

Optimal Approach to Obtaining Mucosal Biopsies for Assessment of Inflammatory Disorders of the Gastrointestinal Tract

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Endoscopic evaluation and mucosal biopsy analysis have assumed important roles in the clinical management of patients with symptoms related to the gastrointestinal tract. Several common inflammatory diseases, including eosinophilic esophagitis, Barrett's esophagus, *Helicobacter pylori* infection, celiac disease, lymphocytic colitis, collagenous colitis, and inflammatory bowel disease, may display a patchy or discontinuous distribution and, thus, multiple mucosal samples may be required to obtain diagnostic tissue in some cases. Not surprisingly, clinicians and pathologists are increasingly challenged to determine the optimum number of procedures and tissue samples necessary to detect, or exclude, the presence of inflammatory disorders of the gastrointestinal tract. Unfortunately, clinical practice varies widely with respect to tissue sample procurement in the evaluation of these disorders, particularly when the endoscopic appearance of the gastrointestinal mucosa is normal or shows only minimal changes. Guidelines concerning the appropriate number of tissue samples are well established for some diseases, such as Barrett's esophagus and chronic gastritis, but are not clear in other instances. The purpose of this review is to discuss the available literature pertaining to appropriate endoscopic sampling in the assessment of medical diseases of the gastrointestinal tract, and to develop recommendations regarding the clinical evaluation of common gastrointestinal disorders.

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INTRODUCTION

Minimally invasive endoscopic evaluation with mucosal biopsy analysis has assumed a critical role in the diagnosis and management of patients with gastrointestinal complaints. Accurate diagnosis of many types of disorders, such as eosinophilic esophagitis, Barrett's esophagus (BE), *Helicobacter pylori* infection, celiac disease, lymphocytic colitis, collagenous colitis, and inflammatory bowel disease (IBD), relies heavily upon appropriately obtained and analyzed mucosal biopsy specimens. Despite the fact that some of these inflammatory conditions often show nonspecific, or minimal, endoscopic changes, establishing an accurate diagnosis is usually possible because each of these disorders exhibits distinct pathologic characteristics. However, many display a patchy, or discontinuous, distribution of disease and, thus, multiple mucosal samples may be required to obtain diagnostic tissue. Unfortunately, guidelines concerning the appropriate number and location of tissue samples required to establish a diagnosis vary widely (1). The

purpose of this review is to provide gastroenterologists with an updated summary of the information they need to know with regard to the number and location of biopsy samples necessary to appropriately evaluate patients with upper and lower gastrointestinal complaints. This review will focus on diseases in which the number and location of tissue samples are important for accurate diagnosis, such as eosinophilic esophagitis, BE, *H. pylori* infection, celiac disease, lymphocytic colitis, collagenous colitis, and IBD (Table 1).

ALLERGIC (“EOSINOPHILIC”) ESOPHAGITIS

Eosinophilic esophagitis is a distinct clinicopathologic entity characterized by a constellation of clinical symptoms (e.g., dysphagia, food impaction, pain, reflux, emesis), endoscopic findings (e.g., rings, luminal narrowing or strictures, furrows, “crêpe” paper mucosa, plaques, exudates, and erosions), and pathologic features (numerous intraepithelial eosinophils,

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Table 1. Optimum location and number of mucosal biopsies for evaluation of common gastrointestinal disorders

Disease	Location and number of biopsy samples
Eosinophilic esophagitis	Multiple esophageal biopsies from several areas, <i>and</i> one biopsy each from duodenal and gastric mucosae ^a At least two biopsies from the proximal (1) and distal (1) esophagus (yield: 80%) ^b Up to five tissue samples, including biopsies from the proximal, mid, and distal esophagus (yield: 100%) ^b
Barrett's esophagus	Detection of goblet cells Four targeted biopsies that straddle the neosquamocolumnar junction (yield: 94%) ^c ; <i>or</i> Eight random samples obtained from the columnar-lined esophagus (yield: 68%) ^d Surveillance for dysplasia ^e Four-quadrant biopsies per 2 cm of columnar-lined esophagus Additional sampling of endoscopically visible lesions Surveillance for early carcinoma in patients with high-grade dysplasia ^f Four-quadrant biopsies per 1 cm of columnar-lined esophagus Additional sampling of endoscopically visible abnormalities
Chronic gastritis	Detection of chronic gastritis and intestinal metaplasia ^g Five biopsies from antrum (2), corpus (2), and incisura angularis (1) Surveillance for dysplasia Minimum of five biopsies from antrum (2), corpus (2), and incisura angularis (1) Additional sampling of endoscopically visible abnormalities
Celiac disease	Assessment of duodenum ^h Three biopsies of the duodenal bulb (1), proximal duodenum (1), and distal duodenum (1) Detection of lymphocytic gastritis One biopsy each of the gastric antrum and corpus Detection of colonic lymphocytosis Two or more biopsies each from transverse, descending, and sigmoid colon
Microscopic colitis	Detection of lymphocytic colitis Two or more biopsies each from the transverse, descending, and sigmoid colon Additional sampling of endoscopically visible abnormalities Detection of collagenous colitis Two or more biopsies each from the right, transverse, descending, and sigmoid colon Additional sampling of endoscopically visible abnormalities
Inflammatory bowel disease	Surveillance for dysplasia ⁱ Thirty-three random samples from patients with pancolitis, including Five to six samples each from the right, transverse, distal, and sigmoid colon, proximal and distal colon, <i>or</i> Four-quadrant biopsies per 10 cm of colitic mucosa, <i>and</i> four-quadrant biopsies per 5 cm of colitic rectal mucosa Additional sampling of endoscopically visible abnormalities

