increased rate of complications including spontaneous perforation.[36] Carbonnel et al[9] evaluated 85 consecutive UC patients with severe clinical symptoms by using

colonoscopy and demonstrated that 93% of patients with extensive deep colonic ulcerations went on to require colectomy. Similarly, in patients with initial moderate endoscopic disease who went on to require surgical therapy, a repeat preoperative colonoscopy revealed severe disease with deep ulcerations into the muscle layer in 5 of 6 (83%) of patients. Conversely, in a study of 34 UC patients with severe clinical symptoms but a lack of severe colonoscopic features, prolonged medical therapy allowed avoidance of colectomy in more than 50% of the patients.[37] Because of the strong association with medical treatment failure, early escalation of medical therapy or even early surgical intervention should be considered in patients with severe deep ulcerations reaching the muscularis layer.[7]

Crohn's Disease

The utility of assessing the extent and severity of endoscopic disease in CD has remained problematic. This is largely due to interobserver variability, inability to completely visualize all involved mucosa, and because of a poor correlation between the mucosal findings and the clinical features in a disease characterized by transmural inflammation. In the late 1980s the GETAID group prospectively studied 142 patients with active CD and developed a quantitative endoscopic index of severity (CDEIS) by dividing the bowel into 5 segments (rectum, sigmoid and left colon, transverse colon, right colon, and ileum) and generating a numeric score based on surface involvement by disease and the presence of deep or superficial ulcerations. They found no correlation between the endoscopic extent or severity and the clinical severity as measured by the Crohn's disease activity index (CDAI). Similarly the GETAID endoscopic score was not able to predict which patients would be responsive or resistant to corticosteroid treatment.[38]

Endoscopic Assessment of Response and Prediction of Relapse

Ulcerative Colitis

Drug-induced clinical remission in active UC is associated with endoscopic and histologic remission in approximately 70% and 50% of patients, respectively. The endoscopic response often lags behind clinical response to therapy, and histologic abnormalities often persist longer. Early studies by Wright and Truelove[39] demonstrated that 40% of patients who reached endoscopic remission after treatment remained symptom free during a 1-year follow-up compared with 18% if the endoscopic lesions remained. Riley et al[40] found that in patients with quiescent UC, histologic evidence of an acute inflammatory cell infiltrate, crypt abscess, or mucin depletion conferred a 2- to 3-fold increase in the relapse rate. The presence of a chronic inflammatory cell infiltrate or crypt architectural irregularities bore no relation to the frequency of relapse. Bitton et al[41] prospectively followed 74 patients with UC in clinical and endoscopic remission for 1 year and found that although there were no specific endoscopic features in quiescent disease that helped predict relapse, a basal plasmacytosis on rectal biopsy was an independent predictor of earlier relapse. Although there are no clinical guidelines on when or how often to repeat the endoscopic evaluation in patients with improved or quiescent UC, in selected UC patients these features could be important parameters to monitor when determining medical management.

Crohn's Disease

Few medical trials in CD have used endoscopic or histologic improvement as an end point for clinical success. This largely reflects the discord between clinical symptoms and endoscopic lesions as well as the poor correlation between steroid-induced clinical remission and mucosal healing. A second study by the GETAID group[42] prospectively assessed the value of colonoscopic monitoring in 136 CD patients who achieved clinical remission with prednisolone. Although there was significant overall endoscopic improvement, only 27% of these patients were in endoscopic remission. Those not in endoscopic remission were randomly assigned to either prednisolone tapering or prolongation of therapy for an additional 5 weeks. The extra course of prednisolone significantly improved the endoscopic score, with 30% achieving endoscopic remission; however, the 2 groups (prednisolone taper and 5 additional weeks of prednisolone) had identical subsequent courses in ability to wean off prednisolone (82% and 80%, respectively) and in the rate of clinical relapse rate at 18 months (69% and 70%, respectively). These results suggest that persistent endoscopic lesions in patients with CD who achieve corticosteroid-induced clinical remission are not predictive of early relapse, and endoscopic monitoring of patients with CD receiving corticosteroids is not of benefit.

By contrast, preliminary studies have suggested that endoscopic monitoring might have a role in CD patients treated with biologic or long-term immunomodulator agents. In addition to clinical improvement, infliximab therapy has also resulted in significant endoscopic healing and disappearance of histologic inflammatory infiltrates.[43] A subgroup analysis of the 54-week ACCENT-1 study demonstrated that when significant mucosal healing is achieved with infliximab, the time to relapse is significantly prolonged. Nine patients who had complete disappearance of ulcers remained in remission for a me-

dian of 20 weeks (range, 14–78 weeks), 6 patients who had significant but incomplete endoscopic healing maintained remission for a median of 19 weeks (range, 17–50 weeks), whereas all 4 patients who were in clinical remission but had no significant endoscopic healing had a clinical relapse after a median of 4 weeks (range, 0–8 weeks). The authors concluded that endoscopic appearance in CD might be a better predictor of the future clinical course than the Crohn's disease activity index, and that endoscopic healing might prove to be a better treatment goal.[44]

Endoscopic Assessment of Pouchitis or Postoperative Crohn's Disease Recurrence

Ulcerative Colitis

Endoscopy is an important modality in helping to establish the diagnosis of pouchitis in patients with ileoanal pouches or ileal reservoirs after surgical resection. Pouchitis is a heterogeneous disorder, and multiple studies have shown that the endoscopic appearance or clinical symptoms alone are poor predictors of pouchitis. Minor endoscopic abnormalities might be present in asymptomatic patients, often some localized perisuture ulcerations, whereas patients with increased stool frequency, urgency, and abdominal pain might have no endoscopic abnormalities. The diagnosis is now standardized on the basis of the Pouchitis Disease Activity Index (PDAI),[45] which incorporates clinical, endoscopic, and histologic features to help differentiate pouchitis from cuffitis, irritable pouch syndromes, and other disorders. The endoscopic features, when present, that are suggestive of pouchitis might appear similar to those of active UC, with a diffusely erythematous, friable, granular mucosa with loss of vascular markings. Ulcerations might be superficial, deep, or irregular. The ileal mucosa proximal to the pouch should be normal, and severe inflammation or extensive ulceration extending well above the pouch should suggest an alternative diagnosis such as CD, ischemia, or infection. Evaluation of the ileoanal pouch should be performed with a gastroscope or sigmoidoscope rather than a colonoscope, because the former facilitate easier maneuverability because of their smaller size and greater tip deflection.

