Communication from the ASGE Standards of Practice Committee

GUIDELINE

The role of endoscopy in the management of patients with diarrhea

This is one of a series of statements discussing the use of GI endoscopy in common clinical situations. The Standards of Practice Committee of the American Society for Gastrointestinal Endoscopy (ASGE) prepared this text. In preparing this guideline, a search of the medical literature was performed by using PubMed. Studies or reports that described fewer than 10 patients were excluded from analysis if multiple series with more than 10 patients addressing the same issue were available. Additional references were obtained from the bibliographies of the identified articles and from recommendations of expert consultants. Guidelines for appropriate use of endoscopy are based on a critical review of the available data and expert consensus at the time the guidelines are drafted. Further controlled clinical studies may be needed to clarify aspects of this guideline. This guideline may be revised as necessary to account for changes in technology, new data, or other aspects of clinical practice. The recommendations are based on reviewed studies and are graded on the strength of the supporting evidence (Table 1).[1] The strength of individual recommendations is based on both the aggregate evidence quality and an assessment of the anticipated benefits and harms. Weaker recommendations are indicated by phrases such as "we suggest," whereas stronger recommendations are typically stated as "we recommend."

This guideline is intended to be an educational device to provide information that may assist endoscopists in providing care to patients. This guideline is not a rule and should not be construed as establishing a legal standard of care or as encouraging, advocating, requiring, or discouraging any particular treatment. Clinical decisions in any particular case involve a complex analysis of the patient's condition and available courses of action. Therefore, clinical considerations may lead an endoscopist to take a course of action that varies from this guideline.

Diarrheal illnesses can be associated with significant morbidity and mortality, especially in high-risk populations such as the very young, the elderly, and those with comorbid medical illnesses. Diarrhea is defined in adults by abnormal stool weight (>200 g/day), consistency (loose or liquid), and/or frequency (>3 times/day).[2,3] A 4-week symptom duration is generally considered as a cutoff point to distinguish acute (≤4 weeks) from chronic (>4 weeks) diarrhea.[2,3] Because the causes of acute and chronic diarrhea are often different, the need, threshold, and timing of endoscopic evaluation for acute versus chronic diarrhea are different. This document describes the role of endoscopy in the management of patients with diarrhea, with separate discussions for immunocompetent and immunocompromised patients, and is an update of a previous ASGE guideline.[4] There are few indications for endoscopy in the management of acute diarrhea, and, although these are briefly discussed, the document primarily focuses on the evaluation on chronic diarrhea.

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IMMUNOCOMPETENT HOST

Infectious diarrheal illnesses in otherwise healthy individuals are common and short-lived and rarely require specific therapy.[5] Therefore, endoscopy is not warranted for the initial evaluation of acute diarrhea.[6] However, an endoscopic evaluation should be considered for patients with persistent symptoms, inconclusive diagnosis after routine blood and stool tests, or failure to respond to empirical therapy.[7]

Flexible sigmoidoscopy

Flexible sigmoidoscopy may be a suitable initial investigation for the evaluation of acute diarrhea in patients with suspected diffuse colitis (eg, suspected *Clostridium difficile* colitis) or chronic diarrhea in patients who are pregnant, have significant comorbidities, or when symptoms characteristic of left-sided colonic disease predominate (eg, tenesmus and urgency). In many situations, flexible sigmoidoscopy may be sufficient as the initial endoscopic test in patients with chronic diarrhea. Biopsies should be performed to obtain specimens for histologic evaluation, even when the mucosa appears normal, to exclude microscopic colitis and other etiologies, as discussed in the next section. Colonoscopy should be considered if the findings at flexible sigmoidoscopy are inconclusive, the symptoms persist, there is large-volume blood loss, or inflammatory bowel disease (IBD) or colorectal cancer is suspected.

