

CME

The Diagnostic Value of Endoscopic Terminal Ileum Biopsies

Jonathan B. McHugh, M.D., Henry D. Appelman, M.D., and Barbara J. McKenna, M.D.
Department of Pathology, University of Michigan, Ann Arbor, Michigan

OBJECTIVES: Biopsy of the terminal ileum (TI) is commonly performed during colonoscopy. The primary utility of this is to diagnose or rule out Crohn's disease in patients with symptoms and/or radiographic findings suggesting this diagnosis. We see many such biopsies in our gastrointestinal pathology service and have been impressed by the subjectively low yield of TI biopsies. Therefore, we studied this to obtain objective data.

METHODS: We retrospectively reviewed 414 consecutive patients with terminal ileal biopsies. Histologic parameters evaluated were primarily those changes diagnostic of chronic inflammation or its sequelae. Histologic findings were then compared with the indication(s) and endoscopic findings.

RESULTS: The TI was histologically normal in 82% and endoscopically normal in 81% with most endoscopic abnormalities having "ileitis" (13%). Known or strongly suspected inflammatory bowel disease was the most common indication (38%) with Crohn's disease accounting for 20% and ulcerative colitis 16% followed by diarrhea (33%), anemia/hematochezia (15%), abdominal pain (6%), and abnormal imaging (5%). Diagnostic yield varied, with indication and endoscopic findings being highest with known suspected Crohn's disease (40%), abnormal imaging (32%), and with endoscopic "ileitis" (84%) or ulcers/erosions (69%).

CONCLUSIONS: Diagnostic yield of TI biopsy varied with indication and endoscopic findings. Our study indicates that biopsy is of greatest value in patients undergoing endoscopy for known or strongly suspected Crohn's disease, or with an abnormal imaging study of the TI. Biopsy of endoscopically normal mucosa is unlikely to yield diagnostically useful information, and is not encouraged as routine. However, when "ileitis," ulcers, or erosions are identified, biopsies can be very helpful.

(Am J Gastroenterol 2007;102:1084-1089)

INTRODUCTION

Endoscopic examination and biopsy of the terminal ileum (TI) is often undertaken in patients clinically suspected of having inflammatory bowel disease, especially Crohn's disease, and in those with an abnormal TI on imaging studies. In addition, patients with abdominal pain, anemia, hematochezia, and diarrhea may undergo this procedure as part of a colonoscopic examination.

Chronic inflammation in the TI suggests a cause for the patient's symptoms, especially when the clinical suspicion is Crohn's disease. Crohn's disease preferentially affects the small intestine, especially the TI, accounting for many of the symptoms associated with this disease. Other conditions, including ulcerative colitis (UC), infections, and medications such as NSAIDs, can affect the TI and may mimic Crohn's disease histologically and endoscopically.

Intubation of the TI during colonoscopy was first reported in 1972 (1). Since then, the procedure has become routine, and endoscopists have become proficient at the technique.

Most recent studies indicate that experienced endoscopists are able to successfully intubate the TI in 95–98% of patients (2–5). In addition, most TI intubations can be performed in about 5 min, adding little time to the procedure (4).

At our institution, a large, busy, academic tertiary care medical center with an appropriately large gastroenterology division, it is not unusual for the surgical pathology service to receive lower gastrointestinal tract biopsies from over 50 patients a day. Many of these biopsies are from patients with known or suspected inflammatory bowel disease, and many include TI biopsies. Our anecdotal experience with such biopsies has been that few are histologically abnormal. There are few published data on the diagnostic value of TI biopsies. Therefore, we reviewed 414 consecutive TI biopsy specimens from our institution to determine the value of endoscopic TI biopsies.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board of the University of Michigan. We reviewed all TI biopsies obtained from January 2000 through December 2002 at

To access a continuing medical education exam for this article, please visit www.acg.gi.org/journalcme.