Crohn's Disease

Endoscopy plays an important role in evaluating for postoperative recurrence in CD patients who have undergone prior bowel resections. Although perioperative endoscopy has not been shown to change management and mild disease at the anastomosis at the time of surgery does not seem to influence CD recurrence,[46] the postoperative endoscopic evaluation can help to predict future relapse. Rutgeerts et al[47] performed ileocolonoscopy in 89 CD patients after undergoing ileocolonic resection. Although 20% of the patients were asymptomatic, endoscopy revealed recurrence of the neoterminal ileum in about 70% of patients within 1 year. Most significantly, the future course of the disease could be predicted by the extent and severity of the early postoperative ileal lesions. On the basis of these findings, some authors recommend postoperative ileocolonoscopy at 6 to 12 months after resection to identify patients at high risk of relapse who might benefit from prophylactic therapy. In clinical practice, many CD patients receive postoperative prophylactic therapy (mesalamine, mercaptopurine, azathioprine), and therefore in these patients routine postoperative endoscopic surveillance is often not indicated.

For patients who have undergone diversion and colostomy procedures, the distal bypassed colon might develop mucosal inflammatory changes termed *diversion colitis*. The endoscopic findings of friability, ulceration, and exudation are common. Rarely are the histologic findings similar to those of CD, and in only a small subset of patients does the colitis represent a recurrence of their disease. The majority of patients with diversion colitis will have normalization after reanastomosis.[48]

For patients who have either a colostomy or ileostomy, direct mucosal visualization can define recurrent disease in those with a change in clinical symptoms, ostomy output, or peristomal ulcerations. For reasons related to size and maneuverability, the use of the more flexible gastroscope or sigmoidoscope should be considered when performing procedures through an ostomy.

Specific Indications for Endoscopy in Inflammatory Bowel Disease

Dysplasia and Colorectal Cancer Surveillance

Patients with long-standing UC and Crohn's colitis are at increased risk for developing colorectal cancer, and despite the lack of randomized controlled clinical trials, colonoscopic surveillance is widely accepted.[49] Despite guidelines there is a tremendous variation in clinical practice. Currently endoscopic surveillance is recommended for patients with extensive UC or Crohn's colitis for longer than 8 years or left-sided UC or patchy Crohn's colitis for longer than 15 years, IBD patients with a family history of colorectal cancer, or patients with primary sclerosing cholangitis (PSC). In patients with long-standing colitis who have undergone a subtotal colec-

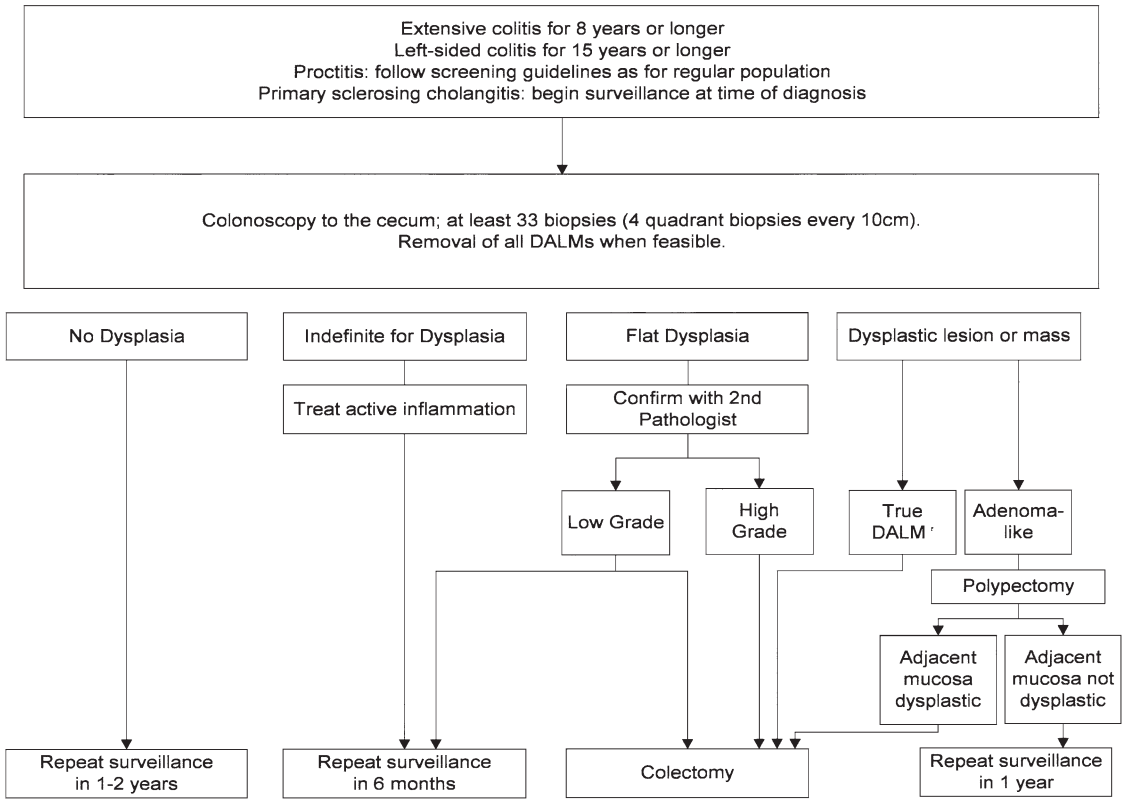

Figure 2. Potential strategy for colorectal cancer screening in chronic ulcerative colitis. Reprinted with permission from Farrell and Peppercorn.[1]

tomy with ileorectal anastomosis, the rectum retains the same cancer risk and should have periodic endoscopic surveillance. Early onset of disease and backwash ileitis might also increase the risk above that of the general population, whereas patients with CD confined to the small bowel or patients with ulcerative proctitis appear to have the same colorectal cancer risk as the general population. The risk of colorectal cancer has been shown to be associated with the extent and duration of colonic inflammation. Recent studies, in contrast to the past belief, have suggested that disease severity might also be a significant risk factor in the development of colorectal cancer in chronic UC.[50]