Colonoscopy

In patients with chronic diarrhea, colonoscopy with biopsy is valuable for the diagnosis of IBD, microscopic inflammatory disorders, and colorectal neoplasia.[8,9] The role of colonoscopy in the diagnosis, surveillance, and endoscopic therapy of IBD was reported in a separate ASGE guideline.[10] For those patients with diarrhea who are candidates for

TABLE 1. GRADE system for rating the quality of evidence for guidelines

Quality of evidence	Definition	Symbol
High quality	Further research is very unlikely to change our confidence in the estimate of effect	⊕⊕⊕⊕
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate	⊕⊕⊕◯
Low quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate	⊕⊕◯◯
Very low quality	Any estimate of effect is very uncertain	⊕◯◯◯

Adapted from Guyatt et al.[1]

routine colorectal cancer screening or surveillance, a diagnostic colonoscopy can be performed to both evaluate the diarrhea and satisfy their cancer screening or surveillance needs.

The type of bowel preparation for colonoscopy in the evaluation of diarrhea should be determined on an individual basis. It is recognized that sodium phosphate–based bowel preparations may cause mucosal changes that can be confused with the macroscopic appearance of IBD, most commonly in the distal colon.[11,12] While these changes may be problematic to differentiate endoscopically, they usually can be differentiated on histology.[13] Nonsteroidal anti-inflammatory drugs (NSAIDs) can cause terminal ileal mucosal changes that mimic IBD.[14]

Histology is essential in the evaluation of chronic diarrhea because of the fact that many etiologies are not macroscopically evident (eg, quiescent IBD, microscopic colitis, eosinophilic colitis, and amyloidosis). The diagnostic yield of colonoscopy in patients with chronic diarrhea ranges from 7% to 32%, with IBD and microscopic colitis being most common.[15-20] There are 2 forms of microscopic colitis: lymphocytic colitis and collagenous colitis. It is characterized by watery diarrhea in the absence of obvious endoscopic abnormalities. In referral centers, microscopic colitis accounts for approximately 10% of patients seen for chronic diarrhea.[19] In a retrospective study of 809 patients with chronic diarrhea who had undergone colonoscopy and biopsy, more than 99% of 122 abnormal pathologic findings were identifiable on distal colonic biopsy samples.[19] The majority (80 of 122) showed microscopic colitis. The authors calculated sigmoidoscopy to be a more cost-effective method of investigation than colonoscopy. However, multiple other studies have shown that the disease distribution of microscopic colitis can be patchy, and when biopsy specimens are taken only from the left side of the colon, the diagnosis may be missed.[8,21-25] Therefore, in patients with chronic diarrhea and normal findings on colonoscopic examination, it is recommended that multiple biopsy samples should be taken from both the right and left sides of the colon.

Retrograde ileoscopy with biopsy in the diagnostic evaluation of diarrheal illness can be helpful.[26] The differential diagnosis for abnormal endoscopic and histologic findings in the terminal ileum of patients with acute or chronic diarrhea includes Crohn's disease, NSAID-induced enteropathy, carcinoid, tuberculosis, lymphoma, and adenocarcinoma.[14,27,28] In a prospective evaluation of 138 patients, ileoscopy provided additional information leading to an incidental, conclusive diagnosis in 2.7% of asymptomatic patients undergoing colonoscopy for polyp surveillance; the rate increased to 18% in 22 non–human immunodeficiency virus (HIV) patients with diarrhea.[29] Terminal ileal biopsy is most helpful in patients with or suspected of having inflammatory diarrhea.[26,30] Biopsy may be of the greatest value in patients undergoing endoscopy for known or strongly suspected Crohn's disease, with abnormal findings on an imaging study of the terminal ileum, or when abnormal terminal ileal mucosa is identified endoscopically.[31,32] In 1 report, microscopic lesions of the terminal ileum were found in 125 (49%) of 257 patients with diarrhea and suspected IBD.[32] Ileal biopsies were essential for the diagnosis in 15 (6%) patients and contributed to the diagnosis in 53 (21%). The diagnostic yield of ileal biopsy of normal-appearing mucosa is not well studied, with reports of significant findings ranging from 0% to 4.2% of patients.[9,18,31,32] Therefore, the value of routine ileal biopsy of normal-appearing mucosa is controversial but overall is probably of low yield.