^aFuruta *et al.* (4). ^bGonsalves *et al.* (7). ^cChandrasoma *et al.* (15). ^dHarrison *et al.* (14). ^eAbela *et al.* (23). ^fReid *et al.* (24). ^gDixon *et al.* (31). ^hBonamico *et al.* (50). ⁱIitzkowitz and Present (79).

superficial eosinophil microabscesses, scale crust containing degranulated eosinophils, and intercellular edema). Eosinophilic esophagitis has been increasingly recognized over the past decade, largely because of raised awareness of the entity, the effects of altered environmental exposures, and increased incidence rates of allergic diseases in general (2,3). The diagnosis is usually established when suggestive clinical and endoscopic features are supported by the presence of abnormal intramucosal eosinophilic infiltrates in esophageal biopsy samples from patients who do not respond well to high dose proton pump inhibitor therapy (4). Unfortunately, universally accepted criteria for the pathologic diagnosis of eosinophilic esophagitis are lacking: the minimum number of eosinophils required for this diagnosis varies among different investigators, and biopsy protocols for the evaluation of patients with suspected disease are not uniformly standardized (5).

Data from several studies have brought to light a number of clinically relevant points regarding appropriate tissue

procurement in the evaluation of patients with suspected eosinophilic esophagitis. One important observation is the recent recognition that the disease often involves the esophagus in a patchy, discontinuous fashion, both macroscopically and microscopically, and histologic abnormalities may be present even when the esophagus is endoscopically normal in appearance (**Figure 1**). Liacouras *et al.* (6) retrospectively evaluated 381 pediatric patients with eosinophilic esophagitis assessed over a 10-year period and found that 32% of patients had endoscopically normal-appearing esophageal mucosae, despite histologic evidence of severe intramucosal eosinophilia. In another study, Gonsalves *et al.* prospectively assessed 341 esophageal mucosal biopsy samples obtained from 66 adult patients who carried a diagnosis of eosinophilic esophagitis based upon characteristic clinical and endoscopic features and the finding of >15 eosinophils/ $\times 400$ magnification field in their initial mucosal biopsy samples. The authors found that the number of mucosal eosinophils varied widely among specimens, ranging from

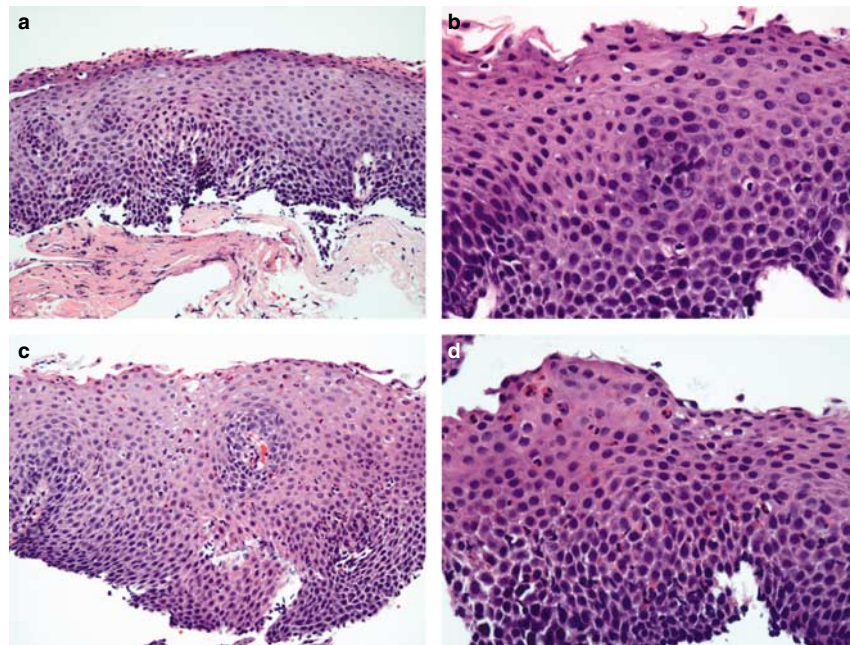


Figure 1. Eosinophilic (“allergic”) esophagitis often shows an irregular or patchy distribution in the esophagus. In this case, samples from the distal esophagus show parakeratotic scale, hyperplasia of basal keratinocytes (a) and occasional (1 eosinophil per 400× magnification field) intraepithelial eosinophils (b). Proximal samples from the same patient show increased numbers of intraepithelial eosinophils (c) that are more numerous in the superficial mucosa (d).

