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Institute for Clinical Systems Improvement

Health Care Guideline

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- physicians, nurses, and other health care professional and provider organizations;
- health plans, health systems, health care organizations, hospitals and integrated health care delivery systems;
- medical specialty and professional societies;
- researchers;
- federal, state and local government health care policy makers and specialists; and
- employee benefit managers.

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This *ICSI Health Care Guideline* is designed to assist clinicians by providing an analytical framework for the evaluation and treatment of patients, and is not intended either to replace a clinician's judgment or to establish a protocol for all patients with a particular condition. An *ICSI Health Care Guideline* rarely will establish the only approach to a problem.

Health Care Guideline:
Dyspepsia and GERD

INSTITUTE FOR CLINICAL SYSTEMS IMPROVEMENT

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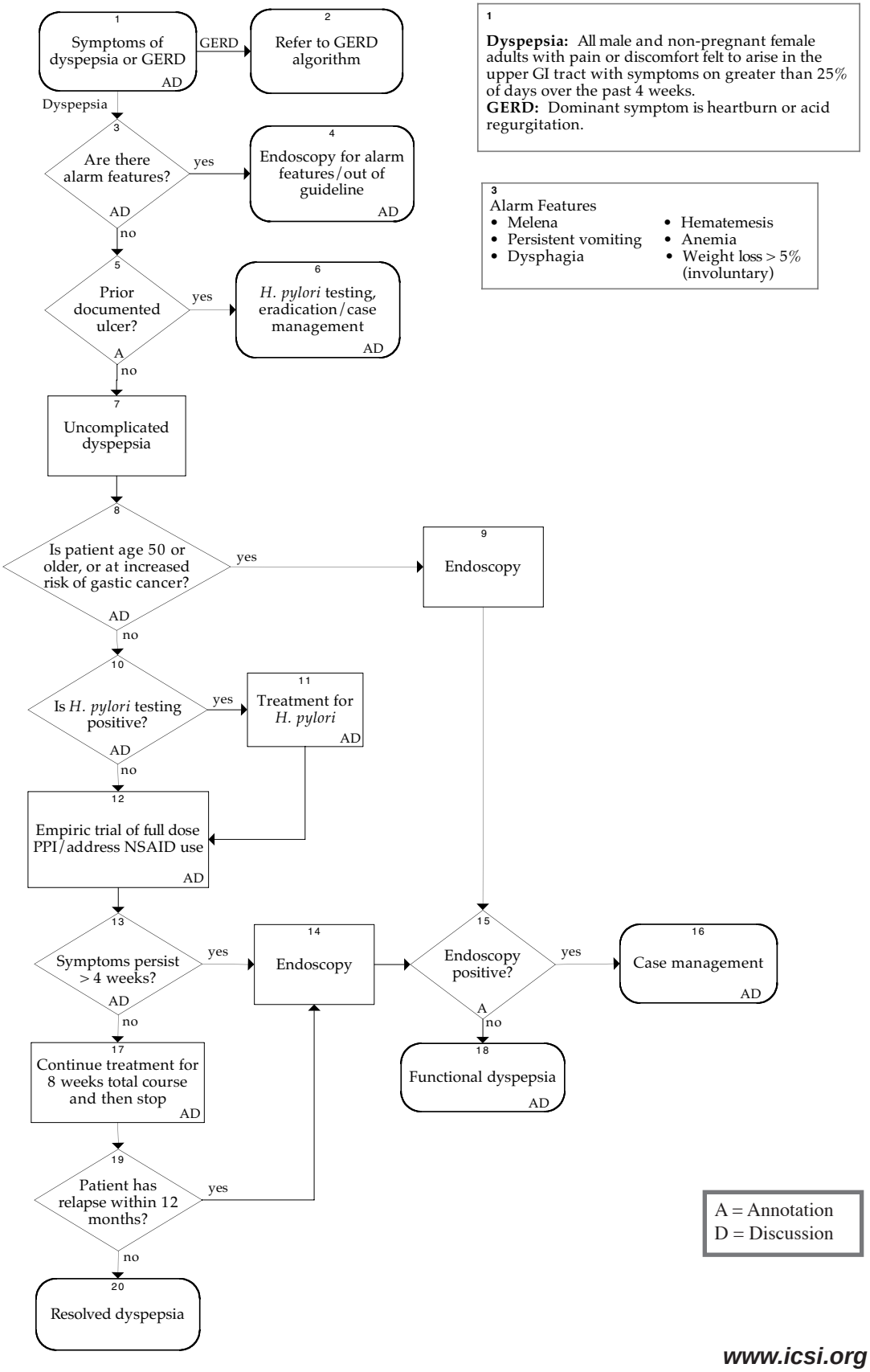
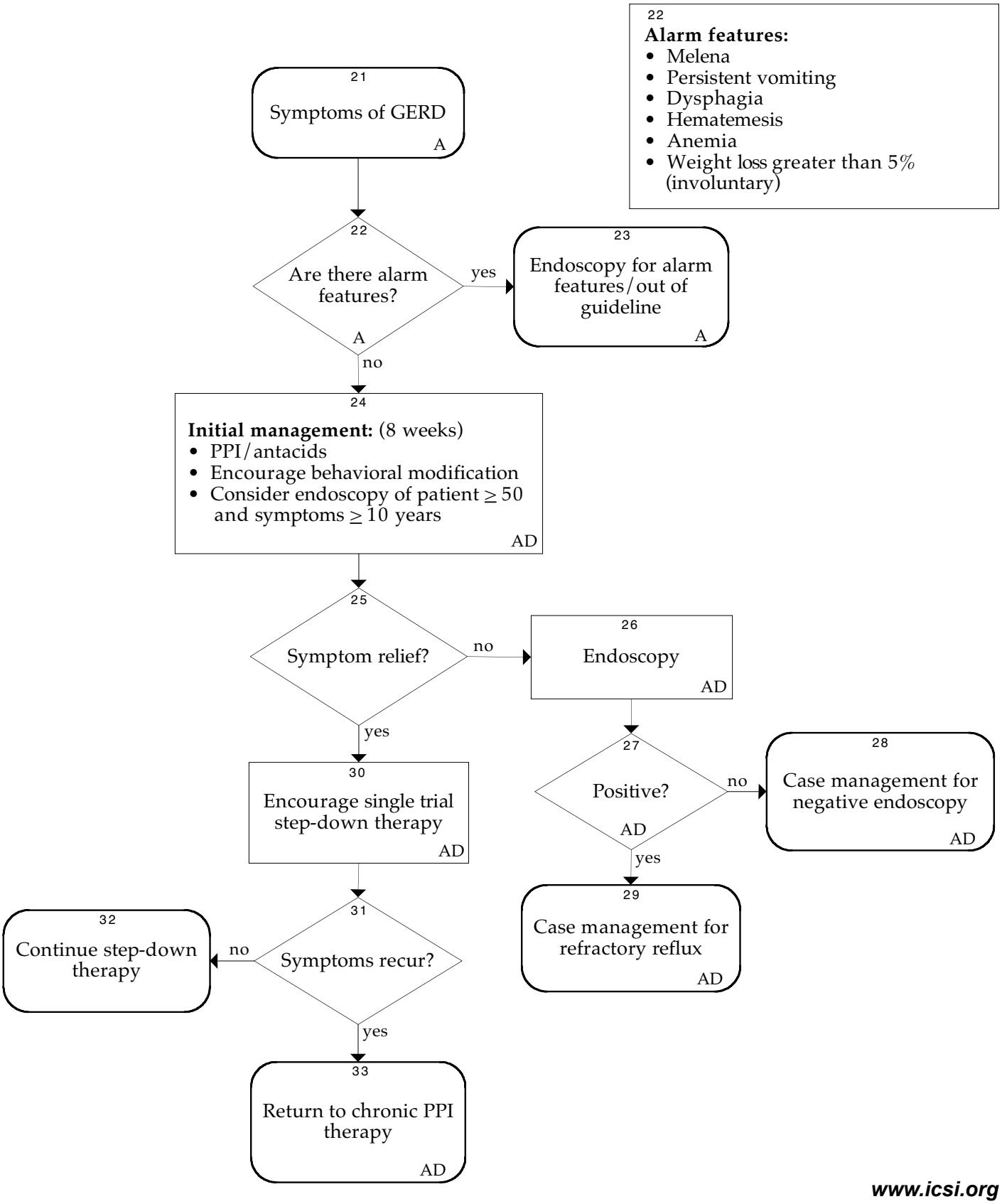


