

## The role of endoscopy in dyspepsia

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This document was reviewed and approved by the governing board of the American Society for Gastrointestinal Endoscopy.

*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 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 few 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 that 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 affecting 20% to 40% of the population in Western countries.<sup>1-4</sup> Many patients with dyspepsia are referred to gastroenterologists for consultation and endoscopy.<sup>5,6</sup> 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.

### DEFINITION

Dyspepsia is a poorly characterized syndrome thought to originate from anatomic or functional disorders of the upper GI tract.<sup>7-9</sup> Dyspepsia encompasses a variety of symptoms including epigastric discomfort, bloating, anorexia, early satiety, belching or regurgitation, nausea, and heartburn. Rome III criteria define dyspepsia as 1 or more of the following 3 symptoms for 3 months within the initial 6 months of symptom onset<sup>10</sup>: (1) postprandial fullness, (2) early satiety, and (3) epigastric pain or burning.

The symptoms of dyspepsia overlap significantly with those associated with peptic ulcer disease (PUD), GERD, other functional disorders such as epigastric pain syndrome and irritable bowel syndrome, malignancy, adverse effects of medications, pancreatitis, biliary tract disease, vascular disease, and motility disorders. The prevalence of GERD and irritable bowel syndrome is higher in patients with dyspepsia compared with patients without dyspepsia.<sup>11,12</sup> Despite the nonspecific nature of symptoms, dyspepsia is associated with poor health-related quality of life and greater psychological distress.<sup>13-16</sup>

For the purposes of this guideline, the ROME III criteria are used, recognizing that practitioners may refer patients with a diagnosis of dyspepsia who experience less-clearly defined symptoms. Patients with GERD are excluded from this guideline. Additional information regarding the

**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.<sup>53</sup>**TABLE 2. Alarm features for dyspeptic patients**

Age ≥ 50 years
Family history of upper GI malignancy in a first-degree relative
Unintended weight loss
GI bleeding or iron deficiency anemia
Dysphagia
Odynophagia
Persistent vomiting
Abnormal imaging suggesting organic disease

management of GERD can be found in a previously published document.<sup>17</sup>

## PATIENTS WITH ALARM FEATURES

Symptoms of dyspepsia do not reliably identify individuals with malignancy or other important upper GI pathology. Therefore, patient age and alarm features (Table 2)<sup>18</sup> have been used to categorize patients with dyspepsia who may harbor true pathology that may be found with endoscopy or other examinations. Patients with new-onset dyspepsia after 45<sup>18</sup> to 55<sup>19</sup> years of age (average age 50 years) and those with symptoms or signs that suggest structural disease are advised to undergo initial endoscopy.

Identification of alarm features, however, has a low predictive value for GI cancer. In a meta-analysis of 15 studies evaluating more than 57,000 patients with dyspepsia, alarm symptoms showed a positive predictive value for GI cancer of less than 11% in all but 1 of these studies.<sup>20</sup> The negative predictive value of an absence of alarm symptoms was much better at more than 97% due to the low prevalence of GI cancer in this population. A second meta-analysis of 26 studies totaling more than 16,000 patients with dyspepsia similarly showed a positive predictive value and negative predictive value of alarm symptoms for upper GI cancer of 5.9% and greater than 99%, respectively.<sup>21</sup> Clinical impression, demographics, risk factors, patient history, and symptoms also do not adequately distinguish structural from functional disease in dyspeptic patients referred for endoscopy.<sup>20,22</sup> It is worth noting

that one-fourth of patients with malignancy and dyspepsia do not report alarm symptoms.<sup>21</sup>

In summary, dyspeptic patients older than 50 years of age or those with alarm features should undergo upper endoscopy. 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

Dyspeptic patients younger than 50 years of age 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) an empiric trial of acid suppression, or (3) initial endoscopy.