0 to 557 eosinophils/×400 magnification field (mean: 107). They also found that, when a threshold of ≥ 15 eosinophils/×400 magnification field was applied, evaluation of a single biopsy sample yielded a sensitivity rate of only 55% for detection of eosinophilic esophagitis, compared to 100% when five samples were obtained from the proximal, mid, and distal regions of the esophagus. Importantly, 20 patients in that study underwent mucosal biopsies of the proximal and distal esophagus and, of these, 4 (20%) had ≥ 15 eosinophils/×400 magnification field in the distal esophagus, but ≤ 15 in the proximal esophagus (7). Finally, tissue preservation and suboptimal staining with hematoxylin and eosin may impair detection of eosinophils in esophageal mucosal biopsy samples at the microscopic level. Eosinophils may not be readily identified in tissue samples fixed in Bouin’s solution, or when the interval between tissue procurement and fixation in buffered formalin is prolonged (4,8).

Recently, a task force of 31 physicians, including participants in the *First International Gastrointestinal Eosinophil Research Symposium*, took part in a consensus conference sponsored by the American Gastroenterological Association Institute and North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition, to compile recommendations regarding the evaluation of patients with suspected eosinophilic esophagitis. They proposed that patients should undergo careful evaluation and documentation of the endoscopic appearance of the esophagus, as well as mucosal biopsy analysis. Although the authors did not suggest a minimum number of tissue samples necessary for the evaluation of patients with suspected

eosinophilic esophagitis, they did advocate that multiple tissue samples should be obtained from the proximal, distal, and intervening esophageal mucosa, regardless of the endoscopic appearance. In addition, participants at the symposium suggested that samples of the duodenum and stomach should also be obtained to exclude the possibility of eosinophilic gastroenteritis, which may be difficult to differentiate from eosinophilic esophagitis based on analysis of a single biopsy sample from the esophagus (4).

BARRETT’S ESOPHAGUS

BE is a premalignant condition defined by the American Gastroenterological Association as the presence of endoscopically apparent columnar cell metaplasia of the distal esophagus (columnar-lined esophagus) in conjunction with pathologic documentation of goblet cells in biopsy specimens (9). Both the frequency with which goblet cells are observed, and their density, increase proportionally with the length of BE, which is classified as long (>3 cm), short (1–3 cm), and ultrashort (<1 cm) segment types (10–12). Patients with BE typically undergo endoscopic surveillance for detection of dysplasia and/or carcinoma, which may be endoscopically imperceptible, or appear as an area of erythema, or as a nodule, polyp, plaque, or ulcer (13). Clinicians are often plagued by two problems related to screening and surveillance of patients with BE. First, according to the American Gastroenterological Association guidelines, goblet cells need to be detected to establish a diagnosis of BE, but their distribution in the columnar-lined

esophagus is uneven. The second problem is related to the number and location of biopsies needed to optimize detection of dysplasia, when present.

Goblet cells are irregularly distributed in BE and thus, multiple samples are usually required to detect them. Harrison *et al.* retrospectively reviewed 1,646 esophageal mucosal biopsy samples obtained from 125 consecutive patients with BE, 82% of whom underwent four-quadrant sampling from every 1–2 cm of columnar-lined esophagus. They detected goblet cells in 68% of cases when eight mucosal biopsy samples were obtained, compared to only 35% when four samples were taken. They also found no significant benefit to acquiring more than eight biopsies, unless greater than 16 samples were procured, in which case goblet cells were detected in 100% of patients (14). In another study, Chandrasoma *et al.* performed a detailed mapping of different cell types present in columnar-lined esophagus utilizing 424 esophageal mucosal biopsy samples from 32 patients. They detected goblet cells most commonly at the neosquamocolumnar junction: 94% of samples obtained from the proximal edge of the columnar-lined esophagus contained goblet cells, compared to 39% of those from the distal esophagus (15).

The limited efficacy of video endoscopy in the evaluation of patients with BE has led to the recent use of vital dyes and other advanced endoscopic techniques that enhance the detection rate of goblet cells (16–18). For instance, Ragunath *et al.* (19) evaluated a series of 57 patients who underwent both conventional video endoscopy with four-quadrant mucosal biopsy and methylene blue-directed biopsy, and found that use of vital dye significantly enhanced the detection rate of goblet cells (75%) compared to the random biopsy technique (68%).

Data regarding the distribution of dysplasia and/or carcinoma in BE are largely derived from mapping studies performed on resection specimens (20). Cameron and Carpenter mapped the distribution of BE, low-grade dysplasia, high-grade dysplasia, and invasive adenocarcinoma in 30 resection specimens obtained from patients with BE-related neoplasia. They found that both dysplasia and carcinoma often occurred in a multifocal fashion and showed no predilection to affect any particular area within the columnar-lined segment. Forty-three percent of patients with high-grade dysplasia lacked grossly apparent lesions (21).