One of the major difficulties in identifying dysplastic mucosa during colonoscopy arises in that the majority of changes occur within macroscopically normal tissue. As a result, the accuracy in predicting dysplasia correlates with the number of biopsy specimens obtained. It has been estimated that to exclude dysplasia with a 90% certainty, 33 biopsy specimens are required, and to increase the accuracy to 95%, nearly twice the number of biopsy specimens are required.[51] Current surveillance strategies call for annual colonoscopy, avoiding periods of clinical relapse, with multiple biopsy specimens (4 circumferential) taken at every 10-cm interval, with additional biopsy specimens at sites of strictures or raised lesions. Figure 2 shows a potential strategy for endoscopic surveillance based on available data and proposed guidelines. A recent prospective randomized trial showed that in patients with chronic UC, chromoendoscopy and mucosal staining with methylene blue allowed for more targeted biopsies with a significantly higher detection rate of dysplasia when compared to patients evaluated with conventional colonoscopy. More specifically, the detection of high- or low-grade dysplasia (LGD) found in macroscopically normal tissue was increased by 6-fold (24 vs 4).[32] Although not yet performed routinely at most centers, chromoendoscopy provides a new method for the early detection of dysplasia, which might have important implications in the medical and surgical management of patients with UC.

Colectomy is indicated when a colorectal cancer, high-grade dysplasia (carcinoma in situ), or dysplasia (high or low grade) is found in a "true" dysplasia-associated lesion or mass that is a lesion, mass, stricture, or broad-based tumor that does not resemble an adenoma. However, 2 studies[52,53] have suggested that an adenoma-like dysplasia-associated lesion or mass can safely be removed by polypectomy just as in non-IBD patients. This was true regardless of the location, either within or outside areas of documented colitis, provided there is no dysplasia in the adjacent flat mucosa or on other surveillance biopsies.

These findings must be tempered with caution in that these studies reported on a relatively small number of patients, some with less than a 5-year follow-up. Although polypectomy with rigorous endoscopic surveillance remains a potential strategy, this decision must be weighed in the context of the patient's age, extent, duration, and severity of disease, as well as other colorectal cancer risk factors.

The optimal strategy for managing flat LGD is more controversial because the predictive value for more advanced pathology is less clear. An earlier analysis of 10 prospective studies of dysplasia surveillance showed that 19% of patients with LGD who underwent immediate colectomy had concurrent carcinoma,[54] whereas the 5-year predictive value of LGD for either cancer or high-grade dysplasia has been reported to be as high as 54%.[55] In a more recent retrospective study in patients with long-standing UC, Ullman et al[56] found that in 46 patients with flat LGD who underwent immediate colectomy, there was unexpected high-grade dysplasia or invasive cancer in 4 of 17 (23.5%), and by actuarial analysis the rate of neoplastic progression increased to 53% at 5 years. They concluded that flat LGD confirmed by a second pathologist, even from a single biopsy specimen, is a powerful predictor of a concurrent advanced neoplasia, and that immediate colectomy should be considered. By contrast, Lim et al[57] in a 10-year follow up of UC patients with and without LGD suggested that previous estimates of the risk of progression to high-grade dysplasia or cancer in patients with LGD are inflated. The British group tracked 126 patients who entered a chronic UC colonoscopic surveillance program before 1990 and who had intact colons through 2000. Among patients with 10-year follow-up, 29 had LGD and 97 had no dysplasia in 1990. By 2000, 10% of patients with LGD and 4% of control subjects had developed high-grade dysplasia or colorectal cancer. Kaplan–Meier analysis showed no significant difference between the LGD and no dysplasia for outcomes such as death or colectomy. However, review of the original histologic slides by 5 pathologists showed marked interobserver variation with a consensus diagnosis (3 of 5 pathologists agreeing with diagnosis of LGD) in only 38% of cases. The authors suggested that a diagnosis of LGD might not be sufficiently reliable to justify prophylactic colectomy. It is our practice to discuss the evidence, risks, and benefits of pursuing colectomy or continuing a surveillance strategy with our patients. We have all pathology specimens reviewed by a dedicated gastrointestinal pathologist. When LGD is confirmed, we lean our recommendations toward what we believe to be the more conservative approach and advocate for prophylactic curative colectomy. This is especially the case when the clinical course has been that of frequent relapses, the patients are young with extensive disease and have many years of mucosa at risk ahead of them, or because of factors (compliance, pseudopolyps, etc) that make surveillance difficult. Ultimately we need more prospective, long-term studies with rigorous biopsy protocols, expert pathologic review, and careful follow-up to resolve these issues.

There are no guidelines on whether to survey for dysplasia or cancer in patients with UC who have undergone ileal pouch–anal anastomosis. Isolated accounts of neoplastic pouch transformation have suggested the need to perform routine ileoanal pouch surveillance, but recent reports in high risk UC patients found the development of pouch dysplasia to be a rare event.[58] A study of 160 patients who underwent biopsy a total of 222 times with an average surveillance time of 8.4 years after surgery showed that in 1800 pouch-years of surveillance, only 1 patient had focal LGD of the pouch, leading the authors to confirm that even with long-term follow-up of patients with ileoanal pouch, there is little evidence to support routine surveillance.[59]

In colonic CD, because of the heterogeneity and distribution of inflammation, the true risk of dysplasia and colorectal cancer is less well defined. However, large observational experiences have identified rates that parallel those of UC.[60] Surveillance might be more technically difficult in CD because of strictures, fistulous tracts, or segments that have been surgically bypassed. In addition, whereas colorectal cancer develops within involved areas of inflammation in UC, up to 20% of dysplasia in Crohn's colitis might arise in colonic segments that were not previously known to be involved. Although there are no official guidelines, colonoscopic surveillance should be offered to patients with Crohn's colitis in a fashion similar to that of UC. There have also been studies reporting an increased incidence of anorectal carcinoma in patients with long-standing severe anorectal CD. Although unproven, some authors advocate surveillance of selected patients.[61] Although a very rare complication, patients with small bowel CD have an increased risk of small bowel cancers. However, because of the location, association with a chronic stricture, fistula, or bypassed segment of bowel, they are typically beyond the reach of ileocolonoscopy and are therefore not routinely surveyed endoscopically.