### Test and treat

The rationale for testing and treating *H pylori* in patients with dyspepsia is that *H pylori* may be associated with true pathologic disorders of the upper GI tract, such as PUD or gastritis, and that eradication may result in reversal or stabilization of the abnormal pathology and improvement in symptoms. Nevertheless, there is no known mechanism to explain a reduction in symptoms by treating *H pylori* in patients with dyspepsia and no pathologic disorders. Several large randomized, controlled trials have evaluated the benefit of empiric *H pylori* treatment in dyspeptic patients. Systematic reviews show that, compared with initial endoscopy, a “test and treat” approach may provide modest improvement in symptoms<sup>23,24</sup> and may also be more cost-effective than initial endoscopy. However, a large, randomized study comparing “test and treat” with initial endoscopy found no significant difference in dyspeptic symptoms between the 2 groups at 1 year.<sup>25</sup> However, 12% of patients in the “test and treat” group were dissatisfied with their treatment plan compared with only 4% in the initial endoscopy group ( $P = .013$ ). After a median of nearly 7 years follow-up, the same authors reported that symptoms remained similar between the 2 groups; however, the reduction in endoscopy use in the “test and treat group” had decreased to 38%.<sup>26</sup> Potential limitations to the “test and treat” approach include the risk of *Clostridium*

*difficile*-associated colitis and induction of antibiotic resistance.<sup>27,28</sup>

It is important to note that the prevalence rates of *H pylori* in the United States are lower than in developing countries and may vary by region and target population. Hence, testing and treating for *H pylori* may be relevant and cost-effective in regions with prevalence rates of *H pylori* of 20% or higher.<sup>18,19,29</sup> Noninvasive testing options for *H pylori* include serology, urea breath testing, and stool antigen testing. Serologic testing has a sensitivity and specificity ranging from 85% to 100% and 76% to 96%, respectively.<sup>30,31</sup> The specificity of urea breath testing and stool antigen is higher than that of serologic testing.<sup>32</sup>

In summary, an initial “test and treat” strategy may be a reasonable and possibly cost-effective approach for the management of younger patients with dyspepsia and no alarm features in regions with a higher prevalence of *H pylori* infection.

### Empiric acid suppression therapy

Many authors and societies advocate acid suppressive therapy as the initial strategy for dyspeptic patients.<sup>18,19,33</sup> These benefits are seen primarily in patients with dyspepsia who have reflux-type symptoms, rather than dysmotility- or nausea-type symptoms. For the treatment of dyspepsia symptoms, empiric proton pump inhibitors (PPIs) are more effective than antacids and histamine receptor antagonists.<sup>34,35</sup> Several randomized, controlled clinical trials have demonstrated the benefit of PPIs compared with placebo in treating symptoms of dyspepsia with absolute risk reductions of 10%<sup>36</sup> to 17%.<sup>37</sup> A meta-analysis of 7 studies showed that PPIs were superior to placebo for reducing dyspeptic symptoms (relative risk reduction, 10%; 95% confidence interval [CI], 2.7%-17.3%)<sup>38</sup> with a significant benefit in treatment efficacy evident only in the reflux-type symptom group and not in those with dysmotility-like symptoms. Initiation of empiric acid suppression will not address underlying *H pylori* infection in patients with *H pylori*-associated PUD, a strategy that may risk recurrence of symptoms when acid suppression is withdrawn. This approach may also lead to long-term acid suppression if no further investigation is performed.<sup>39</sup> In 1 study comparing PPI therapy with the “test and treat” approach in patients younger than 45 years of age, endoscopy was used more frequently in the PPI treatment group (88% vs 55%;  $P < .001$ ).<sup>40</sup> A decision analysis showed that cost-effectiveness of the “test and treat” approach versus empiric acid suppression depends on the prevalence of *H pylori*.

