The role of endoscopy in dyspepsia

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, supplemented by accessing the "related articles" feature of PubMed. Additional references were obtained from the bibliographies of the identified articles and from recommendations of expert consultants. When little or no data exist from well-designed prospective trials, emphasis is given to results from large series and reports from recognized experts. 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 were based on reviewed studies and were graded on the strength of the supporting evidence (Table 1).

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 these guidelines.

Dyspepsia encompasses a constellation of upper-abdominal symptoms that affect approximately a fourth of the population in Western countries.[1-3] Many patients with dyspepsia are referred to gastroenterologists for consultation and endoscopy.[4,5] Given this large burden of referral patients, the appropriate role of endoscopy in the evaluation of dyspepsia is both a pragmatic concern for the gastroenterologist and an important determinant of health care costs.

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DEFINITION

Dyspepsia is a nonspecific term to denote upper-abdominal discomfort that is thought to arise from the upper-GI tract.[6,7] Dyspepsia may encompass a variety of more specific symptoms, including epigastric discomfort, bloating, anorexia, early satiety, belching or regurgitation, nausea, and heartburn. Symptoms of dyspepsia most commonly result from 1 of 4 underlying disorders: peptic ulcer disease, GERD, functional disorders (nonulcer dyspepsia), and malignancy. Dyspeptic symptoms also may result from a myriad of other problems, such as medication intolerance, pancreatitis, biliary-tract disease, or motility disorders. This broad definition of dyspepsia has complicated research efforts and limited the value of research observations to clinical practice. In response, some investigators have attempted to clarify the definition of dyspepsia by using defined criteria. The Rome III Committee defined dyspepsia as 1 or more of the following 3 symptoms[8]:

- Postprandial fullness
- Early satiety
- Epigastric pain or burning

For the purposes of this guideline, this limited definition of dyspepsia is accepted, recognizing that practitioners may refer patients with a diagnosis of dyspepsia who suffer from less clearly defined symptoms. We specifically exclude patients with heartburn from this guideline.

PATIENTS WITH ALARM FEATURES

Dyspepsia is not only a convenient descriptor for upper-GI symptoms but also a marker for the risk of structural disease: malignancy is present in 1% to 3% of patients with dyspepsia, and peptic ulcer disease in another 5% to 15%.[9-12] Endoscopy offers the potential for early diagnosis of structural disease. Yet, given the large numbers of patients with dyspepsia, it is not practical to perform endoscopy in all patients with dyspepsia.

Age and alarm features have been used in an attempt to identify those patients with dyspepsia who harbor structural disease. Patients with a new onset of dyspepsia after 45 to 55 years of age and those with symptoms or signs that suggest structural disease are advised to undergo initial endoscopy.[9] A representative list of alarm features is included in Table 2. These features offer the practitioner genuine but limited guidance in managing patients with dyspepsia.

TABLE 1. Grades of recommendation*

Grade of recommendation	Clarity of benefit	Methodologic strength supporting evidence	Implications
1A	Clear	Randomized trials without important limitations	Strong recommendation; can be applied to most clinical settings
1B	Clear	Randomized trials with important limitations (inconsistent results, nonfatal methodologic flaws)	Strong recommendation; likely to apply to most practice settings
1C+	Clear	Overwhelming evidence from observational studies	Strong recommendation; can apply to most practice settings in most situations
1C	Clear	Observational studies	Intermediate-strength recommendation; may change when stronger evidence is available
2A	Unclear	Randomized trials without important limitations	Intermediate-strength recommendation; best action may differ, depending on circumstances or patient or societal values
2B	Unclear	Randomized trials with important limitations (inconsistent results, nonfatal methodologic flaws)	Weak recommendation; alternative approaches may be better under some circumstances
2C	Unclear	Observational studies	Very weak recommendation; alternative approaches likely to be better under some circumstances
3	Unclear	Expert opinion only	Weak recommendation; likely to change as data become available

**Adapted from* Guyatt G, Sinclair J, Cook D, et al. Moving from evidence to action. Grading recommendations: a qualitative approach. In: Guyatt G, Rennie D, editors. Users' guides to the medical literature. Chicago: AMA Press; 2002. p. 599-608.

Patients with alarm features and dyspepsia have significantly worse outcomes than the population at large. In a prospective questionnaire study, patients with alarm symptoms and dyspepsia had a significant increase in both GI cancer and mortality over a 3-year period.[13] Even though alarm features predict relatively poor patient outcomes, they have a low predictive value for GI cancer. In a meta-analysis of 15 studies that evaluated more than 57,000 patients with dyspepsia, alarm symptoms showed a positive predictive value for GI cancer of <11% in all but 1 of these studies.[11] The negative predictive value of alarm symptoms was much higher, at >97%, because of the low prevalence of GI cancer in this population. A second meta-analysis of 26 studies that totaled more than 16,000 patients with dyspepsia showed similar results: the positive predictive value of alarm symptoms for upper-GI cancer was only 5.9% and the negative predictive value was >99%.[12] Unfortunately, clinical impression, demographics, risk factors, history items, and symptoms also do not adequately distinguish structural disease from functional disease in patients with dyspepsia who are referred for endoscopy.[14] It is worth noting that one fourth of patients with malignancy and dyspepsia have no alarm symptoms.[12]

In summary, patients with dyspepsia who are older than 50 years of age or those with alarm features should undergo an endoscopy. An endoscopy should be considered for patients in whom there is a clinical suspicion of malignancy even in the absence of alarm features.