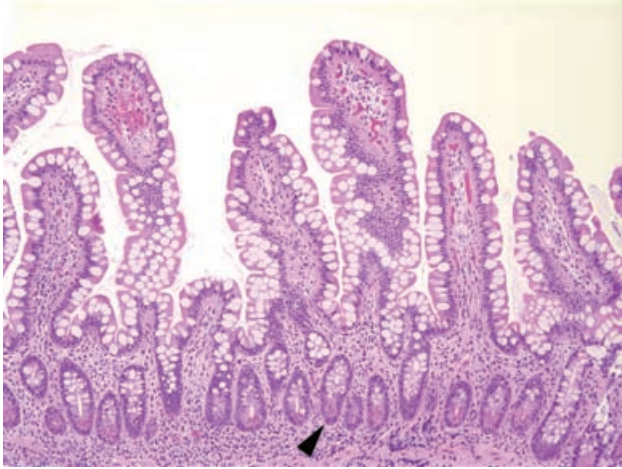


Figure 1. Medium power image of histologically normal TI mucosa. Villi are of regular size, shape, and distribution and 3–4 times longer than crypts with an approximately 3:1 goblet cell to absorptive cell ratio. Crypts are evenly spaced and oriented with basal Paneth cells (arrowhead) and are embedded within a slightly cellular lamina propria.

the University of Michigan Health System. TI biopsies were identified using a SNOMED free text computer search. One author (J.B.M.) blindly reviewed all hematoxylin and eosin-stained slides. Eight to ten serial sections were available for review from each biopsy sample. Biopsies with abnormal histologic findings (see below) were collectively reviewed by all three authors at a multiheaded microscope, where a consensus diagnosis was rendered.

The histologic parameters evaluated were primarily those changes diagnostic of chronic inflammation or its sequelae (Figs. 1–4) (6). These included architectural distortion, lamina propria plasmacytosis and/or eosinophilia, chronic ulcers, pyloric gland metaplasia, increased Paneth cells along the sides of the crypts, and granulomas. The presence of acute inflammation and aphthous ulcers was documented but in none of the cases were these the sole histologic abnormalities. The number of TI biopsies taken during each procedure was also recorded.

Histologic findings were then evaluated in comparison to the indication for ileoscopy and TI biopsy, and the endoscopic findings. These data were obtained from the University of Michigan endoscopy reports, the pathology laboratory information system, and the patient electronic medical record.

Diagnostic yields were determined for each of the clinical indications for endoscopy and also for the various endoscopic findings. In addition, to determine which indication or endoscopic finding was significantly associated with the abnormal histology, each was compared with the absence of the indication or finding using Fisher's exact test.

RESULTS

The study population from which the 414 TI biopsies were obtained consisted of 249 females and 165 males with a mean