Bleeding

Gastrointestinal bleeding is a common manifestation of IBD; however, acute major hemorrhage is uncommon, accounting for 0%–6% of hospitalizations for CD and 1.4%–4.2% for UC.[62] The presence of an endoscopically treatable lesion is uncommon, and endoscopy plays more of a diagnostic and less of a therapeutic role in the manage-

ment of these patients. Because of the diffuse nature of UC, the examination is usually limited to a flexible sigmoidoscopy, which is used to confirm a disease flare rather than to identify a treatable site. In the setting of massive hemorrhage localization of a precise site in UC is not warranted, given that a colectomy is the definitive curative procedure. In CD, colonoscopy can define active disease sites associated with low-grade bleeding and can localize a focal site of bleeding that might be treated endoscopically on a rare occasion. More often endoscopy is helpful in identifying a segment of diseased bowel that could account for the hemorrhage and plays an important role in localizing the site for surgical resection.[62]

Stricture

Benign stricture can occur as a result of repeated episodes of inflammation in both UC and CD, although more typically seen in the latter. In patients with long-standing disease, colonic strictures should be considered malignant until proven otherwise. Laparotomy should be considered for suspicious strictures that cannot be fully evaluated by radiology and endoscopic biopsy. Although most inflammatory strictures will respond to conservative therapy, obstruction caused by fibrotic strictures is the precipitating event for surgical intervention in up to 50% of patients with CD. A subset of patients might benefit from endoscopic therapy, particularly those who have undergone prior extensive bowel resection. In recent years there has been an expanding application of therapeutic endoscopy in IBD. Building on the experience of dilations for ischemic and anastomotic strictures, there have been an increasing number of reports of successful dilations of benign strictures in CD. The majority report dilations by using through-the-scope (TTS) pneumatic balloons, especially for short strictures (<4 cm) at the ileocolonic anastomosis in patients with CD. The procedure is performed under direct visualization with TTS balloon dilations up to a diameter of 18 mm in the majority of cases without complications.[63] The duration of insufflation of the TTS balloons varies from multiple inflations lasting 15–60 seconds to single inflations lasting up to 4 minutes. Pain during balloon dilation is variable but rarely necessitates additional analgesia. Long-term symptomatic improvement is observed in 41%–66% of cases.[64,65] Ileocolonic anastomoses were more often successfully dilated, whereas dilations of ileosigmoid and ileorectal anastomoses were associated with more complications. The risk of major bleeding and perforation is minimized by avoiding overaggressive or repeated dilations. The best candidates for TTS endoscopic dilation are those with short strictures with a length of less than 8 cm,[63] whereas patients with multiple short stenoses might be better served by surgical strictureplasty. It has been hypothesized that long-acting steroid injection into strictures after dilation might decrease the need for further intervention, and although not proven in a controlled trial, an open labeled trial has shown it to be safe and efficacious when used in adjunct with dilation in the management of anastomotic CD strictures.[66] In addition, there are limited reports of both metallic stenting of strictures at ileocolonic anastomosis[67] and the use of sphincterotomes to carve out the stricture as an alternative to surgery.[68]

Toxic Megacolon

Toxic megacolon occurs as a rare complication in UC and in even a smaller percentage of patients with Crohn's colitis. Historically, endoscopy has been an absolute contraindication. However, because of successful reports of colonoscopic decompression in Ogilvie's syndrome, several authors have attempted similar treatment in IBD patients. Riedler et al[69] undertook colonoscopic decompression as a preoperative procedure and believed that subsequent colectomy was facilitated, whereas Banez et al[70] described its use in 3 patients with UC and a single patient with CD with successful colonoscopic placement of a long tube and steroid "colonoclysis." The authors stressed that their approach should not be interpreted as definitive therapy for IBD-related megacolon, because half of patients with toxic megacolon will require surgery, with the majority occurring on an emergent basis. Although acknowledging the significant risk of inducing perforation, colonoscopic decompression could be considered as a temporizing measure in the very select patient deemed to be an extremely high surgical risk.

Upper Gastrointestinal and Biliary Tract Disease

Upper Gastrointestinal Disease

With the exception of the hepatobiliary manifestations, upper gastrointestinal tract lesions in IBD are limited to CD for the most part. There are no indications for upper endoscopy in asymptomatic CD patients, unless it is believed to yield information that will change the subsequent management course. As noted above, an upper endoscopy with biopsy might be indicated in indeterminate colitis, when finding granulomas would help to secure the diagnosis of CD. When the proximal gastrointestinal tract is involved in CD, concomitant lesions are usually present elsewhere in the ileum or colon. Upper gastrointestinal CD, defined as disease proximal to the ligament of Treitz, is rare with a prevalence of 0.5%–13%.[71] However, routine upper

endoscopy in adults with lower gastrointestinal CD in the absence of upper gastrointestinal symptoms has not been widely studied, and this might be an underestimation of the true prevalence. The endoscopic findings are not specific for CD, and they must be differentiated from other peptic, infectious, and inflammatory disorders. Whereas prospective pediatric studies performing upper endoscopy at the time of the diagnosis of lower gastrointestinal IBD have shown nonspecific changes in the majority (80%) of patients, definitive histologic evidence (granulomas) occurred in 12.5% of patients.[72]

Esophageal involvement has been infrequently reported in CD.[73] Patients with CD with symptoms localizing to the esophagus, most commonly dysphagia, should undergo upper endoscopy with biopsies. Although there are no specific endoscopic appearances, aphthoid ulceration, deep and discrete ulcers, strictures, cobblestoning, and mucosal bridging have been described.[74] Gastric CD might cause cobblestoning and thickened folds, aphthoid ulcers, and tubular stenosis of the antrum and pyloric channel. More commonly, gastric CD is endoscopically visualized as antral or fundic erythema, edema, or erosions. In a study of 225 patients with distal small bowel or colonic CD, Schmitz-Moormann et al[75] found erosive or erythematous gastric changes in 49% of patients and a granuloma on biopsy in approximately one third of patients. More recent studies suggested that systematic upper endoscopy with gastric mucosal biopsy might reveal granulomas, even in absence of endoscopic lesions.[27]