### Initial upper endoscopy

Dyspepsia without alarm features is not an absolute indication for endoscopy, but endoscopy may facilitate the diagnosis of structural disorders in a small subset of patients. The risk of malignancy is very low in young patients without alarm features.<sup>41</sup> The most common structural disorders identified in patients with dyspepsia are erosive

esophagitis and PUD, with reported prevalence rates of 8% to 43% for erosive esophagitis and 4% to 18% for PUD.<sup>42</sup> Compared with nondyspeptic controls, only PUD was more commonly found in patients with dyspepsia (odds ratio 2.07; 95% CI, 1.5-2.8). Many practitioners choose to perform an upper endoscopy to obtain small-bowel biopsy samples to evaluate for celiac disease. However, the prevalence of celiac disease in patients with dyspepsia is similar to that in patients without dyspepsia (3.2% vs 1.3%) (odds ratio 2.85; 95% CI, 0.60-13.38),<sup>43</sup> and dyspepsia symptoms alone do not warrant routine small-bowel biopsies.

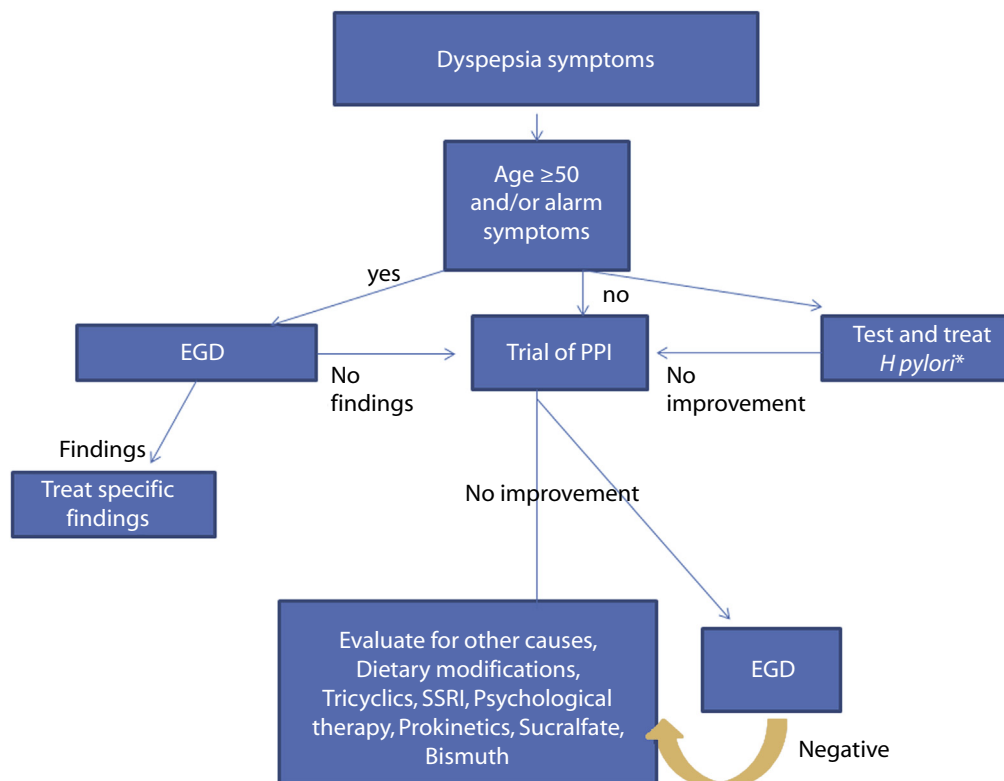
Studies comparing the “test and treat” approach with endoscopy have reported no difference in symptom control, with most studies also showing increased cost with the initial endoscopic approach.<sup>44</sup>