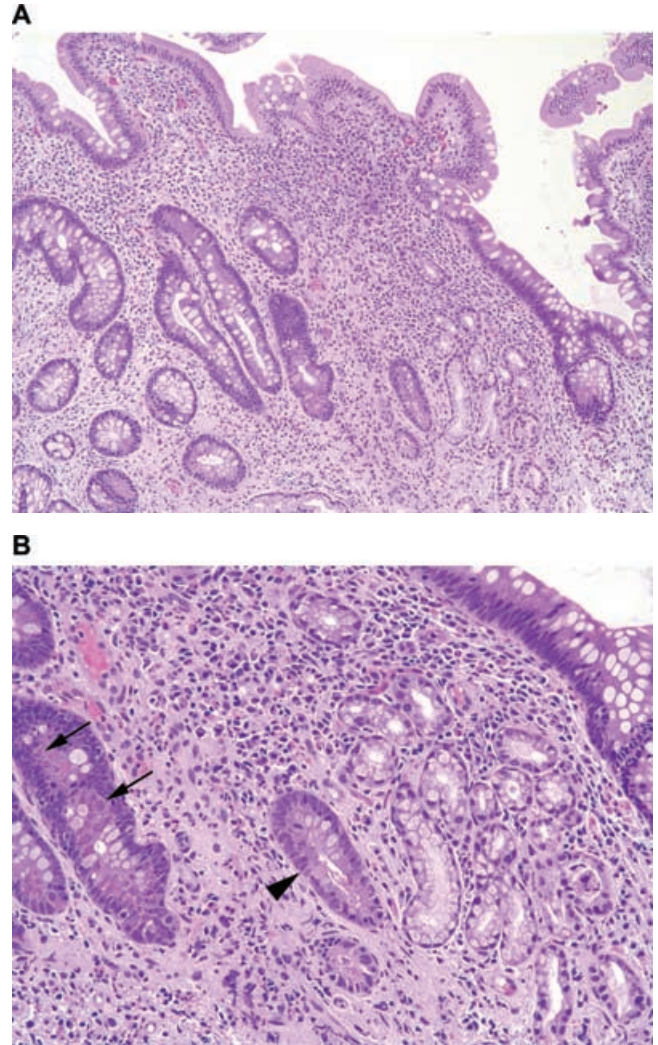


Figure 2. (A) Medium power image of chronically inflamed TI mucosa. Villi are of irregular size and shape, and crypts are elongated and irregular in size and shape (distortion). The lamina propria contains markedly increased inflammatory cells. Pyloric gland metaplasia (PGM) in the bottom right is the evidence of prior ulcer. (B) High power image of PGM. Compared with a more normal crypt (arrowhead), PGM resembles the glands normally present in the gastric cardia and antrum and is a metaplasia that occurs typically at the site of a healed ulcer. Also, on the left, note the abnormally located Paneth cells (arrows).

age of 37.6 (range 1–88). No patient had more than one set of biopsies. The median number of tissue fragments in each biopsy set was 3 (range 1–11). The endoscopic exams were performed by over 20 full-time faculty gastroenterologists at the University of Michigan, with varying numbers of years of experience.

The most common indication (Table 1) for TI biopsy was known or suspected inflammatory bowel disease. This was the indication in 157 (37.9%) patients; 83 (20%) were for Crohn's disease, 68 (16.4%) for ulcerative colitis, and 6 (1.4%) for unclassifiable chronic colitis. The next most common indication was diarrhea in 135 patients (32.6%), followed by

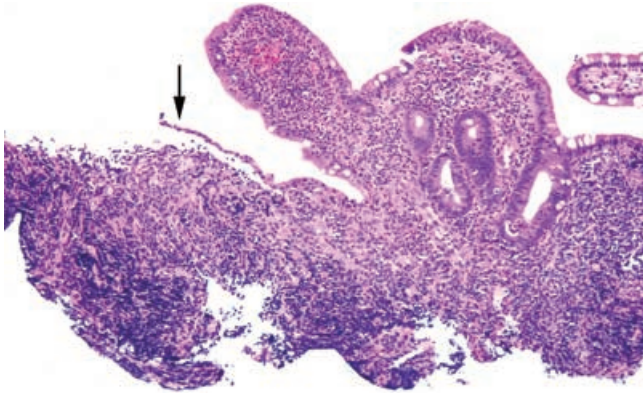


Figure 3. Low power image of distorted TI mucosa with markedly inflamed lamina propria and an aphthous ulcer on the left. Aphthous ulcers are mucosal erosions overlying lymphoid follicles that must be distinguished from artifactually stripped mucosa overlying lymphoid follicles, a common occurrence. The presence of regenerative mucosa (arrow) adjacent to the aphthous ulcer allows this distinction.

anemia/hematochezia in 62 (15%), abdominal pain in 23 (5.6%), and an abnormal imaging study in 19 (4.6%). The indications for the remaining 18 cases (4.3%) were varied but included family or personal history of cancer, weight loss, obstruction, and screening in patients with primary sclerosing cholangitis.

The TI was endoscopically normal in 334 (80.7%) cases (Table 2). The most common endoscopic abnormality reported, present in 55 (13.3%) cases, was “ileitis.” This endoscopic finding consisted of a constellation of features considered by the endoscopists to be gross evidence of chronic inflammation. Of the remaining cases, 13 (3.1%) had erosions or ulcers, 8 (1.9%) had nodularity, 3 (0.7%) had erythema, and 1 (0.2%) had a stricture.