The first and second portions of the duodenum are the most frequent locations of upper gastrointestinal tract involvement in CD.[76] In a review of 89 patients with symptomatic duodenal CD, 60% were found to have disease that was contiguous with the stomach. The most frequently reported endoscopic appearance was of a diminished duodenal distensibility or stenosis, friability with aphthoid or heterogeneous appearing ulcerations.[77] Duodenal lesions might occasionally fistulize into the biliary tract, small bowel, or colon. More frequently it is lesions of the distal small bowel that fistulize into the stomach or duodenum, and in these cases no intrinsic gastroduodenal CD might be seen.[76,78] Duodenal biopsies display granulomas more frequently than colonic biopsies and have been reported in 48%–68% of patients.[76,77] Gastroduodenal CD infrequently results in gastroduodenal obstruction. Matsui et al[79] reported the safe and successful dilation of 5 patients with obstructing gastroduodenal CD. Although 60% developed recurrent obstructive symptoms during a mean follow-up period of 4 years, all of the patients were able to avoid gastrojejunostomy with repeat dilations.

Hepatobiliary Tract and Pancreas

Although a variety of hepatobiliary tract lesions have been described in association with IBD, PSC presents a particular challenge to therapeutic endoscopy. PSC occurs in approximately 3%–5% of patients with UC and in a smaller number of patients with CD.[80] ERCP has played an important role in displaying the characteristic cholangiogram appearances of "beads on a string," diminished arborization, ectasia, and stenosis. Magnetic resonance cholangiopancreatography has a sensitivity and diagnostic accuracy comparable to that of ERCP and in some cases has replaced ERCP for purely diagnostic purposes.[81,82] Nevertheless, ERCP remains the dominant approach for brushing and cytologic examination to exclude cholangiocarcinoma and to perform therapeutic interventions. Endoscopic therapy includes biliary sphincterotomy, balloon extraction of debris and pigment stones, as well as hydrostatic and pneumatic balloon dilation of strictures. Nasobiliary drains have been placed to allow duct lavage with saline, ursodeoxycholic acid, or corticosteroids. Retrospective reviews have shown that endoscopic therapeutic interventions improve overall survival in patients with PSC with dominant strictures.[83] An early prospective trial demonstrated that the endoscopic management of dominant strictures in PSC with biliary sphincterotomy and balloon dilation with or without plastic stent placement was associated with significantly improved levels of bilirubin and fewer episodes of cholangitis during the 1-year follow-up.[84] However, more recent studies have shown that stenting after balloon dilation of dominant strictures in PSC patients is associated with more complications including stent-related cholangitis, and now stenting in this situation is less often performed.[85]

Pancreatitis is a rare extraintestinal manifestation of IBD. Chronic pancreatitis associated with UC differs from that observed in CD by the presence of more frequent bile duct involvement, weight loss, and pancreatic duct stenosis, possibly giving a pseudotumor pattern.[86] Diagnostic ERCP in patients with PSC has shown changes consistent with chronic pancreatitis in 15%; however, the association between chronic pancreatitis and PSC remains uncertain.

Endoscopic Ultrasonography

Ultrasonography has been used in the diagnosis and management of IBD for years. Recognizing that CD tends to be transmural and UC is a superficial mucosal inflammatory process, hopes were raised that EUS would be effective in discriminating cases of indeterminate colitis. However, although initial results were promis-

ing, there have been few conclusive studies, and EUS plays a limited role in differentiating UC from CD.

Currently the largest role of EUS is in the diagnosis of suspected perianal fistulas in patients with CD. Recently a prospective study was performed to determine the accuracy of EUS in the diagnosis of perianal fistulas. Thirty-four patients with CD underwent EUS, magnetic resonance imaging, and an examination under anesthesia. The accuracy in detecting a fistula was 91% for EUS, 87% for magnetic resonance imaging, and 91% for examination under anesthesia. The authors concluded that although EUS, magnetic resonance imaging, and examination under anesthesia are all reasonably accurate tests for determining fistula anatomy, an optimal strategy would combine any 2 of the 3 methods that produced 100% accuracy rates.[87] Higaki et al[88] recently demonstrated that catheter probe–assisted endoluminal ultrasonography might predict relapse in UC. In a 1-year prospective study of 23 UC patients without a recent relapse (>1 month), the rectal wall thickness of the first to the third layers evaluated by EUS at entry into the study was found to be significantly larger in those who relapsed compared to the nonrelapsing group.

Emerging Endoscopic Technology

The future of diagnostic endoscopy lies in the potential to make clinical decisions in real time and allow histologic interpretation without removing tissue. These future technologies might utilize alterations in cellular size, architecture, or metabolism to detect differences between healthy and disease tissues. Endoscopic magnification, chromoendoscopy, fluorescence endoscopy, spectroscopy, and optical coherence tomography all strive to make the "optical biopsy" a reality. These techniques when refined might facilitate the localization and detection of subtle mucosal changes associated with clinical relapse or with early dysplasia in long-standing colitis that might ultimately alter the natural history of disease. Future endoscopic therapeutics in IBD might incorporate the targeted delivery of medical therapies. Endoscopic treatment of strictures might be improved through the use of injectable medications, absorbable or drug eluting stents.

Conclusion

The major indications for endoscopy in IBD are to establish the diagnosis, differentiate UC from CD, define the extent and severity of disease activity, as well as diagnose and manage complications. Therapeutic endoscopy might ultimately play a role in delivering anti-inflammatory or biologic agents directly to local areas of inflamed bowel, whereas emerging endoscopic technologies might significantly improve our ability to diagnose and treat premalignant mucosal conditions.