These clinical guidelines are designed to assist clinicians by providing an analytical framework for the evaluation and treatment of patients, and are not intended either to replace a clinician's judgment or to establish a protocol for all patients with a particular condition. A guideline will rarely establish the only approach to a problem.

GERD Algorithm



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Foreword

Scope and Target Population

This guideline addresses the evaluation of epigastric discomfort and the management of gastroesophageal reflux disease (GERD) and dyspepsia in adult males and non-pregnant adult females with symptoms on greater than 25% of days over the past 4 weeks.

Related ICSI Scientific Documents

There are no other ICSI scientific documents at this time whose scope and/or recommendations are closely related to the content of this guideline.

Clinical Highlights and Recommendations

1. Send patients with dyspepsia plus one of the following alarm features for urgent endoscopic evaluation. Suggested time frames for the urgency of endoscopy are provided in italics behind each of the alarm features listed. *(Annotations #3, 4)*

    - Melena *(within 1 day if ill)*
    - Persistent vomiting *(7-10 days)*
    - Acute onset of total dysphagia *(within 1 day)*
    - Hematemesis *(within 1 day if ill)*
    - Anemia *(7-10 days)*
    - Weight loss greater than 5% (involuntary) *(7-10 days)*

2. Patients 50 years of age and older with symptoms of uncomplicated dyspepsia should be evaluated with non-urgent upper endoscopy. *(Annotation #8)*

3. Patients with dyspepsia, but no alarm features or reflux symptoms, should receive *H. pylori* testing and if positive, eradicative therapy. *(Annotations #5, 6, 10, 11)*

4. Patients with dyspepsia and negative testing results for *H. pylori* should be treated empirically with Proton Pump Inhibitors (PPIs). *(Annotation #12)*

5. Patients age 50 or older and who have had symptoms of GERD for 10 years or more should be considered for endoscopy during initial management. *(Annotation #24)*

6. Patients with gastroesophageal reflux should receive single trial step-down therapy. *(Annotations #24, 28, 29, 30, 33)*

7. Patients with GERD usually require long-term PPI therapy. (*Annotation #33*)

Priority Aims and Suggested Measures

1. To increase the use of recommended methods for evaluating dyspepsia.

   Possible measures of accomplishing this aim:

   a. Percentage of patients evaluated for dyspepsia with discussion regarding appropriate *H. pylori* testing.

   b. Percentage of patients evaluated for dyspepsia without standard single phase contrast studies.

   c. Percent of patients evaluated for dyspepsia with endoscopy prior to receiving a therapeutic trial who do not have an alarm feature present.