Esophagogastroduodenoscopy

Acute diarrheal illnesses are generally caused by infectious agents involving the lower part of the GI tract. Routine use of esophagogastroduodenoscopy (EGD) in these self-limited disorders is therefore not indicated. In the absence of significant findings on laboratory studies and lower endoscopy, an upper GI evaluation for small-bowel disease should be considered in patients with chronic diarrhea. The differential diagnosis in these patients includes celiac disease, *Giardia* infection, Crohn's disease, eosinophilic gastroenteropathy, Whipple's disease, intestinal amyloid, and pancreatic insufficiency.

Mucosal biopsies of the small intestine should be performed even when the endoscopic appearance is normal. It is important to include the clinical suspicion in the pathology request form so that special histochemical and immunohistochemical stains of biopsy specimens can be

performed, as indicated.[33] Some studies have shown that orientation of biopsy specimens is important for accurate histologic evaluation.[34-36]

Celiac serology should be considered as the first-line diagnostic modality in patients suspected of having celiac disease.[2] The tissue transglutaminase assay has demonstrated the highest performance characteristics for the serologic diagnosis of celiac disease in the absence of IgA deficiency.[37] Most experts recommend that a positive serologic test result for celiac disease should be confirmed with a tissue biopsy.[38,39] Although a diagnosis of celiac disease cannot be definitively made based on the endoscopic appearance of the small bowel (eg, scalloped mucosal folds), magnification endoscopy may enhance the diagnostic yield and may be helpful in highlighting the diseased area for targeted biopsy.[40,41] Biopsy specimens obtained from the second or third portion of the duodenum with standard forceps are usually sufficient.[39,42,43] A study of 102 patients showed that if 2, 3, and 4 biopsy specimens were obtained, celiac disease was confirmed in 90%, 95%, and 100% of the cases, respectively.[43] Therefore, we recommend obtaining a minimum of 4 biopsy specimens. The distribution of celiac disease may be patchy, particularly in pediatric patients,[44] and isolated jejunal involvement by celiac disease can occur.[45] Evaluation of the more distal small bowel may be of benefit in selected patients (eg, those with persistent symptoms in suspected celiac disease and those with suspected small-bowel lymphoma). Because concurrent celiac disease and microscopic colitis are common,[46,47] celiac serology and/or upper endoscopy with proximal small-bowel biopsy may be considered to rule out celiac disease in patients with a diagnosis of microscopic colitis who do not respond to treatment.

Patients at high risk of *Giardia* infection with negative findings on stool studies may benefit from upper endoscopy with duodenal biopsies for touch preparation and/or duodenal aspirates to identify trophozoites.[48,49] Upper endoscopy with quantitative culture of small-bowel biopsies or aspirate is useful for the diagnosis of small-bowel bacterial overgrowth.[50,51] Endoscopy-assisted pancreatic function tests may be useful for the diagnosis of pancreatic insufficiency in chronic pancreatitis.[52]

Video capsule endoscopy

Video capsule endoscopy (VCE) has been studied in patients with chronic diarrhea with concurrent abdominal pain and other abdominal symptoms.[53,54] Diagnostic yield ranged from 13% to 24%, with findings consistent with Crohn's disease, NSAID-induced enteropathy, celiac disease, and submucosal masses.[53-55] VCE may be more sensitive for the detection of mucosal changes of celiac disease than EGD with a sensitivity of 70% to 85% and a specificity of 100% in untreated celiac disease.[55,56] However, because of the modest diagnostic yield, inability to obtain tissue, and risk of capsule retention, VCE is not recommended for the routine evaluation of chronic diarrhea.