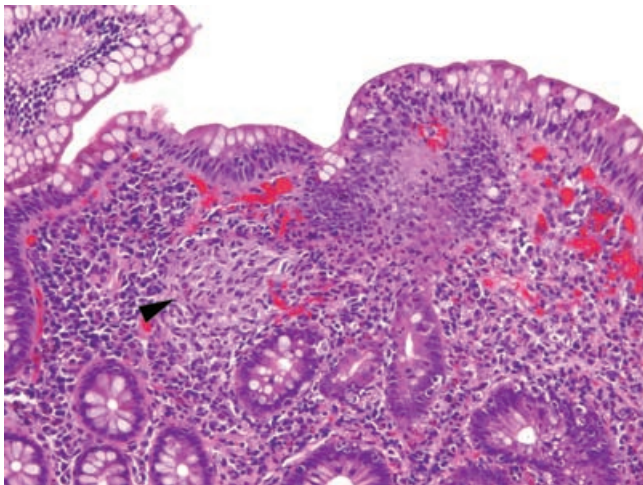


Figure 4. Another example of distorted TI mucosa with increased lamina propria inflammatory cells. In the center is a loosely formed granuloma (arrowhead) composed of spindled and epithelioid macrophages and suggestive of a diagnosis of Crohn’s disease.

The TI was histologically normal in 338 (81.6%) biopsies. Findings diagnostic of chronic inflammation or its sequelae were present in 74 (17.9%) biopsies. In addition, two (0.5%) biopsies had only features of healing or healed acute injury. The indications for biopsy in these two cases were hematochezia and abnormal imaging study.

The diagnostic yield of TI biopsy varied with the indication for ileoscopy (Table 1). Known or suspected Crohn’s disease was the one indication that was statistically significantly associated with histologic abnormality, with a diagnostic yield of 39.8% ($P < 0.001$). The yield was lower in patients with known or suspected ulcerative colitis (17.6%). Thus, the yield for all inflammatory bowel disease patients was 28.7%. After Crohn’s disease, the highest yield was in patients with abnormal TI findings on imaging, 36.8%; the association of abnormal imaging with histologic abnormality approached statistical significance ($P = 0.06$). In patients with anemia or hematochezia, 14.5% had abnormal biopsies; 10.4% of patients with diarrhea had abnormal biopsies, and only 4.3% of patients with abdominal pain had abnormal biopsies.

In cases in which the TI was endoscopically normal, 317 (94.9%) of the endoscopic TI biopsies were also normal (Table 2). Of the 17 cases (5.1%) with normal endoscopy and abnormal biopsies, significant chronic inflammatory changes were identified in 14 (4.2%), one of which was consistent with backwash ileitis in a patient with ulcerative colitis. In the other three, one had healed acute injury, one had only granulomas, and one had only distortion. In contrast, in the 80 cases in which endoscopic TI abnormalities were identified, 59 (73.8%) also had histologic abnormalities, all but four of which were considered by the authors to be those of significant chronic inflammation. In these four cases, distortion was the only abnormal histologic feature present in three and healing acute injury in one.

Similar to the findings comparing diagnostic yield with the indication for ileoscopy, diagnostic yield also varied with respect to the endoscopic findings (Table 2). Endoscopic “ileitis” and ulcers/erosions were the two endoscopic findings statistically significantly associated with abnormal histology. The yield was highest in cases of endoscopic “ileitis” with 83.6% having histologic evidence of chronic inflammation ($P < 0.001$). The next highest yield was in cases with endoscopic ulcers or erosions, in which 69.2% had abnormal biopsies ($P < 0.001$). The yield was lower (12.5%) when nodularity was the reported abnormality. All three patients with erythema had abnormal biopsies and the patient with the stricture had normal histology.