2. To increase appropriate pharmaceutical treatment of patients with dyspepsia.

   Possible measures of accomplishing this aim:

   a. Percentage of patients with dyspepsia positive for *H. pylori* who receive antibiotic therapy.

   b. Percentage of patients with dyspepsia treated with antibiotics for positive *H. pylori* who receive effective therapy.

   c. Percentage of patients with dyspepsia treated with a PPI without previous endoscopic examination.

3. To decrease complications associated with peptic ulcer disease.

   Possible measure of accomplishing this aim:

   a. Number or rate of hospital admissions for ulcer hemorrhage.

4. To improve functional outcomes and satisfaction of patients with dyspepsia.

   Possible measures of accomplishing this aim:

   a. Percentage of patients with dyspepsia with improved symptoms following treatment as measured by a dyspepsia-specific health status instrument.

   b. Percentage of patients with dyspepsia who report that they are satisfied or very satisfied following treatment for dyspepsia.

5. Increase the use of initial treatment recommendations for evaluating GERD.

   Possible measures for accomplishing this aim:

   a. Percentage of patients with GERD following behavioral modification recommendations.

   b. Percentage of patients with GERD treated with PPI for an 8 week period.

   c. Percentage of patients with GERD reporting relief of symptoms after 8 week trial of PPI.

   d. Percentage of patients with GERD and control of symptoms with a PPI who have had a trial of step down therapy.

6. To increase appropriate treatment for patients who have ongoing symptoms after initial treatment recommendations.

   Possible measures for accomplishing this aim:

   a. Percentage of patients with continued symptoms of GERD after an 8 week trial of PPI having an endoscopy.

   b. Percentage of patients age 50 (and over) who have GERD or a history of GERD for 10 years or more who have been evaluated with endoscopy.

   c. Percentage of patients with ongoing symptoms of GERD (see annotation #1) and a BMI greater than 35 referred for surgical opinion regarding fundoplication, bariatric surgery and/ or endoscopic approaches.

Evidence Grading

Individual research reports are assigned a letter indicating the class of report based on design type: A, B, C, D, M, R, X.

Key conclusions are assigned a conclusion grade: I, II, III, or Grade Not Assignable.

A full explanation of these designators is found in the Discussion and References section of the guideline.

Disclosure of Potential Conflict of Interest

In the interest of full disclosure, ICSI has adopted the policy of revealing relationships work group members have with companies that sell products or services that are relevant to this guideline topic. The reader should not assume that these financial interests will have an adverse impact on the content of the guideline, but they are noted here to fully inform readers. Readers of the guideline may assume that only work group members listed below have potential conflicts of interest to disclose.

G. Richard R. Locke, MD is a consultant for Glaxo Wellcome and Novartis and receives grant support from AstraZeneca, Forest Laboratories, Glaxo Wellcome, Janssen Pharmaceutica, SmithKline Beecham, and Solvay.

No other work group members have potential conflicts of interest to disclose.

ICSI's conflict of interest policy and procedures are available for review on ICSI's website at www.icsi.org.

Algorithm Annotations

1. Symptoms of Dyspepsia or GERD

Dyspepsia

Dyspepsia is defined as pain or discomfort felt to arise in the upper gastrointestinal (GI) tract with symptoms on greater than 25% of days over the past 4 weeks. Patients with epigastric pain or discomfort, or nausea are eligible.

GERD

GERD is the probable diagnosis if the patient has heartburn (retrosternal pain) or acid regurgitation (a sour or bitter taste in mouth) as the dominate symptom. These symptoms are sought because their presence is associated with a probability of 89% and 95%, respectively, of GERD based on studies using esophageal pH monitoring as the reference standard. The goal is to minimize the number of patients with ulcer referred to the GERD algorithm.

Supporting evidence is of classes: C, R

3. Are There Alarm Features?

Alarm features should be sought in all patients presenting with dyspepsia. If alarm features are present, endoscopy should be performed (suggested time frames for urgency of endoscopy have been provided in italics behind each of the alarm features listed). Alarm features is a term that is used frequently in the dyspepsia literature to describe clinical features that may suggest underlying disease that should be diagnosed and treated without the delay of an empiric therapeutic trial. Alarm features frequently cited are:

- Anemia *(7-10 days)*
- Acute onset of total dysphagia *(within 1 day)*
- Hematemesis *(within 1 day if ill)*
- Melena *(within 1 day if ill)*
- Persistent vomiting *(7-10 days)*
- Weight loss greater than 5% (involuntary) *(7-10 days)*

Supporting evidence is of class: D

4. Endoscopy for Alarm Features/Out of Guideline

Endoscopy is the procedure of choice for evaluation of dyspepsia. A single contrast barium study is not an acceptable alternative. Multiphase upper gastrointestinal (UGI) studies performed by radiologists with specific training in gastrointestinal radiology are an acceptable alternative to endoscopy.