There are several studies comparing acid suppression therapy with early endoscopy. In a study that compared empiric histamine receptor antagonists with early endoscopy, endoscopy was eventually performed in 66% of the histamine receptor antagonist group. Costs were higher in the group that underwent early endoscopy primarily due to days lost from work and the cost of medications.<sup>45</sup> There are limited comparative studies of empiric PPI therapy and endoscopy in this population. A meta-analysis evaluating these 2 strategies showed no difference in dyspepsia symptoms or quality of life, but the endoscopic arm was more costly.<sup>46</sup> Other studies show mixed results with respect to cost-effectiveness.<sup>47,48</sup>

It is unclear whether patients with dyspepsia whose symptoms are controlled with prolonged PPI use should undergo endoscopy. Endoscopy may still be considered in the group of nonresponders to exclude structural disease.<sup>43</sup> A potential advantage of a negative endoscopy in the evaluation of dyspeptic patients is a reduction in anxiety and an increase in patient satisfaction,<sup>49,50</sup> yet there is little evidence to suggest significant improvement in outcomes by this approach.

### Endoscopy-negative, persistent dyspepsia

Many patients with dyspepsia and negative findings on endoscopy continue to experience symptoms despite acid suppression and/or *H pylori* eradication. These patients can be difficult to manage. The majority have functional dyspepsia, for which treatment options include stopping nonsteroidal anti-inflammatory drugs, a trial of antispasmodics, dietary and lifestyle changes, prokinetic agents, sucralfate, simethicone, tricyclic antidepressants, selective serotonin reuptake inhibitors, and cognitive behavior therapy.<sup>51,52</sup> More research is required to understand the pathophysiology of symptoms in these patients and the role of medications and other therapies. Other conditions that may cause upper abdominal pain or discomfort (which may be confused with dyspepsia) should be considered, including irritable bowel syndrome, GERD, gastroparesis, pancreatic or biliary disorders, celiac



**Figure 1.** Suggested algorithm for evaluation of dyspepsia. A 4- to 8-week trial of a proton pump inhibitor (PPI) after test and treat for *Helicobacter pylori* nonresponders has not been formally studied. \*Depending on prevalence of *H pylori*. SSRI, selective serotonin reuptake inhibitor.

disease, and other functional disorders. Further testing is warranted in patients with pain that is worsening or atypical for dyspepsia or that is accompanied by other worrisome symptoms or signs but should be avoided in young patients with presumed functional disease.

A suggested algorithmic approach to dyspepsia is shown in Figure 1.

### RECOMMENDATIONS

1. We recommend initial endoscopy for new-onset dyspepsia in patients 50 years of age or older or those with alarm features. ⊕⊕⊕○
2. We recommend that dyspeptic patients younger than 50 years of age and without alarm features undergo either an initial “test and treat” approach for *H pylori* or empiric therapy with a PPI, depending on the prevalence of *H pylori* infection in their population. For *H pylori* prevalence greater than 20%, “test and treat” is recommended. ⊕⊕⊕○
3. We suggest that dyspeptic patients who are younger than 50 years of age, lack alarm features, and are *H pylori* negative may be offered a trial of PPI acid suppression. ⊕⊕○○
4. We suggest that endoscopy be performed in dyspeptic patients who are *H pylori* negative and do not respond to empiric PPI therapy. ⊕⊕○○

### DISCLOSURES

*Dr Fanelli is the owner and director of New Wave Surgical Inc, is an advisor for and receives royalties from Cook Medical, is a consultant for EndoGastric Solutions, and is an owner of Allurion Technologies Inc and Mozaic Medical Inc. Dr Khasbab is a consultant for and on the advisory board of Boston Scientific, a consultant for Olympus, and has received research support from Cook Medical. Dr Muthusamy is a consultant for Boston Scientific and Covidien GI Solutions and a stockholder in Capsovision Inc. Dr Chandrasekhara is a consultant for Boston Scientific. Dr Chathadi is a consultant for Boston Scientific. All other authors disclosed no financial relationships relevant to this article.*

*Abbreviations: CI, confidence interval; PPI, proton pump inhibitor; PUD, peptic ulcer disease.*

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