DISCUSSION

Intubation and biopsy of the TI during colonoscopy has become a standard procedure in the evaluation and management of patients suspected or known to have inflammatory bowel disease. The most important use of this procedure is in patients suspected of having Crohn’s disease, as the TI is

Table 1. Diagnostic Yield of TI Biopsy Compared With Indication for Endoscopy

Indication	N	Abnormal TI Biopsy #	Abnormal TI Biopsy %	95% CI	P Value
Inflammatory bowel disease	157	45	28.7	22.2–36.2	–
Crohn's disease	83	33	39.8	29.9–50.5	<0.0001
Ulcerative colitis	68	12	17.6	10.4–28.9	ns
Unclassifiable chronic colitis	6	0	0	0–39.0	ns
Diarrhea	135	14	10.4	6.3–16.6	ns
Anemia/hematochezia	62	9	14.5	7.8–25.4	ns
Abdominal pain	23	1	4.3	0.8–21.0	ns
Abnormal imaging study	19	7	36.8	19.2–59.0	0.06
Other	18	0	0	0–17.6	–
Total	414	76	18.4	14.9–22.4	

ns = not significant.

the most common site of involvement in this disease. Finding chronic ileitis on TI biopsy material, in the right clinical context, is diagnostic of Crohn's disease. On the other hand, finding no significant abnormality on TI biopsy material may help to exclude the diagnosis of Crohn's disease, at least in some patients. We see many TI biopsies in our daily practice, and we have been impressed by the low yield of histologic abnormalities in such specimens. We performed this study to obtain objective data on this subject, as there are currently few data available in the literature.

We retrospectively analyzed 414 consecutive patients with TI biopsies and compared the histologic findings with the clinical indications for TI intubation and biopsy, as well as with the endoscopic TI findings and follow-up information. In addition, we determined the diagnostic yield of TI biopsies compared with the procedure indications and endoscopic abnormalities.

Histologically unremarkable TI mucosa was identified in the majority of the patients in this study, with 81.6% having no significant histologic abnormalities. Similarly, 80.7% of the TIs in the study were grossly unremarkable by endoscopic examination. Only 18.4% of patients undergoing TI intubation and biopsy had histologically abnormal TI mucosa. More significantly, when the TI was grossly normal, only 5.1% of biopsies were histologically abnormal and only 4.2% had significant histologic chronic inflammation.

The diagnostic yield of TI biopsies was dependent on the indication for TI endoscopy and biopsy. When Crohn's disease was known or strongly suspected, nearly 40% had abnormal

biopsies with histologic evidence of significant chronic inflammation ($P < 0.001$). This yield was more than twice that when the indication was known or strongly suspected ulcerative colitis (39.8% vs 17.6%). Ulcerative colitis as the indication was not statistically significantly associated with finding chronic inflammation on biopsy. This is not surprising and conforms to the low rate of inflammation in the TI in UC, the so-called "backwash ileitis." Interestingly, the 17.6% of our UC patients with ileitis closely matches that recently reported by Haskell and colleagues (7). The only indication, other than Crohn's disease, that approached statistical significance in terms of its association with histologic chronic inflammation was an abnormal imaging study, most often thickening of the TI on computed tomography scan (36.8%, $P = 0.06$).

Finding histologic evidence of chronic TI inflammation was also significantly more likely when certain endoscopic findings were reported. At our institution, endoscopists refer to a constellation of features considered to represent gross evidence of chronic inflammation as "ileitis." When "ileitis" was reported as an endoscopic TI abnormality, over 80% of the time histologic chronic inflammation was identified ($P < 0.001$). Similarly, when ulcers or erosions were seen, nearly 70% had histologic chronic inflammation ($P < 0.001$). Nodularity was not significantly associated with finding histologic chronic inflammation, but chronic inflammation was more often seen with nodularity than with normal endoscopy (12.5% vs 4.2%). Although all patients with erythema and no patients with stricture had histologic evidence of chronic

Table 2. Diagnostic Yield of TI Biopsy Compared With Endoscopic Findings

Endoscopic Finding	N	Abnormal TI Biopsy #	Abnormal TI Biopsy %	95% CI	P Value
Normal	334	17	5.1	3.2–8.0	–
"Ileitis"	55	46	83.6	71.7–91.2	<0.0001
Ulcers or erosions	13	9	69.2	42.4–87.3	<0.0001
Nodularity	8	1	12.5	2.2–47.1	ns
Erythema	3	3	100	43.8–100.0	–
Stricture	1	0	0	0–79.4	–
Total	414	76	18.4	14.9–22.4	

ns = not significant.

inflammation, the numbers were too small to make any definitive conclusions.