If specialty radiologic expertise with multiphase barium UGI is available, UGI study should be viewed as an alternative to endoscopy. Otherwise, endoscopy provides greater sensitivity for the diagnosis of peptic ulcer disease. *[Conclusion Grade III: See Conclusion Grading Worksheet – Appendix A – Annotation #4 (Endoscopy)]*

Supporting evidence is of classes: A, C

5. Prior Documented Ulcer?

In patients presenting with dyspepsia and a prior documented ulcer, a referral to either a gastroenterologist or direct-access endoscopy is appropriate. Documentation of the prior ulcer must include an endoscopy or barium UGI report confirming the presence of an ulcer.

6. *H. pylori* Testing, Eradication/Case Management

Case management should begin with *H. pylori* testing. Several tests are available with different sensitivity, specificity and costs. Those who are positive should receive eradicative therapy. (Refer to Main Algorithm Annotation #10, "Is *H. pylori* Testing Positive?" and Annotation #11 "Treatment for *H. pylori*.")

Diagnostic Tests for *Helicobacter Pylori*

Test	Sensitivity %	Specificity %	Approx. Cost to Patient
In office, serum	88-94	74-88	$10 - $30
In office, whole blood	67-88	75-91	$10 - $30
Urea Breath Test	90-96	88-98	$250 - $350 ^{13}C $20 - $65 ^{14}C
Biopsy Urease Test	88-95	95-100	$6 - $20 plus endoscopy
Stool Antigen Assay	86-94	86-95	$60
Histology	93-96	98-99	$60 - $ 250 plus endoscopy
Culture	80-98	100	$150

Adapted from Smoot DT, Cutler AF. "*Helicobacter pylori:* diagnostic tests." Gastroenterology and Endoscopy News. McMahon Publishing Group, October, New York, 48:28, 1997.

Patients who continue NSAIDs during treatment for peptic ulcers should have the duration of PPI treatment extended to twelve weeks total.

Symptoms continuing for a month or more into treatment should prompt endoscopy regardless of initial treatment. Further evaluation may be necessary.

Maintenance PPI treatment is not indicated for those experiencing symptom resolution after treatment. Patients with complicated peptic ulcer disease may be considered for maintenance treatment using PPI at one-half the therapeutic dose after successful treatment. Documenting *H. pylori* eradication should be limited to those with a history of complicated peptic ulcer disease.

Supporting evidence is of classes: A, C, D, M, R

8. Is Patient Age 50 or Older, or at Increased Risk of Gastric Cancer?

Environmental and genetic factors along with a number of disorders are associated with an increased risk of gastric cancer. The precursor conditions associated with increased risk for gastric cancer include chronic atrophic gastritis and intestinal metaplasia, pernicious anemia, benign gastric ulcer disease, *Helicobacter pylori* infection, Menetrier's disease, gastric adenomatous polyps, immunodeficiency syndromes, and Barrett's esophagus.

Genetic and environmental factors for an increased risk of gastric cancer include a family history of gastric cancer, blood type A, hereditary nonpolyposis colon cancer syndrome, low consumption of fruits and vegetables, consumption of salted, smoked, or poorly preserved foods, cigarette smoking, alcohol use, and obesity.

Esophagogastroduodenoscopy, performed within 4 weeks, may be appropriate in patients age 50 or over because the incidence of gastric cancer is increased, but no study to date has shown improved outcomes. *[Conclusion Grade II: See Conclusion Grading Worksheet – Appendix B – Annotation #8 (Esophagogastroduodenoscopy)]*

Initial endoscopy may be cost-effective in this age group, however, sensitivity analysis shows the cost-effectiveness is driven by the cost of endoscopy and so will vary.

Supporting evidence is of classes: A, C, D

10. Is *H. pylori* Testing Positive?

An approach to possible gastric or duodenal ulcer disease should include a strategy to eliminate *Helicobacter pylori*. Sensitive and specific point-of-care testing is commercially available and can provide 5-10 minute turnaround using whole blood, serum or plasma. *Helicobacter pylori* urea breath testing (UBT) has similar sensitivity and superior specificity. If the cost and availability of UBT is similar to serology in the local practice environment, it would be the preferred test.

Helicobacter pylori testing appears to be a cost-effective approach for long-term dyspepsia management. *[Conclusion Grade II: See Conclusion Grading Worksheet – Appendix C – Annotation #10 (H. pylori Testing)]*

Supporting evidence is of classes: A, C, M, R

11. Treatment for *H. pylori*

There are multiple regimens FDA approved for treatment of *Helicobacter*. In addition, many more are published in the literature. The two following therapies are equally effective in eradicating *H. pylori* (95% effective) and in preventing GI ulcer recurrence (80% effective). These two therapies represent a combination of ease of adherence and cost. Patient adherence is very important. The patient can and should take all drugs simultaneously. The choice of regimen may be influenced by frequency of dosing or patient tolerance or highly variable local acquisition costs.

Regardless of which therapy course is chosen, patients with significant symptoms at presentation may continue to use a standard dose of a PPI for 3 extra weeks at the end of the combination drug treatment.