References

1. Farrell RJ, Peppercorn MA. Ulcerative colitis. Lancet 2002;359:331–340.
2. Chutkan RK, Wayne JD. Endoscopy in inflammatory bowel disease. In: Kirsner JB, ed. Inflammatory bowel disease. 5th ed. Baltimore: Williams and Wilkins, 2000:453–477.
3. Kim B, Barnett JL, Kleer CG, Appelman HD. Endoscopic and histological patchiness in treated ulcerative colitis. Am J Gastroenterol 1999;94:3258–3262.
4. Bernstein CN, Shanahan F, Anton PA, Weinstein WM. Patchiness of mucosal inflammation in treated ulcerative colitis: a prospective study. Gastrointest Endosc 1995;42:232–237.
5. D'Haens G, Geboes K, Peeters M, Baert F, Ectors N, Rutgeerts P. Patchy cecal inflammation associated with distal ulcerative colitis: a prospective endoscopic study. Am J Gastroenterol 1997;92:1275–1279.
6. Matsumoto T, Nakamura S, Shimizu M, Iida M. Significance of appendiceal involvement in patients with ulcerative colitis. Gastrointest Endosc 2002;55:180–185.
7. Bouhnik Y, Lemann M, Maunoury V, Bitoun A, Colombel JF. Inflammatory bowel diseases. In: Classen M, Tytgat GNJ, Lightdale CJ, eds. Gastroenterological endoscopy. New York: Georg Thieme Verlag, 2002.
8. Deutsch DE, Olson AD. Colonoscopy or sigmoidoscopy as the initial evaluation of pediatric patients with colitis: a survey of physician behavior and a cost analysis. J Pediatr Gastroenterol Nutr 1997;25:26–31.
9. Carbonnel F, Lavergne A, Lemann M, Bitoun A, Valleur P, Hautefeuille P, Galian A, Modigliani R, Rambaud JC. Colonoscopy of acute colitis: a safe and reliable tool for assessment of severity. Dig Dis Sci 1994;39:1550–1557.
10. Fujimura Y, Kamoi R, Iida M. Pathogenesis of aphthoid ulcers in Crohn's disease: correlative findings by magnifying colonoscopy, electron microscopy, and immunohistochemistry. Gut 1996;38:724–732.
11. Lengeling RW, Mitros FA, Brennan JA, Schulze KS. Ulcerative ileitis encountered at ileo-colonoscopy: likely role of nonsteroidal agents. Clin Gastroenterol Hepatol 2003;1:160–169.
12. Lewis BS. Ileoscopy should be part of standard colonoscopy: a comparison of radiographic and endoscopic evaluation of the ileum. J Clin Gastroenterol 2000;31:103–104.
13. Potzi R, Walgram M, Lochs H, Holzner H, Gangl A. Diagnostic significance of endoscopic biopsy in Crohn's disease. Endoscopy 1989;21:60–62.
14. Ramzan NN, Leighton JA, Heigh RI, Shapiro MS. Clinical significance of granuloma in Crohn's disease. Inflamm Bowel Dis 2002;8:168–173.
15. Korelitz BI, Sommers SC. Rectal biopsy in patients with Crohn's disease: normal mucosa on sigmoidoscopic examination. JAMA 1977;237:2742–2744.
16. Perez-Cuadrado E, Macenlle R, Iglesias J, Fabra R, Lamas D. Usefulness of oral video push enteroscopy in Crohn's disease. Endoscopy 1997;29:745–747.
17. Herrerias JM, Caunedo A, Rodriguez-Tellez M, Pellicer F, Herrerias JM Jr. Capsule endoscopy in patients with suspected Crohn's disease and negative endoscopy. Endoscopy 2003;35:564–568.
18. Mow WS, Lo SK, Targan SR. Initial experience with wireless capsule enteroscopy in the diagnosis and management of inflammatory bowel disease. Clin Gastroenterol Hepatol 2004;2:31–40.
19. Tedesco FJ, Hardin RD, Harper RN, Edwards BH. Infectious colitis