Enteroscopy

There are limited data on the diagnostic value of enteroscopy solely for the evaluation of diarrhea. Push enteroscopy has been evaluated as a complementary investigation for small-bowel follow-through, EGD, and colonoscopy, with a diagnostic yield of as high as 22% in patients with chronic diarrhea and/or malabsorption.[57,58] There is increasing use of antegrade and retrograde balloon-assisted enteroscopy for the assessment of small-bowel pathology, including those associated with diarrhea.[59-62] It is reasonable to perform enteroscopy when there is a high suspicion of small-bowel pathology and when EGD and colonoscopy with biopsies are not conclusive or when lesions of the distal small bowel are detected by radiographic imaging or VCE.

IMMUNOCOMPROMISED HOST

Causes of diarrheal illnesses in immunocompromised patients are often different from those in immunocompetent patients. Stool testing for pathogens is the first-line evaluation, whereas endoscopy is generally indicated only when the diarrheal illness is persistent and stool tests fail to reveal a cause.[63,64] In patients with severe diarrhea, it may be possible to omit the bowel preparation.

One of the more common infectious etiologies of diarrhea in patients immunocompromised by organ or stem cell transplantation, HIV, or immunosuppressive medications for other reasons is cytomegalovirus (CMV) colitis. It is important to note that CMV infection diagnosed by quantitative CMV polymerase chain reaction, viral culture, or positive serology results may not necessarily indicate a tissue-invasive disease and an endoscopic biopsy may be necessary. If suspicion of CMV remains high despite the absence of a histologic diagnosis, then in situ hybridization, immunohistochemistry, and tissue culture for CMV may be required for diagnosis.[65]

HIV

Patients with HIV infection often have diarrheal illnesses. In a study of more than 15,000 hospitalized HIV patients in 1998, 2.8% were admitted for a diarrheal diagnosis.[66] Data on the endoscopic evaluation of patients with HIV are mostly from studies that preceded the use of highly active antiretroviral therapy.[67] Although CMV is the most common pathogen detected in these patients, histopathologic evaluation may identify other pathogens, such as adenovirus and enteropathogenic bacteria.[68-70] Furthermore, a pathogen may be identified by endoscopy despite negative results of stool studies.[71] The yield of colonoscopy is significantly higher in patients with a CD4 count of less than 100 cells/mm^3 because opportunistic infections are more common when the CD4 count is low.[69,71]

There is some debate as to the need to evaluate both the left and right sides of the colon in immunocompromised patients with diarrhea. In a retrospective study of 307 HIV-infected patients with unexplained chronic diarrhea,

colonoscopy had a greater diagnostic yield than sigmoidoscopy (39% vs 22%, respectively; $P = .009$) and was more cost-effective.[72] In another report of 317 patients, 30% of pathogens and 75% of lymphomas were identified only on biopsy samples taken from the proximal colon, well beyond the reach of the flexible sigmoidoscope.[69] Other investigators have shown that most lesions can be identified with a flexible sigmoidoscope. In 2 studies of 79 and 48 HIV-infected patients with diarrhea undergoing colonoscopy, 82% to 93%, respectively, of infectious etiologies were identified from biopsy specimens of the left side of the colon.[70,73] Therefore, although flexible sigmoidoscopy is a reasonable initial investigation in HIV patients with chronic diarrhea, there is evidence showing that colonoscopy has a higher diagnostic yield and is more cost-effective. Upper endoscopy may also be considered if diarrhea persists despite appropriate therapy or there are upper GI symptoms, such as nausea, vomiting, and odynophagia.[74,75] In a retrospective evaluation of 442 patients with HIV-related chronic diarrhea undergoing upper endoscopy with small-bowel biopsy and aspirate, a pathogen was identified in 28%.[76] Jejunal biopsy specimens may have a better diagnostic yield than those obtained from the duodenum.[76]