Treatment choice #1: 7-day treatment

- PPI standard dose twice daily x 7 days
- Clarithromycin: 500 mg twice daily x 7 days**
- Amoxicillin: 1 gram twice daily x 7 days*

Treatment choice #2: 7-day treatment

- PPI standard dose twice daily x 7 days
- Tetracycline: 250 mg qid x 7 days*
- Metronidazole: 500 mg twice daily x 7 days**
- Bismuth: chew 2 tablets four times daily x 7 days

* Substitute metronidazole 500 mg twice daily x 7 days if patient is intolerant to tetracycline or amoxicillin.

** Substitute amoxicillin 1 gram twice daily x 7 days if suspect *H. pylori* resistance to metronidazole.

Proton Pump Inhibitors (PPI)

Generic Name	Trade Name	Usual Adult Dose
Esomeprazole	Nexium®	40 mg daily
Lansoprazole	Prevacid®	30 mg daily
Omeprazole	Prilosec®	20 mg daily
Pantoprazole	Protonix®	40 mg daily
Rabeprazole	Aciphex®	20 mg daily

12. Empiric Trial of Full Dose PPI/Address NSAID Use

Empiric Trial

The available proton pump inhibitors (PPI) appear to be equivalent in efficacy and in adverse event profiles in the management of acid-peptic disorders when given in equipotent acid-suppressive doses. Full-dose therapy for four weeks as an empiric trial is recommended.

Supporting evidence is of classes: A, D, R

Proton Pump Inhibitors (PPI)

Generic Name	Trade Name	Usual Adult Dose
Esomeprazole	Nexium®	40 mg daily
Lansoprazole	Prevacid®	30 mg daily
Omeprazole	Prilosec®	20 mg daily
Pantoprazole	Protonix®	40 mg daily
Rabeprazole	Aciphex®	20 mg daily

Patients on nonsteroidal anti-inflammatory drugs (NSAIDs)

Patient on NSAIDs should have these discontinued if possible. If it is not possible to discontinue NSAIDs, a duration of therapy of 12 weeks is recommended. This recommendation is based on well documented higher healing rates in patients with gastric as well as duodenal ulcers treated for a duration of twelve weeks compared to eight weeks. (See also Main Algorithm Discussion and References #16, "Case Management.")

Supporting evidence is of classes: A, C, D, M

13. Symptoms Persist > 4 Weeks?

Although ulcer healing may take 8 weeks or more, the majority of patients with gastric or duodenal ulcer have improvement in symptoms at 4 weeks.

Supporting evidence is of classes: A, D

15. Endoscopy Positive?

Endoscopy is the procedure of choice in most situations for evaluation of dyspepsia. If an ulcer is seen, a biopsy for *Helicobacter pylori* should be taken. A single contrast barium study is not an acceptable alternative. Multiphasic UGI studies performed by radiologists with specific training in gastrointestinal radiology are an acceptable alternative to endoscopy.

16. Case Management

Patients with an ulcer should have an *H. pylori* breath test if their stomach was not biopsied at the time of endoscopy. Treatment to eradicate *H. pylori* should be provided to those infected. If previously treated for *H. pylori*, a different regimen should be used and provided. Metronidazole should be substituted for amoxicillin in the patient who has received amoxicillin previously. If not infected with *H. pylori*, review NSAID use and smoking history as appropriate. If esophogitis is seen, refer to the GERD Algorithm (#22).

Supporting evidence is of class: C

17. Continue Treatment for 8 Weeks Total Course and Then Stop

Data on healing rates in both gastric and duodenal ulcers suggest that treatment with antiulcer agents should be continued to complete a course of eight weeks. The most effective agents for the majority of patients are PPI. Patients who continue NSAIDs during treatment for peptic ulcers, particularly gastric ulcers, should have the duration of PPI treatment extended to twelve weeks total.

Supporting evidence is of classes: A, R

18. Functional Dyspepsia

Most patients who undergo endoscopy for dyspepsia will not have a positive finding to explain the symptoms. The terms "non-ulcer" or "functional dyspepsia" have been used to label this situation. No medical treatment is clearly of proven benefit. On a case-by-case basis, elimination of certain foods (e.g., caffeine, alcohol, fat, etc.) or medications (e.g., NSAIDs) may help. On a similar individual basis, eradication of *Helicobacter pylori* (if not already done), treatment with a PPI (if not already done), prokinetic or low-dose tricyclic antidepressant, and exploration of the contribution of psychologic distress may prove beneficial. Additional testing may be necessary, but overtesting, overtreatment, and over-referral should be avoided. Short-term empiric trials could be considered.

Supporting evidence is of classes: A, R

GERD Algorithm Annotations

21. Symptoms of GERD

GERD is the probable diagnosis if the patient has heartburn (retrosternal pain) or acid regurgitation (a sour or bitter taste in mouth) as the dominate symptom. These symptoms are sought because their presence is associated with a probability of 89% and 95%, respectively, of GERD based on studies using esophageal pH monitoring as the reference standard. The goal is to minimize the number of patients with ulcer referred to the GERD algorithm.