Current recommendations for detection of dysplasia in patients with BE advocate the use of conventional video endoscopy with four-quadrant mucosal biopsies every 1–2 cm from the gastroesophageal junction to the neosquamocolumnar junction (22). Abela *et al.* retrospectively evaluated the natural history of BE among patients who underwent four-quadrant mucosal biopsy surveillance ($n=180$), compared to patients who had nonsystematic biopsies ($n=182$) obtained over a 10-year period. The authors found a 13-fold difference in the prevalence rate of dysplasia between the two groups: systematic biopsies detected low-grade and high-grade dysplasia in 18.9% and 2.8% of patients, respectively, which was significantly higher than nonsystematic sampling (1.6% and 0%, respectively). Systematic surveillance detected incident

high-grade dysplasia in 2.8% of patients, which was almost always amenable to endoscopic resection, whereas three patients with nonsystematic sampling died of invasive esophageal adenocarcinoma (23). In another study of 45 BE patients with high-grade dysplasia, Reid *et al.* (24) found that biopsies obtained at 2 cm intervals missed 50% of early cancers that were detected when sampling at 1 cm intervals was performed. The results of these studies indicate that four-quadrant mucosal biopsies are superior to nonsystematic sampling in the detection of BE-related neoplasia, and that more extensive sampling should be performed on patients with high-grade dysplasia.

Data regarding the use of advanced endoscopic techniques in the detection of dysplasia are also conflicting. Some investigators have found that both narrow band imaging and magnification chromoendoscopy detect dysplasia at rates comparable to that of four-quadrant mucosal biopsy sampling, whereas others have not (25–27). Lim *et al.* (27) evaluated 30 BE patients with ($n=18$), or without ($n=12$), dysplasia in a crossover study to compare the utility of methylene blue-directed biopsies to random four-quadrant biopsy assessment, and found that random biopsy analysis detected dysplasia in 17 (94%) patients compared to 9 (50%) cases detected by methylene blue enhancement.

In summary, several mucosal samples should be obtained from the neosquamocolumnar junction in patients with suspected BE to maximize the chance of detecting goblet cells (28). Individuals with a documented history of BE are recommended to undergo surveillance consisting of four-quadrant mucosal biopsies from every 2 cm from the gastroesophageal junction to the neosquamocolumnar junction and at 1 cm intervals when high-grade dysplasia is present (24). Additional biopsies ought to be obtained from endoscopically abnormal areas, such as polyps, nodules, ulcers, or erosions. Enhancing techniques may improve detection of goblet cells, but their efficacy has not been compared to that of directed sampling of the neosquamocolumnar junction and, thus, their utility in routine clinical practice remains unknown.

CHRONIC GASTRITIS AND *HELICOBACTER PYLORI* INFECTION

Both chronic *H. pylori* infection and immune-mediated (autoimmune) chronic gastritis may lead to the development of atrophic gastritis, intestinal metaplasia, dysplasia, and carcinoma (16). Thus, patients with chronic gastritis may undergo gastric mucosal biopsy samples to (i) establish the specific type of gastritis, (ii) detect intestinal metaplasia, and (iii) identify foci of dysplasia and early carcinoma. Recommendations regarding the optimum anatomic site, and number, of mucosal biopsies are aimed at detecting the most common types of chronic gastritis: *H. pylori* infection and autoimmune gastritis. *H. pylori*-associated gastric injury shows a predilection for the antrum and incisura angularis with variable involvement of the gastric body and fundus, whereas autoimmune gastritis

predominantly affects the gastric corpus. Xia *et al.* evaluated eight gastric mucosal biopsy samples from 268 patients with dyspepsia, including 113 infected with *H. pylori*. They found that a greater proportion of *H. pylori*-infected individuals showed antral-type mucosa (84%) or intestinal metaplasia (13%) at the incisura angularis, compared to uninfected patients (18% and 3%, respectively) (29). Eriksson *et al.* evaluated at least six gastric mucosal biopsy samples from 272 consecutive patients who underwent upper endoscopic evaluation, including two obtained from the incisura angularis, antrum, and corpus. Overall, 9% of patients had chronic inflammation limited to the incisura angularis, one patient had *H. pylori* infection at this site only, and 6% had intestinal metaplasia at the incisura angularis, but not in the antrum or corpus, indicating that sampling of this area should always be included in the assessment of patients with chronic gastritis (30).