PATIENTS WITHOUT ALARM FEATURES

Patients with dyspepsia who are younger than age 50 and without alarm features are commonly evaluated by 1 of 3 methods: (1) noninvasive testing for *Helicobacter pylori,* with subsequent treatment if positive (the ''test-and-treat'' approach); (2) a trial of acid suppression; or (3) an initial endoscopy.

Test-and-treat approach

Approximately 5% to 15% of patients in the United States who present with dyspepsia will have peptic ulcer disease, and the majority of these patients will have *H pylori* infection.[15] Noninvasive testing options for *H pylori* include serology, urea breath testing (UBT), and stool antigen. Serologic testing has a sensitivity that ranges from 85% to 100%, with a specificity of 76% to 96%.[16,17] The specificities of UBT and stool antigen are higher than serologic testing.

There is growing evidence that patients who undergo the test-and-treat approach have similar outcomes when

compared with those undergoing initial endoscopy. In addition, the test-and-treat approach is more cost effective. Results from a meta-analysis of 5 randomized studies of test-and-treat versus an initial endoscopy showed a negligible improvement of symptoms in the endoscopy group but a savings of $389 per patient in the test-and-treat group.[18] Results from a large, randomized study that compared test-and-treat with initial endoscopy found no significant difference in dyspeptic symptoms at 1 year but with a 60% reduction in endoscopy utilization in the test-and-treat group. However, 12% of patients in the test-and-treat group were dissatisfied with their treatment plan versus only 4% in the endoscopy group.[19] At 6.7 years, there remained no significant differences in symptoms; however, in the test-and-treat group, the reduction in endoscopy utilization was now 38%.[20] Drawbacks to the test-and-treat approach include the risk of *Clostridium difficile*-associated colitis and induction of antibiotic resistance.[21,22]

Initial upper endoscopy

An endoscopy is the standard for the diagnosis of structural disease in patients with dyspepsia. Barium evaluation of the upper-GI tract has a low sensitivity and specificity compared with endoscopy and does not allow for biopsy specimens to be obtained.[23,24] Therefore, use of barium radiography in lieu of endoscopy should generally be limited to patients at high risk for endoscopic complications.

One advantage of early endoscopy is the possibility of establishing a specific diagnosis, such as peptic ulcer disease or erosive esophagitis.[9,15,19] The risk of malignancy is quite low in young patients without alarm features.[25] However, many patients with early stage malignancy do not have alarm symptoms.[26] Another advantage of a negative endoscopy in the evaluation of patients with dyspepsia is a reduction in anxiety and an increase in patient satisfaction.[27,28] Yet, there is little evidence to suggest significant improvement in outcomes by the initial endoscopy approach. Most studies demonstrate an increased cost with the initial endoscopic approach compared with the test-and-treat method.[18,29]

Acid-suppression therapy

Many investigators and societies advocate acid-suppressive therapy as the initial strategy for patients with dyspepsia.[30-32] Proton pump inhibitors (PPI) are more effective than H2 blockers in this approach.[29] Initiation of empiric acid suppression will not address underlying *H pylori* in those patients with *H pylori*–associated peptic ulcer disease, risking recurrent symptoms when acid suppression is withdrawn. This may prompt long-term acid suppression if no further investigation is performed.[33] In 1 study that compared PPI therapy with the test-and-treat approach in patients <45 years of age, a higher endoscopy rate was seen in the PPI treatment group (88% vs 55%).[34] This was likely because of a high prevalence of *H pylori* in this population. A decision analysis showed that cost-effectiveness of the test-and-treat approach versus empiric acid suppression depends on the prevalence of *H pylori*. If the incidence of *H pylori* is <20%, then empiric acid-suppression therapy is more cost effective.[35] There are few studies that compared acid suppression with early endoscopy in young patients. In a study that compared empiric H2 blockers with early endoscopy, endoscopy was eventually performed in 66% of the H2 blocker group. Costs were higher in this group primarily because of days lost from work and the cost of medications.[36] There are limited comparative studies of empiric PPI therapy and endoscopy, and the results are mixed with respect to cost-effectiveness.[37-39]

The most common structural diseases identified in patients with dyspepsia are erosive esophagitis and peptic ulcer disease.[40] Patients with peptic ulcer disease and underlying *H pylori* have a high recurrence rate when antisecretory medication is discontinued unless appropriate treatment for *H pylori* is given. Patients with dyspepsia and without peptic ulcer disease who respond to acid suppression have not been well defined but may be largely composed of patients with underlying GERD. This group also is likely to have a high recurrence rate of symptoms when medication is discontinued.[34] It is unclear whether patients with dyspepsia who require prolonged PPI use should undergo an endoscopy. An endoscopy may still need to be considered in the group of nonresponders to exclude structural disease. A suggested algorithmic approach to dyspepsia is seen in Figure 1. It should be noted that a short trial of PPI for patients without alarm symptoms, who are younger than age 50 years, and who do not respond after the test-and-treat approach has not been formally evaluated.