Although we found no previous studies looking specifically at the diagnostic yield of TI biopsy and comparing it with the indications for ileoscopy and the endoscopic findings, there are some related data in the literature. In a prospective study of 295 patients undergoing colonoscopy for standard indications (not specifically indicated) as addressed by the American Society for Gastrointestinal Endoscopy, the TI was successfully intubated in 213 (3). Of these, only four had gross abnormalities and only one was histologically abnormal (0.5%); however, not all patients had TI biopsies. Others have concluded that, similar to this study, biopsy of a grossly normal-appearing TI is not helpful (8).

Recent reports indicate that in some patients with collagenous and lymphocytic colitis, there is inflammation in the TI. These changes include surface epithelial lymphocytosis, villous shortening, and subepithelial collagen, but not the distortion, chronic inflammation, or pyloric gland metaplasia that predominate in the abnormal TI biopsies in our study (9–11). In the few cases of microscopic colitis with TI abnormalities, the diagnosis is based on the colonic biopsies, and the TI biopsies, although interesting, are superfluous.

We found only three papers evaluating the utility of ileoscopy. However, none evaluated the utility of TI biopsy considering the specific indications and endoscopic findings as in this study. In 1985, Borsch and Schmidt prospectively evaluated 400 consecutive patients successfully undergoing TI endoscopy with biopsy (12). Pathologic abnormalities were identified in only 5% of these biopsies; however, diagnostically useful information was provided in 30%, as normal endoscopy and biopsy ruled out certain diagnoses in an additional 98 patients. The authors concluded that endoscopic examination and biopsy was useful in patients with suspected or established inflammatory bowel disease, diarrhea, lower gastrointestinal tract bleeding, or irritable bowel syndrome.

In 1995, Zwas *et al.* prospectively evaluated 144 patients undergoing colonoscopy, including asymptomatic patients undergoing colorectal cancer screening or inflammatory bowel disease surveillance and symptomatic patients with diarrhea, anemia/bleeding, abdominal pain, and weight loss (4). Biopsy of the TI was successful in 130 patients. Among the asymptomatic group, only 2.7% had histologic abnormalities as opposed to 12.5% of symptomatic patients. In contrast to our findings, 29% of patients with diarrhea in this study had abnormal TI biopsies. This can likely be attributed to a high proportion of HIV-positive patients in this study. Unfortunately, no information comparing diagnostic yield with specific endoscopic findings was reported and low patient numbers in the nonscreening and nondiarrhea groups preclude making meaningful conclusions from these patient groups.

Finally, in 1998, Geboes *et al.* prospectively studied the impact of ileoscopy in 300 patients undergoing colonoscopy for colorectal cancer screening (control group, N = 43) or for workup of enterocolitis (N = 257) (13). In the control

group, no gross or microscopic lesions were identified. In the enterocolitis group, 48% had an abnormal TI endoscopically and 49% were histologically abnormal. Only two patients (0.8%) with normal TI endoscopy had abnormal TI biopsies. They concluded that only in carefully selected patients with inflammatory bowel disease-related symptoms is ileoscopy with biopsy useful.

Similar to previous endoscopic studies, our findings support the conclusion that biopsy of the TI is of greatest value in patients who are undergoing endoscopy for known or strongly suspected Crohn's disease, or with an abnormal imaging study of the intestine, particularly TI thickening. Biopsy of an endoscopically normal or nodular-appearing TI is unlikely to yield any diagnostically useful information, and is not encouraged as routine. In contrast, when "ileitis," ulcers, or erosions are identified, TI biopsy can be very helpful diagnostically.

ACKNOWLEDGMENTS

The results of this study were presented in part at the 94th Annual Meeting of the United States and Canadian Academy of Pathologists in San Antonio, Texas, February 2005.