The most widely advocated biopsy protocol for patients with chronic gastritis is that proposed by the updated Sydney system, which involves collection of five separately submitted biopsy samples: two antral samples obtained from the greater and lesser curvatures 2–3 cm proximal to the pylorus, two corpus samples from the greater and lesser curvatures 8 cm distal to the cardia, and one sample from the incisura angularis (Figure 2) (31). This method has been shown to detect *H. pylori* infection in virtually all infected patients, although the presence of intestinal metaplasia may be missed in >50% of cases when using this protocol (32). In an effort to determine the minimum number of gastric samples required to detect chronic gastritis and preneoplastic gastric lesions, Guarner *et al.* assessed 3,969 gastric mucosal biopsy samples obtained during 733 endoscopic examinations, and compared the diagnostic yields of three and five gastric biopsies per examination to that of seven biopsy samples. They found that three tissue samples from the antrum and corpus yielded sensitivities of 99%, 82%, and 81% for detection of *H. pylori* infection, intestinal metaplasia, and dysplasia, respectively, compared to

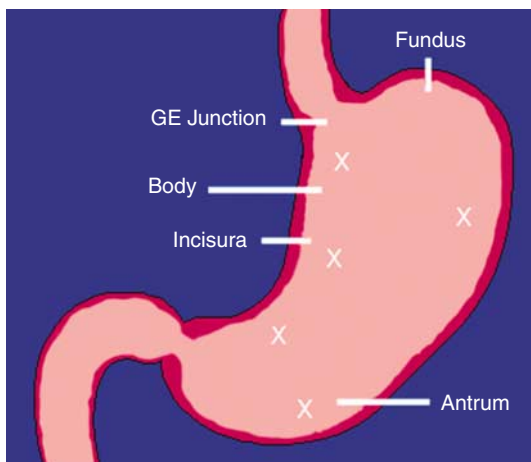


Figure 2. The Sydney protocol advocates obtaining five biopsy samples of the gastric mucosa, including two each from the greater and lesser curvatures of the antrum and body, and one sample from the incisura.

100%, 95%, and 95%, respectively, when five tissue samples were obtained (33).

Some investigators have assessed the value of biomarkers in the evaluation of patients with atrophic gastritis and intestinal metaplasia (34). Korstanje *et al.* evaluated mucosal biopsy samples from patients with documented corpus-predominant atrophic gastritis, and assessed them for serologic evidence of gastric atrophy (low serum ratio of pepsinogen A-to-pepsinogen C and elevated gastrin levels). Of the 20 patients with abnormal serologic testing, 17 (85%) had atrophic gastritis on biopsy analysis (35). In another prospective study of 404 consecutive patients, Vaananen *et al.* (36) found a significant relationship between decreasing gastrin-17 and pepsinogen I levels and increasingly severe atrophy of the antrum and corpus, respectively.

Overall, current data suggest that obtaining five mucosal biopsy samples from the antrum (two samples), body (two samples), and incisura angularis (one sample), as suggested by the Sydney system, reliably detects *H. pylori* and chronic gastritis in patients without a history of intestinal metaplasia or dysplasia. More extensive sampling of normal-appearing mucosa may be performed when intestinal metaplasia or dysplasia is suspected. Visible lesions, such as polyps, nodules, ulcers, or mucosal irregularities should always be sampled as well. Finally, although serum biomarker analysis for gastric peptides represents a noninvasive adjunct to the evaluation of patients with dyspepsia and suspected atrophic gastritis, this type of testing has not been proven to be more efficacious than assessment of mucosal biopsies by pathologists.

CELIAC DISEASE

The optimal method of obtaining biopsies in patients with celiac disease is controversial. Although classic endoscopic features may lead one to suspect a diagnosis of celiac disease, they may be lacking in some patients, particularly when the disease is patchy or segmental (37). Histologic documentation of small-intestinal changes compatible with gluten sensitivity is currently regarded as the gold standard method of establishing a diagnosis of celiac disease. The histologic features of celiac disease range from normal villous architecture with increased CD3+/CD8+ intraepithelial lymphocytes, to complete villous shortening with crypt hyperplasia and increased lamina propria mononuclear cell-rich inflammation (38). Celiac disease is also frequently associated with intraepithelial lymphocytosis in other parts of the gastrointestinal tract, particularly the stomach and colon (39–43). In fact, the prevalence rate of “lymphocytic gastritis” is estimated to be 10–45% among patients with celiac disease. Conversely, prevalence rates of celiac disease among adults and pediatric patients with lymphocytic gastritis are 33% and 60–100%, respectively (44–48).

Unfortunately, celiac disease may affect the small intestine in a discontinuous, patchy fashion, and strategies for optimum diagnostic tissue procurement have not yet been fully established. Ravelli *et al.* prospectively evaluated 110 pediatric