Graft-Versus-Host Disease

Graft-Versus-Host Disease (GVHD), a complication of hematopoietic stem cell transplantation (HSCT), commonly presents with secretory diarrhea in the first 3 months after transplantation. GVHD is categorized into acute and chronic forms and can involve any part of the GI tract.[77] In acute GVHD, diarrhea is often severe and can be watery or bloody. The differential diagnosis includes side effects of chemotherapeutic agents or other medications, lymphoma, and viral, bacterial, fungal, or parasitic infections.[78] Endoscopic findings in GVHD are associated with the stage of disease, ranging from normal mucosa to erythema, edema, erosions, ulcerations, and mucosal sloughing.[78-80] Endoscopic mucosal biopsies are necessary because there is no correlation between abnormal mucosal appearance at endoscopy and histologic findings.[81,82] Therefore, in symptomatic patients undergoing an endoscopic procedure after HSCT, biopsy samples should be taken from both endoscopically normal- and abnormal-appearing mucosa.[81] EGD and/or colonoscopy with biopsies of the stomach, small bowel, colon, and rectum are all suitable for diagnostic purposes.[82] In patients at risk of acute GVHD undergoing endoscopic procedures for GI symptoms, the biopsy site with the highest yield is the distal colon with a sensitivity of 82% to 95%.[81,83,84] There are also reports of a significant risk of duodenal hematoma with duodenal biopsy.[81,85] Risk factors include a diagnosis of acute GVHD and thrombocytopenia.[81,85] Therefore, flexible sigmoidoscopy with distal colon biopsy is preferred as the initial evaluation for acute GVHD. However, if sigmoidoscopic biopsy samples are negative or if upper GI symptoms predominate, EGD with biopsies is recommended for the diagnosis of acute GVHD.[77] Some centers advocate combined upper endoscopy and colonoscopy as the initial evaluation of diarrhea after HSCT to expedite diagnosis.

RECOMMENDATIONS

1. Stool and laboratory tests should be the initial step for the evaluation of clinical scenarios suggestive of infectious diarrhea. ⊕⊕⊕◯
2. In patients with chronic unexplained diarrhea, we suggest colonoscopy with random biopsies of the right and left side of the colon. Sigmoidoscopy is an alternative option, although this may miss right-sided organic disease. ⊕⊕◯◯
3. We recommend intubation of the terminal ileum during colonoscopy for patients undergoing evaluation of chronic diarrhea. ⊕⊕⊕◯ There are insufficient data to determine whether biopsy of an endoscopically normal-appearing terminal ileum should be routinely performed, but the yield of this is likely low.
4. We recommend EGD with small-bowel biopsy in patients with chronic diarrhea or suspected malabsorption and inconclusive evaluation after colonoscopy with biopsy and in patients with positive celiac serology. ⊕⊕⊕◯
5. We recommend obtaining a minimum of 4 duodenal biopsy specimens for evaluation of suspected celiac disease. ⊕⊕⊕◯
6. Enteroscopy is not recommended for the routine evaluation of chronic diarrhea but may be useful for evaluation of small-bowel disease when other investigations are nondiagnostic. ⊕⊕◯◯
7. VCE is not recommended for the routine evaluation of chronic diarrhea. ⊕⊕◯◯
8. In patients with HIV and diarrhea, we suggest either flexible sigmoidoscopy or colonoscopy if laboratory evaluation is nondiagnostic. ⊕⊕◯◯
9. In the absence of a diagnosis on flexible sigmoidoscopy, we recommend a full colonoscopy with biopsy and/or EGD with biopsy for HIV patients with persistent diarrhea. ⊕⊕⊕◯
10. In patients with suspected GVHD and diarrhea, we suggest flexible sigmoidoscopy with distal colon biopsies as the initial endoscopic evaluation. ⊕⊕◯◯ In the event of negative colonic histology findings or when upper GI symptoms predominate, we recommend an EGD with biopsies. ⊕⊕⊕◯

Abbreviations: CMV, cytomegalovirus; EGD, esophagogastroduodenoscopy; GVHD, graft-versus-host disease; HIV, human immunodeficiency virus; HSCT, hematopoietic stem cell transplantation; IBD, inflammatory bowel disease; NSAID, nonsteroidal anti-inflammatory drug; VCE, video capsule endoscopy.

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