STUDY HIGHLIGHTS

What Is Current Knowledge

- Intubation and biopsy of the terminal ileum (TI) is a very common endoscopic procedure, yet few data exist regarding the diagnostic yield of this technique.

What Is New Here

- Of 414 terminal ileal biopsies, only 18.4% had histologic abnormalities. Only 4.2% of those without endoscopic abnormalities had significant histologic inflammation.
- We demonstrated that the diagnostic yield of biopsies varies significantly with the indication for the procedure, being greatest in those with known or strongly suspected Crohn's disease, or with an abnormal TI on radiography.
- We also demonstrated that the diagnostic yield of biopsies varies with specific endoscopic findings, being greatest when the endoscopist reports "ileitis," ulcers, or erosions.
- Our findings indicate that the utility of TI biopsy may be limited to those with specific indications and/or endoscopic findings. Biopsy of normal-appearing mucosa is discouraged, as the diagnostic yield is quite low.

Reprint requests and correspondence: Barbara J. McKenna, M.D., University of Michigan Health System, Department of Pathology, 2G332 University Hospital, 1500 East Medical Center Drive, Ann Arbor, MI 48109-0054.

Received May 17, 2006; accepted October 30, 2006.

REFERENCES

1. Nagasako K, Yazawa C, Takemoto T. Biopsy of the terminal ileum. *Gastrointest Endosc* 1972;19:7–10.
2. Belaiche J, Van Kemseke C, Louis E. Use of the enteroscope for colo-ileoscopy: Low yield in unexplained lower gastrointestinal bleeding. *Endoscopy* 1999;31:298–301.
3. Kundrotas LW, Clement DJ, Kubik CM, et al. A prospective evaluation of successful terminal ileum intubation during routine colonoscopy. *Gastrointest Endosc* 1994;40:544–6.
4. Zwas FR, Bonheim NA, Berken CA, et al. Diagnostic yield of routine ileoscopy. *Am J Gastroenterol* 1995;90:1441–3.
5. Morini S, Lorenzetti R, Stella F, et al. Retrograde ileoscopy in chronic nonbloody diarrhea: A prospective, case-control study. *Am J Gastroenterol* 2003;98:1512–5.
6. Appelman HD. Biopsies of the terminal ileum in inflammatory bowel disease. Do they help? *Pathol Case Rev* 2004;9:115–22.
7. Haskell H, Andrews CW, Reddy SI, et al. Pathologic features and clinical significance of “backwash ileitis” in ulcerative colitis. *Am J Surg Pathol* 2005;29:1472–81.
8. Yusoff IF, Gormonde DG, Hoffman NE. Routine colonic mucosal biopsy and ileoscopy increases diagnostic yield in patients undergoing colonoscopy for diarrhea. *J Gastroenterol Hepatol* 2002;17:276–80.
9. Padmanabhan V, Callas PW, Li SC, et al. Histopathological features of the terminal ileum in lymphocytic and collagenous colitis: A study of 32 cases and review of literature. *Mod Pathol* 2003;16:115–9.
10. Marteau P, Lavergne-Slove A, Lemann M, et al. Primary villous atrophy is often associated with microscopic colitis. *Gut* 1997;41:561–4.
11. Dickey W, Hughes DF. Histology of the terminal ileum in celiac disease. *Scand J Gastroenterol* 2004;39:665–7.
12. Borsch G, Schmidt G. Endoscopy of the terminal ileum. Diagnostic yield in 400 consecutive examinations. *Dis Colon Rectum* 1985;28:499–501.
13. Geboes K, Ectors N, D’Haens G, et al. Is ileoscopy with biopsy worthwhile in patients presenting with symptoms of inflammatory bowel disease? *Am J Gastroenterol* 1998;93:201–6.

CONFLICT OF INTEREST**Guarantor of the article:** Barbara J. McKenna, M.D.**Specific author contributions:** All authors contributed meaningfully to the study design and execution, and to manuscript development.**Financial support:** None.**Potential competing interests:** None.