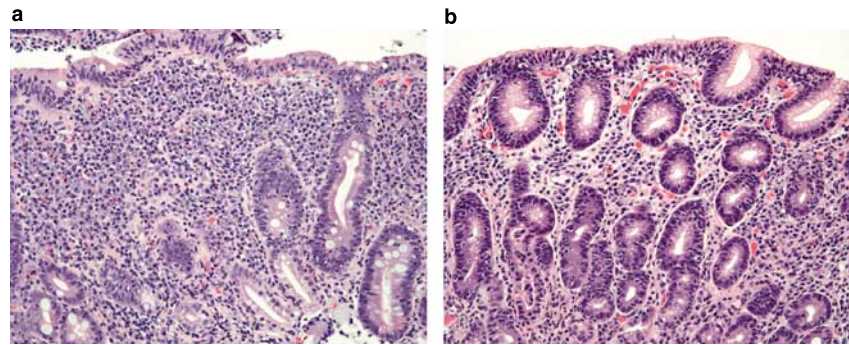


Figure 3. Duodenal biopsies from patients with celiac disease display a variable degree of villous shortening with increased lymphocytes in the lamina propria and epithelium (a). Gastric samples from these patients may also display lymphocytic gastritis (b).

patients with elevated serum endomysial and/or tissue transglutaminase antibodies and clinical symptoms of celiac disease. Each patient underwent mucosal biopsy of the duodenal bulb, proximal duodenum, intervening duodenum, and distal duodenum near the ligament of Treitz. Ninety-three percent of patients had changes compatible with celiac disease in at least one tissue sample, and fifty percent had similar findings in all samples. None of the patients had any tissue samples that were histologically normal, although complete loss of villous architecture was more commonly observed in samples from the distal small intestine (49). In another study, Bonamico *et al.* studied 102 pediatric patients with confirmed celiac disease by obtaining at least five duodenal mucosal biopsy samples, including one from the duodenal bulb. They found that 16% of patients had patchy mucosal disease. Importantly, disease involvement of the duodenal bulb was present in all patients, and was the only site of injury in 25% of the patients (50). Finally, Hopper *et al.* evaluated 56 patients with elevated endomysial and/or tissue transglutaminase serum levels, by obtaining nine duodenal mucosal biopsies (one from the duodenal bulb, four from the proximal duodenum, and four from the distal duodenum) from each patient. Overall, 53 patients proved to have celiac disease, which was patchy in 10 (19%) cases. All 53 of these patients were identified by analyzing only three tissue samples, including one from the duodenal bulb (51).

These results suggest that samples of the duodenal bulb should be considered in the evaluation of patients with suspected celiac disease. However, peptic injury may cause changes that mimic celiac disease and is a frequent finding in biopsies from this region. Thus, from a pathologist's perspective, if samples of the duodenal bulb are obtained, samples from other sites of the duodenum should be considered as well. Finally, sampling of other sites of the gastrointestinal tract, particularly the stomach, may yield findings that help support the diagnosis of celiac disease in diagnostically difficult patients (Figure 3).

MICROSCOPIC COLITIS

Lymphocytic and collagenous colitis are the two most common forms of microscopic colitis. These disorders are

characterized by the presence of chronic watery diarrhea and normal, or nearly normal, colonoscopic and radiologic findings (52). A diagnosis of either lymphocytic or collagenous colitis relies exclusively on histologic evaluation of colonic mucosal biopsies. Lymphocytic colitis is characterized by the presence of a diffuse, mononuclear cell-rich inflammatory infiltrate and increased intraepithelial T cells (53). Collagenous colitis is histologically similar, but also shows expansion of the subepithelial collagen layer (54).

Lymphocytic colitis usually displays an even distribution of disease throughout the colon, but the findings may be patchy, thereby necessitating multiple biopsy samples to establish a diagnosis with certainty. Thijs *et al.* identified 12 patients with lymphocytic colitis from a cohort of 103 individuals with a history of chronic diarrhea and found that only 83% had diffuse disease throughout the colon. Two patients had disease limited to the proximal colon (55). Similarly, Matteoni *et al.* identified 58 patients with "microscopic" colitis, including 34 with lymphocytic colitis and 24 with collagenous colitis, all of whom had mucosal biopsies obtained from both the right and left colon. They found that an accurate diagnosis of lymphocytic colitis could be made by analysis of left-sided mucosal samples in 33 (97%) cases. However, one patient had only one tissue sample from the left colon, and this specimen was entirely normal (56).

Biopsy samples of the proximal (transverse and right) colon are considered even more important in patients suspected of having collagenous colitis. In this disorder, samples from the rectosigmoid colon show diagnostic histologic features in only 66% of cases (Figure 4) (57). In a study of 56 patients with collagenous colitis, Offner *et al.* (58) found that biopsy samples from the transverse colon yielded a diagnosis in 83% of cases. Tanaka *et al.* evaluated mucosal biopsy samples from 33 patients with collagenous colitis and found that a diagnosis could be established confidently in 82% of patients who had at least one sample obtained from the "left" colon. However, thickening of the subepithelial collagen layer was limited to the cecum in 9% of patients. In addition, "rectal" biopsy samples showed completely normal histologic findings in 73% of cases (59).

In summary, although flexible sigmoidoscopy with evaluation of mucosal biopsies may be used as an initial proce-

ture in patients being evaluated for microscopic colitis, the absence of diagnostic findings is insufficient to exclude this disorder. In this situation, a full colonoscopic examination with sampling of both the transverse and ascending colon may be necessary.