endoscopically simulating inflammatory bowel disease: a prospective evaluation. Gastrointest Endosc 1983;29:195–197.
20. Bayerdorffer E, Hochter W, Schwarzkopf-Steinhauser G, Blumel P, Schmiedel A, Ottenjann R. Bioptic microbiology in the differential diagnosis of enterocolitis. Endoscopy 1986;18:177–181.
21. Fochios SE, Korelitz BI. The role of sigmoidoscopy and rectal biopsy in diagnosis and management of inflammatory bowel disease: personal experience. Am J Gastroenterol 1988;83:114–119.
22. Matsumoto T, Iida M, Kimura Y, Fujishima M. Culture of colonoscopically obtained biopsy specimens in acute infectious colitis. Gastrointest Endosc 1994;40:184–187.
23. Surawicz CM, Belic L. Rectal biopsy helps to distinguish acute self-limited colitis from idiopathic inflammatory bowel disease. Gastroenterology 1984;86:104–113.
24. Dundas SA, Dutton J, Skipworth P. Reliability of rectal biopsy in distinguishing between chronic inflammatory bowel disease and acute self-limiting colitis. Histopathology 1997;31:60–66.
25. Pera A, Bellando P, Caldera D, et al. Colonoscopy in inflammatory bowel disease: diagnostic accuracy and proposal of an endoscopic score. Gastroenterology 1987;92:181–185.
26. Moum B, Ekbom A, Vatn MH, et al. Clinical course during the 1st year after diagnosis in ulcerative colitis and Crohn's disease: results of a large, prospective population-based study in southeastern Norway, 1990-93. Scand J Gastroenterol 1997;32:1005–1012.
27. Alcantara M, Rodriguez R, Potenciano JL, Carrobles JL, Munoz C, Gomez R. Endoscopic and bioptic findings in the upper gastrointestinal tract in patients with Crohn's disease. Endoscopy 1993;25:282–286.
28. Lo SK, Zaidel O, Tabibzadeh S, et al. Utility of wireless capsule endoscopy and IBD serology in re-classifying indeterminate colitis. Gastronenterology 2003;124:S1310.
29. Lew RJ, Ginsberg GG. The role of endoscopic ultrasound in inflammatory bowel disease. Gastrointest Endosc Clin N Am 2002;12:561–571.
30. Waye JD. The role of colonoscopy in the differential diagnosis of inflammatory bowel disease. Gastrointest Endosc 1977;23: 150–154.
31. Floren CH, Benoni C, Willen R. Histologic and colonoscopic assessment of disease extension in ulcerative colitis. Scand J Gastroenterol 1987;22:459–462.
32. Kiesslich R, Fritsch J, Holtmann M, et al. Methylene blue-aided chromoendoscopy for the detection of intraepithelial neoplasia and colon cancer in ulcerative colitis. Gastroenterology 2003;124: 880–888.
33. Meucci G, Vecchi M, Astegiano M, et al. The natural history of ulcerative proctitis: a multicenter, retrospective study—Gruppo di Studio per le Malattie Infiammatorie Intestinali (GSMII). Am J Gastroenterol 2000;95:469–473.
34. Langholz E, Munkholm P, Davidsen M, Nielsen OH, Binder V. Changes in extent of ulcerative colitis: a study on the course and prognostic factors. Scand J Gastroenterol 1996;31:260–266.
35. Baron JH, Connell AM, Lennard-Jones JE. Variation between observers in describing mucosal appearances in proctocolitis. Br Med J 1964;5375:89–92.
36. Buckell NA, Williams GT, Bartram CI, Lennard-Jones JE. Depth of ulceration in acute colitis: correlation with outcome and clinical and radiologic features. Gastroenterology 1980;79:19–25.
37. Alemayehu G, Jarnerot G. Colonoscopy during an attack of severe ulcerative colitis is a safe procedure and of great value in clinical decision making. Am J Gastroenterol 1991;86:187–190.
38. Modigliani R, Mary JY, Simon JF, et al. Clinical, biological, and endoscopic picture of attacks of Crohn's disease: evolution on prednisolone—Groupe d'Etude Therapeutique des Affections Inflammatoires Digestives. Gastroenterology 1990;98:811–818.
39. Wright R, Truelove SR. Serial rectal biopsy in ulcerative colitis during the course of a controlled therapeutic trial of various diets. Am J Dig Dis 1966;11:847–857.
40. Riley SA, Mani V, Goodman MJ, Dutt S, Herd ME. Microscopic activity in ulcerative colitis: what does it mean? Gut 1991;32:174–178.
41. Bitton A, Peppercorn MA, Antonioli DA, et al. Clinical, biological, and histologic parameters as predictors of relapse in ulcerative colitis. Gastroenterology 2001;120:13–20.
42. Landi B, Anh TN, Cortot A, et al. Endoscopic monitoring of Crohn's disease treatment: a prospective, randomized clinical trial—The Groupe d'Etudes Therapeutiques des Affections Inflammatoires Digestives. Gastroenterology 1992;102:1647–1653.
43. D'Haens G, Van Deventer S, Van Hogezand R, et al. Endoscopic and histological healing with infliximab anti-tumor necrosis factor antibodies in Crohn's disease: a European multicenter trial. Gastroenterology 1999;116:1029–1034.
44. D'Haens G, Noman M, Baert F, Hiele M. Endoscopic healing after Infliximab treatment for Crohn's disease provides a longer time to relapse. Gastroenterology 2002;122:100A.
45. Sandborn WJ, Tremaine WJ, Batts KP, Pemberton JH, Phillips SF. Pouchitis after ileal pouch-anal anastomosis: a Pouchitis Disease Activity Index. Mayo Clin Proc 1994;69:409–415.
46. Klein O, Colombel JF, Lescut D, et al. Remaining small bowel endoscopic lesions at surgery have no influence on early anastomotic recurrences in Crohn's disease. Am J Gastroenterol 1995;90:1949–1952.
47. Rutgeerts P, Geboes K, Vantrappen G, Beyls J, Kerremans R, Hiele M. Predictability of the postoperative course of Crohn's disease. Gastroenterology 1990;99:956–963.
48. Korelitz BI, Cheskin LJ, Sohn N, Sommers SC. The fate of the rectal segment after diversion of the fecal stream in Crohn's disease: its implications for surgical management. J Clin Gastroenterol 1985;7:37–43.
49. Kornbluth A, Sachar DB. Ulcerative colitis practice guidelines in adults: American College of Gastroenterology, Practice Parameters Committee. Am J Gastroenterol 1997;92:204–211.
50. Rutter M, Saunders B, Wilkinson K, et al. Severity of inflammation is a risk factor for colorectal neoplasia in ulcerative colitis. Gastroenterology 2004;126:451–459.
51. Rubin CE, Haggitt RC, Burmer GC, et al. DNA aneuploidy in colonic biopsies predicts future development of dysplasia in ulcerative colitis. Gastroenterology 1992;103:1611–1620.
52. Rubin PH, Friedman S, Harpaz N, et al. Colonoscopic polypectomy in chronic colitis: conservative management after endoscopic resection of dysplastic polyps. Gastroenterology 1999;117:1295–1300.
53. Engelsgjerd M, Farraye FA, Odze RD. Polypectomy may be adequate treatment for adenoma-like dysplastic lesions in chronic ulcerative colitis. Gastroenterology 1999;117:1288–1294; discussion 1488–1491.
54. Bernstein CN, Shanahan F, Weinstein WM. Are we telling patients the truth about surveillance colonoscopy in ulcerative colitis? Lancet 1994;343:71–74.
55. Connell WR, Lennard-Jones JE, Williams CB, Talbot IC, Price AB, Wilkinson KH. Factors affecting the outcome of endoscopic surveillance for cancer in ulcerative colitis. Gastroenterology 1994;107:934–944.
56. Ullman T, Croog V, Harpaz N, Sachar D, Itzkowitz S. Progression of flat low-grade dysplasia to advanced neoplasia in patients with ulcerative colitis. Gastroenterology 2003;125:1311–1319.
57. Lim CH, Dixon MF, Vail A, Forman D, Lynch DA, Axon AT. Ten year follow up of ulcerative colitis patients with and without low grade dysplasia. Gut 2003;52:1127–1132.
58. Thompson-Fawcett MW, Marcus V, Redston M, Cohen Z, McLeod RS. Risk of dysplasia in long-term ileal pouches and pouches with chronic pouchitis. Gastroenterology 2001;121:275–281.
59. Herline AJ, Meisinger LL, Rusin LC, et al. Is routine pouch surveillance for dysplasia indicated for ileoanal pouches? Dis Colon Rectum 2003;46:156–159.
60. Friedman S, Rubin PH, Bodian C, Goldstein E, Harpaz N, Present