22. Are there Alarm Features?

Alarm features should be sought in all patients presenting with GERD. If alarm features are present, endoscopy should be performed (suggested time frames for urgency of endoscopy have been provided in italics behind each of the alarm features listed). Alarm features is a term that is used frequently in the dyspepsia literature to describe clinical features that may suggest underlying disease that should be diagnosed and treated without the delay of an empiric therapeutic trial. Alarm features frequently cited are:

- Anemia *(7-10 days)*
- Acute onset of total dysphagia *(within 1 day)*
- Hematemesis *(within 1 day if ill)*
- Melena *(within 1 day if ill)*
- Persistent vomiting *(7-10 days)*
- Weight loss greater than 5% (involuntary) *(7-10 days)*

For further discussion, please refer to Discussion and References #3.

23. Endoscopy for Alarm Features/Out of Guideline

For further discussion, please refer to Discussion and References #4

24. Initial Management (8 Weeks)

Initial treatment of GERD should consist of an eight-week trial of PPI therapy, more long-term behavioral modifications, and possibly endoscopy, designed to help reduce reflux both structurally and promoting proper function of the lower esophageal sphincter (LES), and also reducing acidity of gastric juices.

Proton Pump Inhibitors (PPI)

Generic Name	Trade Name	Usual Adult Dose
Esomeprazole	Nexium®	40 mg daily
Lansoprazole	Prevacid®	30 mg daily
Omeprazole	Prilosec®	20 mg daily
Pantoprazole	Protonix®	40 mg daily
Rabeprazole	Aciphex®	20 mg daily

1. Dietary changes.
   A. Avoid caffeine, chocolate, fats, alcohol, caffeinated and decaffeinated tea and coffee, caffeinated soft drinks, citrus juices, peppermint, and spearmint.
   B. Weight loss if indicated.
   C. Avoid large meals that may increase intra-abdominal pressure.
2. Avoid lying down after eating for 2-3 hours.
3. Elevate the head of the bed by 6-8 inches.

4. Avoid use of tobacco, with promotion of tobacco and nicotine cessation. Also consider changing medications that can lower the LES pressure, i.e., Theophylline, calcium channel blockers, and barbiturates.
5. Use of antacids on an as needed basis as well as the use of over-the-counter PPI may be of benefit.

These modifications may also take longer than eight weeks to implement for the best effect, regarding weight loss and tobacco and alcohol abuse. These factors should be re-discussed with the patient in each subsequent phase of treatment for GERD.

For patients age 50 and more or who have had symptoms for 10 years or more, consider endoscopy prior to treatments to evaluate for Barrett's esophagus.

Following up at 8 weeks to see if there has been some improvement in symptoms may be done. If there is no improvement, the patient should be referred for endoscopy.

If these modifications have already been tried by the patient and have been successful, then advancement to maintenance therapy would be appropriate.

Supporting evidence is of class: R

26. Endoscopy

Flexible esophagogastroduodenoscopy should be used for the initial evaluation of esophageal symptoms in patients suspected of having gastroesophageal reflux disease (GERD) with refractory heartburn, odynophagia, or extra-esophageal symptoms. Endoscopy permits direct inspection and biopsy of the esophageal lining, aiding detection of grade 1 or grade 2 esophagitis – changes not apparent on x-rays. Endoscopy also permits detection and biopsy of Barrett's esophagus.

Supporting evidence is of classes: C, D

27. Positive?

Patients with erosions, ulcerations, strictures or intestinal metaplasia (Barrett's esophagus) are considered to have a positive endoscopy. Patients who have either a normal esophageal examination or only distal esophageal erythema are considered to have a negative endoscopy.

Supporting evidence is of class: C

28. Case Management for Negative Endoscopy

Diagnosing gastroesophageal reflux disease (GERD) can be difficult in patients with atypical symptoms, non-cardiac chest pain, or normal endoscopy. Many diagnostic tests to find pathological reflux have been developed. Few of them have withstood rigorous scientific testing and lack relevance to clinical management. 24-hour pH monitoring has been adopted as the diagnostic test of choice in patients with symptoms of unknown cause. pH testing should be done after the patient has discontinued therapy for a week. Alternatively, a trial and practical experience suggest short-term administration of high-dose proton pump inhibitors (PPIs) can reduce symptoms and offer a reasonably accurate diagnostic discrimination in selected groups of patients with suspected GERD. All patients with complaints of heartburn do not necessarily have GERD. Patients who don't respond to therapy, and have negative pH studies should be considered to have functional heartburn. These patients should be individually managed, as are patients with other functional gastrointestinal disorders (i.e. – irritable bowel syndrome, non-ulcer dyspepsia.)

Supporting evidence is of class: C

29. Case Management for Refractory Reflux

Patients with erosive esophagitis or worse should be treated with proton pump inhibitors (PPI) in a double therapeutic dose. If Esomeprazole (Nexium®) has not been used at this point, it would be reasonable to try a therapeutic trial. Patients intolerant of PPIs may receive a quadruple therapeutic dose of H_2RA. Failure to respond should prompt doubling the dose of the antisecretory medication and referral to gastroenterology. Duration of treatment should be indefinite within a single trial of step-down.

Patients requiring long-term maintenance therapy, or those who are incompletely controlled on maintenance therapy with a single trial of step-down, may wish a surgical opinion regarding fundoplication or bariatric surgery (BMI greater than 35), or GI opinion regarding endoscopic approaches.