ILEAL AND COLONIC MUCOSAL BIOPSIES IN PATIENTS WITH CHRONIC DIARRHEA

The efficacy of obtaining colonic and/or ileal biopsies in patients with chronic diarrhea and a normal colonoscopic examination is a subject of debate. Yusoff *et al.* (60) evaluated 362 patients with chronic diarrhea and normal colonoscopic findings and found that a specific pathologic diagnosis was rendered in only 5% of cases. In a similar study of 111 diarrheal patients with normal colonoscopic examinations, Marshall *et al.* (61) did not detect IBD or “microscopic” colitis in any of the biopsies. However, more recent data suggest that a substantial number of patients with unexplained chronic diarrhea benefit from colonoscopy and mucosal biopsy analysis (62–66). da Silva *et al.* evaluated 162 patients with chronic diarrhea and normal colonoscopic examinations, and found that 69% had histologic abnormalities, including 31 with “microscopic” colitis and 22 with granulomas, some of whom proved to have infectious colitis. These authors also noted that of the 52 patients with clinically important findings in their biopsy samples, 15% had changes confined to the proximal colon (64). As a result, most authorities advocate biopsies in endoscopically normal patients with chronic diarrhea.

There is little evidence to support ileal biopsies in the assessment of patients with chronic diarrhea and normal endoscopic findings, but they are often helpful when an endoscopic or radiographic abnormality is present (60). In the study by Yusoff *et al.* (60) cited above, only 5% of patients with chronic diarrhea had abnormal-appearing ileal mucosa and pathologic findings on biopsies, but biopsies failed to detect significant pathology when ileoscopy was normal. McHugh *et al.* evaluated 414 consecutive patients who underwent intubation and biopsy of the terminal ileum. They found that the diagnostic yield of ileal biopsies was highest in patients with suspected Crohn’s

disease (40%), abnormal imaging studies (32%), endoscopically apparent ileitis (84%), or ulcers and erosions (69%), but ileal sampling was not helpful when the endoscopic appearance of the ileal mucosa was normal (67). Interestingly, ileal biopsies from patients with celiac disease may reveal increased numbers of intraepithelial lymphocytes and, thus, this finding may prompt upper endoscopic examination, or serologic studies, in patients with chronic diarrhea (Figure 5) (68).

DYSPLASIA SURVEILLANCE IN INFLAMMATORY BOWEL DISEASE

Patients with either ulcerative colitis (UC) or Crohn’s disease are at increased risk for the development of colorectal carcinoma, particularly if they have greater than 8–10 years of colitis, concomitant primary sclerosing cholangitis, a family history of colorectal carcinoma, or severe pancolitis (69–71). Although less common than UC, extensive colitis secondary to Crohn’s disease also carries an increased risk for cancer: recent data obtained from a cohort of 692 patients with IBD indicate that the standardized incidence ratio of colorectal carcinoma among Crohn’s disease patients is 1.9, compared to 2.4 for patients with UC (72).

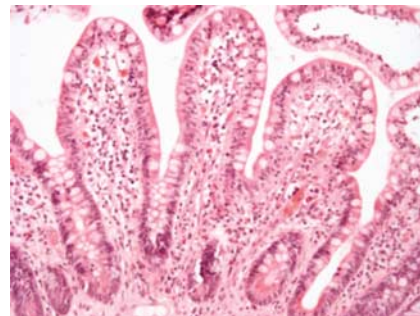


Figure 5. Sampling of the normal-appearing ileum may have diagnostic utility in the evaluation of patients with either celiac disease or “microscopic” colitis, because both of these conditions may be associated with increased intraepithelial lymphocytes.

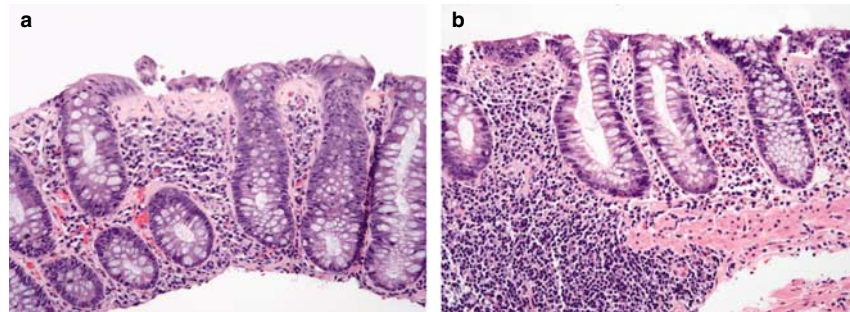


Figure 4. Classic features of collagenous colitis are often better developed in the proximal colon, and include mildly increased lamina propria and intraepithelial inflammation with marked subepithelial collagen deposition (a). In contrast, samples from the distal colon may show a relatively normal, or irregularly thickened, subepithelial collagen layer that, viewed in isolation, is not diagnostic of this disorder (b).