DH. Screening and surveillance colonoscopy in chronic Crohn's colitis. Gastroenterology 2001;120:820–826.
61. Connell WR, Sheffield JP, Kamm MA, Ritchie JK, Hawley PR, Lennard-Jones JE. Lower gastrointestinal malignancy in Crohn's disease. Gut 1994;35:347–352.
62. Pardi DS, Loftus EV Jr, Tremaine WJ, et al. Acute major gastrointestinal hemorrhage in inflammatory bowel disease. Gastrointest Endosc 1999;49:153–157.
63. Breysem Y, Janssens JF, Coremans G, Vantrappen G, Hendrickx G, Rutgeerts P. Endoscopic balloon dilation of colonic and ileocolonic Crohn's strictures: long-term results. Gastrointest Endosc 1992;38:142–147.
64. Thomas-Gibson S, Brooker JC, Hayward CM, Shah SG, Williams CB, Saunders BP. Colonoscopic balloon dilation of Crohn's strictures: a review of long-term outcomes. Eur J Gastroenterol Hepatol 2003;15:485–488.
65. Blomberg B, Rolny P, Jarnerot G. Endoscopic treatment of anastomotic strictures in Crohn's disease. Endoscopy 1991;23:195–198.
66. Brooker JC, Beckett CG, Saunders BP, Benson MJ. Long-acting steroid injection after endoscopic dilation of anastomotic Crohn's strictures may improve the outcome: a retrospective case series. Endoscopy 2003;35:333–337.
67. Matsuhashi N, Nakajima A, Suzuki A, Yazaki Y, Takazoe M. Long-term outcome of non-surgical strictureplasty using metallic stents for intestinal strictures in Crohn's disease. Gastrointest Endosc 2000;51:343–345.
68. Bedogni G, Ricci E, Pedrazzoli C, et al. Endoscopic dilation of anastomotic colonic stenosis by different techniques: an alternative to surgery? Gastrointest Endosc 1987;33:21–24.
69. Riedler L, Wohlgenannt D, Stoss F, Thaler W, Schmid KW. Endoscopic decompression in "toxic megacolon." Surg Endosc 1989;3:51–53.
70. Banez AV, Yamanishi F, Crans CA. Endoscopic colonic decompression of toxic megacolon, placement of colonic tube, and steroid colonclysis. Am J Gastroenterol 1987;82:692–694.
71. Wagtmans MJ, van Hogezand RA, Griffioen G, Verspaget HW, Lamers CB. Crohn's disease of the upper gastrointestinal tract. Neth J Med 1997;50:S2–S7.
72. Ruuska T, Vaajalahti P, Arajarvi P, Maki M. Prospective evaluation of upper gastrointestinal mucosal lesions in children with ulcerative colitis and Crohn's disease. J Pediatr Gastroenterol Nutr 1994;19:181–186.
73. Decker GA, Loftus EV Jr, Pasha TM, Tremaine WJ, Sandborn WJ. Crohn's disease of the esophagus: clinical features and outcomes. Inflamm Bowel Dis 2001;7:113–119.
74. Mashako MN, Cezard JP, Navarro J, et al. Crohn's disease lesions in the upper gastrointestinal tract: correlation between clinical, radiological, endoscopic, and histological features in adolescents and children. J Pediatr Gastroenterol Nutr 1989;8:442–446.
75. Schmitz-Moormann P, Malchow H, Pittner PM. Endoscopic and bioptic study of the upper gastrointestinal tract in Crohn's disease patients. Pathol Res Pract 1985;179:377–387.
76. Rutgeerts P, Onette E, Vantrappen G, Geboes K, Broeckaert L, Talloen L. Crohn's disease of the stomach and duodenum: a clinical study with emphasis on the value of endoscopy and endoscopic biopsies. Endoscopy 1980;12:288–294.
77. Nugent FW, Roy MA. Duodenal Crohn's disease: an analysis of 89 cases. Am J Gastroenterol 1989;84:249–254.
78. Jacobson IM, Schapiro RH, Warshaw AL. Gastric and duodenal fistulas in Crohn's disease. Gastroenterology 1985;89:1347–1352.
79. Matsui T, Hatakeyama S, Ikeda K, Yao T, Takenaka K, Sakurai T. Long-term outcome of endoscopic balloon dilation in obstructive gastroduodenal Crohn's disease. Endoscopy 1997;29:640–645.
80. Bernstein CN, Blanchard JF, Rawsthorne P, Yu N. The prevalence of extraintestinal diseases in inflammatory bowel disease: a population-based study. Am J Gastroenterol 2001;96:1116–1122.
81. Vitellas KM, El-Dieb A, Vaswani KK, et al. MR cholangiopancreatography in patients with primary sclerosing cholangitis: interobserver variability and comparison with endoscopic retrograde cholangiopancreatography. AJR Am J Roentgenol 2002;179:399–407.
82. Textor HJ, Flacke S, Pauleit D, et al. Three-dimensional magnetic resonance cholangiopancreatography with respiratory triggering in the diagnosis of primary sclerosing cholangitis: comparison with endoscopic retrograde cholangiography. Endoscopy 2002;34:984–990.
83. Baluyut AR, Sherman S, Lehman GA, Hoen H, Chalasani N. Impact of endoscopic therapy on the survival of patients with primary sclerosing cholangitis. Gastrointest Endosc 2001;53:308–312.
84. Johnson GK, Geenen JE, Venu RP, Hogan WJ. Endoscopic treatment of biliary duct strictures in sclerosing cholangitis: follow-up assessment of a new therapeutic approach. Gastrointest Endosc 1987;33:9–12.
85. Kaya M, Petersen BT, Angulo P, et al. Balloon dilation compared to stenting of dominant strictures in primary sclerosing cholangitis. Am J Gastroenterol 2001;96:1059–1066.
86. Barthet M, Hastier P, Bernard JP, et al. Chronic pancreatitis and inflammatory bowel disease: true or coincidental association? Am J Gastroenterol 1999;94:2141–2148.
87. Schwartz DA, Wiersema MJ, Dudiak KM, et al. A comparison of endoscopic ultrasound, magnetic resonance imaging, and exam under anesthesia for evaluation of Crohn's perianal fistulas. Gastroenterology 2001;121:1064–1072.
88. Higaki S, Nohara H, Saitoh Y, et al. Increased rectal wall thickness may predict relapse in ulcerative colitis: a pilot follow-up study by ultrasonographic colonoscopy. Endoscopy 2002;34:212–219.
89. Farrell RJ, Peppercorn MA. Endoscopy. In: Sartor RB, Sandborn W, eds. Kirsner's inflammatory bowel disease. 6th ed. Philadelphia: Saunders, 2004:385.

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