Proton Pump Inhibitors (PPI)

Generic Name	Trade Name	Double Adult Dose
Esomeprazole	Nexium®	40 mg twice daily
Lansoprazole	Prevacid®	30 mg twice daily
Omeprazole	Prilosec®	20 mg twice daily
Pantoprazole	Protonix®	40 mg twice daily
Rabeprazole	Aciphex®	20 mg twice daily

Supporting evidence is of classes: A, M, R

30. Encourage Single Trial Step-Down Therapy

Patients with uncomplicated reflux may benefit from step-down therapy. Step-down therapy gradually reduces the intensity of treatment as tolerated to maintain the patient in remission. Lifestyle modifications should be continued indefinitely. Patients whose initial symptoms were controlled by lifestyle measures initially may require only occasional PPIs.

Supporting evidence is of classes: A, D, R

33. Return to Chronic PPI Therapy

Most patients with typical reflux symptoms will respond to acid suppressive therapy. This guideline encourages trying to reduce the therapy over time but many patients will stay on such therapy for months if not years. As outlined in this guideline, as long as these patients are not symptomatic they do not require an endoscopy.

Some groups have suggested, however, that patients with reflux should have an endoscopy to screen for Barrett's esophagus (BE). BE is a change in the lining of the esophagus from the normal squamous mucosa to a metaplastic intestinal columnar mucosa. Patients with BE are at increased risk of adenocarcinoma of the esophagus and thus patients with BE are placed into endoscopic surveillance programs.

The American College of Gastroenterology recommends: "Patients with chronic GERD symptoms are those most likely to have Barrett's esophagus and should undergo endoscopy."

At present there are no data to demonstrate the cost-effectiveness of such a strategy. Patients with longer duration of symptoms, (greater than 10 years) are more likely to have BE. White men are at increased risk.

Selecting patients on the basis of risk would improve the cost-effectiveness but has not been incorporated into guidelines. Given the absence of clear evidence of benefit, screening for Barrett's esophagus in patients with GERD cannot be advocated in all patients.

Patients requiring long-term maintenance therapy, or those who are incompletely controlled on maintenance therapy with a single trial of step-down, may wish a surgical opinion regarding fundoplication or bariatric surgery (BMI greater than 35), or GI opinion regarding endoscopic approaches.

Supporting evidence is of class: R

Annotation Appendix A – Abbreviations and Glossary of Terms

GERD:	The reflux of gastric contents into the esophagus, usually resulting from incompetence of the lower esophageal sphincter (LES) and characterized by the symptom of heartburn.
Esophagitis:	Inflammation of the esophagus diagnosed through endoscopic visualization and described by a histologic grading system.
Heartburn:	A painful or burning sensation felt behind the breastbone and sometimes in the neck and throat.
Acid regurgitation:	A sour or bitter taste in the mouth.
Alarm features:	Alarm features is a term that is used frequently in the dyspepsia literature to describe clinical features that may suggest underlying disease that should be diagnosed and treated without the delay of an empiric therapeutic trial. Alarm features frequently cited are: • Anemia • Dysphagia • Hematemesis • Melena • Persistent vomiting • Weight loss greater than 5% (involuntary)

EGD	upper endoscopy
GERD	gastroesophageal reflux disease
GI	gastrointestinal
H. pylori	*Helicobacter pylori*
H_2RA	histamine-2 receptor agonists
IBS	irritable bowel syndrome
LES	lower esophageal sphincter
MALT	mucosa associated lymphoid tissue
NSAID	nonsteroidal anti-inflammatory drug
OTC	over-the-counter
PPI	proton pump inhibitor
PUD	peptic ulcer disease
UBT	urea breath testing
UGI	upper gastrointestinal

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Evidence Grading System

I. CLASSES OF RESEARCH REPORTS

A. Primary Reports of New Data Collection:

Class A: Randomized, controlled trial

Class B: Cohort study

Class C: Non-randomized trial with concurrent or historical controls
Case-control study
Study of sensitivity and specificity of a diagnostic test
Population-based descriptive study

Class D: Cross-sectional study
Case series
Case report

B. Reports that Synthesize or Reflect upon Collections of Primary Reports:

Class M: Meta-analysis
Systematic review
Decision analysis
Cost-effectiveness analysis

Class R: Consensus statement
Consensus report
Narrative review

Class X: Medical opinion

II. CONCLUSION GRADES

Key conclusions (as determined by the work group) are supported by a conclusion grading worksheet that summarizes the important studies pertaining to the conclusion. Individual studies are classed according to the system defined in Section I, above, and are assigned a designator of +, -, or ø to reflect the study quality. Conclusion grades are determined by the work group based on the following definitions:

Grade I: The evidence consists of results from studies of strong design for answering the question addressed. The results are both clinically important and consistent with minor exceptions at most. The results are free of any significant doubts about generalizability, bias, and flaws in research design. Studies with negative results have sufficiently large samples to have adequate statistical power.

Grade II: The evidence consists of results from studies of strong design for answering the question addressed, but there is some uncertainty attached to the conclusion because of inconsistencies among the results from the studies or because of minor doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from weaker designs for the question addressed, but the results have been confirmed in separate studies and are consistent with minor exceptions at most.

Grade III: The evidence consists of results from studies of strong design for answering the question addressed, but there is substantial uncertainty attached to the conclusion because of inconsistencies among the results from different studies or because of serious doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from a limited number of studies of weak design for answering the question addressed.