Colitis-related dysplasia may be present in endoscopically flat mucosa, or it may grow as a polyp, nodule, ulcer, or plaque. Early detection of dysplasia is vital to prevention of colorectal carcinoma in patients with chronic colitis (73–77). Current surveillance strategies recommend extensive sampling of colonic mucosa and raised lesions, ulcers, or other suspicious areas. Rubin *et al.* (78) evaluated 101 UC patients, including 81 high-risk and 20 low-risk patients, and found that at least 56 jumbo sized, nontargeted mucosal biopsies were necessary to exclude the possibility of dysplasia with 95% confidence, but 90% confidence was achieved with 33 samples. This observation has led to the common practice of obtaining multiple tissue samples from every 10–12 cm of colon, or, alternatively, five to six samples each from the right colon, transverse colon, descending colon, sigmoid colon, proximal rectum, and distal rectum. Several professional societies have proposed more refined surveillance protocols that vary slightly with respect to the time at which screening is performed following a diagnosis of colitis, the interval between surveillance examinations, and the number and location of tissue samples procured. For instance, the American College of Gastroenterology recommends that surveillance commence 8–10 years after the initial diagnosis of colitis and be repeated every 1–2 years with multiple biopsy samples obtained from every 10 cm of colon, regardless of the extent of colitis. In contrast, the British Society of Gastroenterology recommends 3-year intervals between examinations for patients with ≤ 20 years of colitis, 2-year intervals for those with 20–30 years of colitis, and annual examinations for patients with > 30 years of colitis (74).

Most recently, the Crohn's and Colitis Foundation of America developed detailed guidelines for IBD surveillance. Specific recommendations are as follows. First, a minimum of 33 biopsy samples should be obtained from patients with extensive colitis, representing four-quadrant samples procured from every 10 cm of the colon. Four-quadrant sampling every 10 cm from the anorectal junction to the proximal extent of disease is likely adequate for patients with microscopically confirmed limited colitis, as determined by a prior screening colonoscopy. Clinicians may consider obtaining four-quadrant mucosal biopsies from every 5 cm of the rectosigmoid colon because of an increased frequency of carcinoma in this region among patients with UC (79). In addition to these guidelines, samples from different regions of the colon should always be submitted in individually labeled containers. Raised lesions should be indicated as such, and submitted separately.

Unfortunately, undersampling of patients during surveillance colonoscopy is a widespread problem. Eaden *et al.* performed a questionnaire-based study that included 341 community practice and academic gastroenterologists in the United Kingdom, to assess IBD screening practices in that country. Although they found that all clinicians offered surveillance colonoscopy to their IBD patients, only 50% obtained 10 or more mucosal samples during the examination (80). Rodriguez *et al.* (76) performed a similar study in the United States and found that

54% of 312 gastroenterologists obtained 31 or more tissue samples from IBD patients during surveillance colonoscopy.

Emerging evidence suggests that advanced endoscopic techniques may improve dysplasia detection in IBD patients. Kiesslich *et al.* (81) randomly assigned 165 UC patients to either conventional colonoscopy or colonoscopy with chromoendoscopy, and found that the dysplasia detection rate was threefold higher in the latter. The yield of dysplasia detection is further enhanced by combined use of high-magnification colonoscopy with chromoendoscopy, which increases detection of dysplastic lesions by 4.75-fold compared to conventional techniques, despite procurement of significantly fewer (50%) mucosal biopsy samples (82). Other techniques, including narrow band imaging, fluorescence endoscopy, optical coherence tomography, and confocal laser endomicroscopy also enhance the detection rate of dysplasia. Whether these techniques will prove to be comparable, or superior, to chromoendoscopy, remains to be tested.

SUMMARY

Many types of inflammatory disorders of the gastrointestinal tract show a patchy, discontinuous pattern of injury and, as a result, limited endoscopic sampling of the gastrointestinal mucosa may fail to detect disease. The systematic procurement of multiple mucosal samples greatly enhances the diagnostic yield of tissue analysis in many circumstances, particularly when sampling includes endoscopically abnormal areas. Current recommendations for the evaluation of eosinophilic esophagitis include obtaining multiple samples of the proximal, distal, and intervening esophagus. Patients with BE are recommended to receive four-quadrant biopsy samples from every 1–2 cm of the involved mucosa. Patients with chronic gastritis should be evaluated with five tissue samples, as recommended by the modified Sydney system. In contrast, three samples from different areas within the duodenum, including the duodenal bulb, are recommended to reliably diagnose celiac disease. Both lymphocytic and collagenous colitis may be detected with a high degree of sensitivity by initial use of sigmoidoscopy, particularly when multiple samples are obtained, but full colonoscopy should be performed if the initial samples are nondiagnostic. Complete colonoscopy with four-quadrant mucosal biopsy samples obtained from every 10 cm of colon is suggested for surveillance of IBD. It is likely that some of these recommendations will undergo modification in the future, as evaluation of at-risk patients with the use of new endoscopic techniques, will likely improve identification of dysplastic lesions.

CONFLICT OF INTEREST

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