TABLE 2. Alarm features for patients with dyspepsia

Age >50 y, with new onset symptoms
Family history of upper-GI malignancy
Unintended weight loss
GI bleeding or iron deficiency anemia
Progressive dysphagia
Odynophagia
Persistent vomiting
Palpable mass or lymphadenopathy
Jaundice

RECOMMENDATIONS

- Patients with dyspepsia who are older than 50 years of age and/or those with alarm features should undergo endoscopic evaluation. (1C)

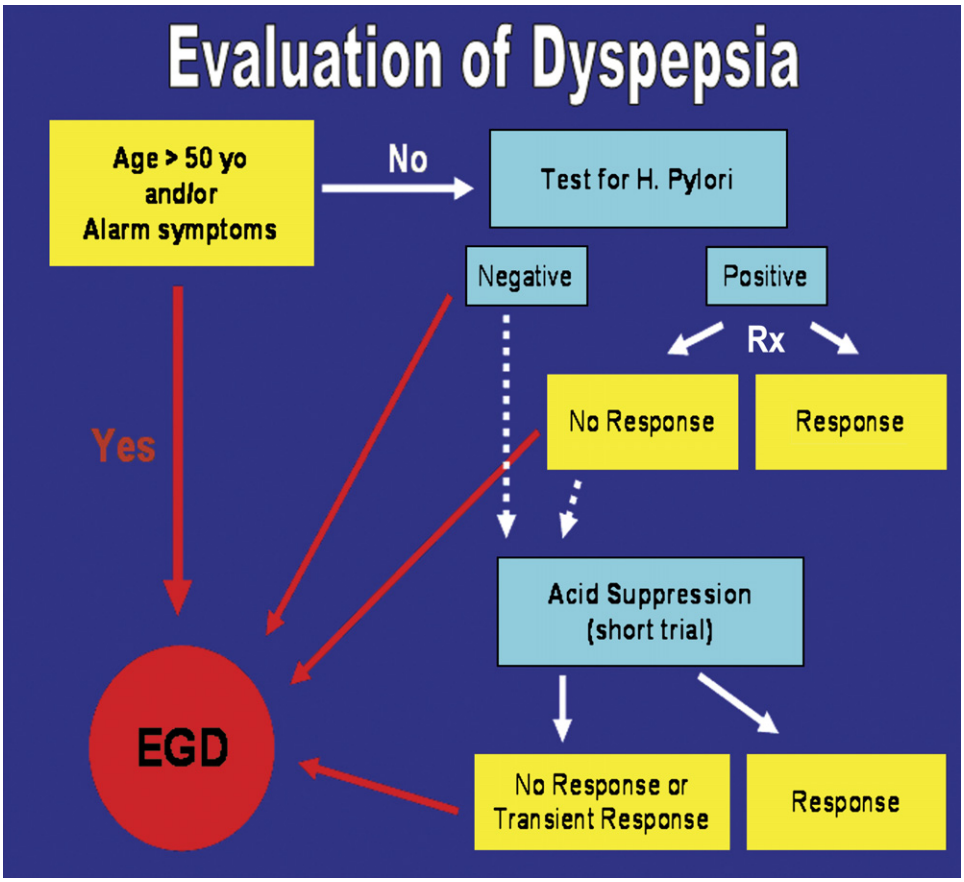

Figure 1. Suggested algorithm for evaluation of dyspepsia. A short trial of PPI after test-and-treat approach for *H pylori* nonresponders has not been formally studied.

- Patients with dyspepsia who are younger than 50 years of age and without alarm features may undergo an initial test-and-treat approach for *H pylori*. (1B)
- Patients who are younger than 50 years of age and are *H pylori* negative can be offered an initial endoscopy or a short trial of PPI acid suppression. (2B)
- Patients with dyspepsia who do not respond to empiric PPI therapy or have recurrent symptoms after an adequate trial should undergo endoscopy. (3)

Abbreviations: ASGE, American Society for Gastrointestinal Endoscopy; PPI, proton pump inhibitors; UBT, urea breath testing.

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Prepared by:
ASGE STANDARDS OF PRACTICE COMMITTEE
Steven O. Ikenberry, MD
M. Edwyn Harrison, MD
David Lichtenstein, MD
Jason A. Dominitz, MD, MHS
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