Grade Not Assignable: There is no evidence available that directly supports or refutes the conclusion.

The symbols **+**, **–**, **ø**, and **N/A** found on the conclusion grading worksheets are used to designate the quality of the primary research reports and systematic reviews:

+ indicates that the report or review has clearly addressed issues of inclusion/exclusion, bias, generalizability, and data collection and analysis;

– indicates that these issues have not been adequately addressed;

ø indicates that the report or review is neither exceptionally strong or exceptionally weak;

N/A indicates that the report is not a primary reference or a systematic review and therefore the quality has not been assessed.

Discussion and References

Dyspepsia Algorithm Discussion and References

1. Symptoms of Dyspepsia or GERD

Dyspepsia

The term dyspepsia comes from the Greek, dys = bad, peptein = to digest. This is not a term used by patients, but rather a term used by physicians to encompass the symptoms associated with disorders of the upper gastrointestinal tract. Definitions in the literature have varied and have included epigastric pain or discomfort, nausea, vomiting, retching, post-prandial fullness, early satiety, bloating, heartburn, acid regurgitation and belching. Although consensus definitions of dyspepsia exist, they have been developed primarily for research. This guideline does not stipulate the exact symptoms that define dyspepsia, thus allowing the clinician some latitude in identifying the patients to whom this guideline can be applied.

In this guideline, dyspepsia is defined as pain or discomfort felt to arise in the upper gastrointestinal tract with symptoms on greater than 25% of the days over the past four weeks. The emphasis is on pain or discomfort which is present in the epigastrium. The upper GI tract includes the stomach, distal esophagus and proximal duodenum. Patients should have symptoms at least seven days a month. This guideline should not be applied to patients with symptoms that are occasional (i.e., one day a week or less) or acute (i.e., present less than one week). However, patients with symptoms every day for seven days are eligible. Most of the patients will have symptoms which the clinician feels are suspicious for either peptic ulcer disease (PUD) or gastroesophageal reflux disease (GERD).

Many other conditions may present with upper abdominal pain. This guideline should not be applied to patients in whom the clinician is suspicious of biliary tract disease or pancreatic disease. Thus, patients with right upper quadrant pain, inter-scapular pain, or pain that radiates straight through to the back should not be included. Similarly, patients with fever, jaundice, pruritis or other signs of biliary obstruction should not be included.

Irritable bowel syndrome (IBS) is a common condition which may manifest as upper abdominal pain. Like dyspepsia, IBS represents a constellation of symptoms. An international panel of experts defined IBS as chronic or recurrent abdominal pain, relieved by defecation or associated with a change in the frequency or consistency of stool.

Many patients who meet the definition of dyspepsia will also meet the definition of IBS. Physicians should use discretion in utilizing this guideline. Patients with typical IBS symptoms and minimal upper gut symptoms should not be included, whereas patients with typical dyspepsia and minimal bowel complaints should be included. Patients with significant overlap should be included if the dyspepsia symptoms are the primary reason for the patient to seek medical care.

Agréus L, Svärdsudd K, Nyrén O, et al. "Irritable bowel syndrome and dyspepsia in the general population: overlap and lack of stability over time." *Gastroenterology* 109:671-80, 1995. (Class C)

Kahn K, Greenfield S. "Endoscopy in the evaluation of dyspepsia." *Ann Intern Med* 102:266-69, 1985. (Class R)

Talley NJ, Stanghellini V, Heading RC, et al. "Functional gastroduodenal disorders." *Gut* 45(suppl II):II37-42, 1999. (Class R)

Thompson WG, Longstreth GF, Drossman DA, et al. "Functional bowel disorders and functional abdominal pain." *Gut* 45(suppl II):II43-47, 1999. (Class R)

GERD

A study of patients with possible gastroesophageal reflux disease demonstrated that the minority of patients with a single dominant symptom of heartburn or acid regurgitation had gastroesophageal reflux disease with high specificity. For heartburn, the specificity was 89%. In the case of acid regurgitation, the specificity was 95%. Neither of these symptoms was sensitive for the diagnosis of gastroesophageal reflux disease.

Symptoms are varied in gastroesophageal reflux disease. In the study noted above of 304 patients undergoing esophageal pH monitoring at a single institution, outcome of the study was related to the symptoms elicited. A wide variety of symptoms were reported including odynophagia, pharyngeal pain, nausea, belching, epigastric pain, retrosternal pain, acid regurgitation, retrosternal burning and heartburn.

If the patient has multiple symptoms, the specificity of these symptoms falls dramatically. Because of this, patients who may have gastroesophageal reflux disease but who have multiple symptoms should remain in the main dyspepsia algorithm and undergo *Helicobacter pylori* serology testing. The goal of this step is to ensure that those who may have gastric or duodenal ulcer undergo this serologic testing.

Klauser AG, Schindlbeck NE, Müller-Lissner SA. "Symptoms in gastro-esophageal reflux disease." *Lancet* 335:205-08, 1990. (Class C)

The authors then examined the specificity of these symptoms when given as the dominant symptom by the patient. For acid regurgitation, the associated specificity was 95% and for heartburn the specificity was 89%. It should be noted that neither of these symptoms was sensitive for the prediction of an abnormal esophageal pH study as the sensitivity figure for a dominant symptom of heartburn was only 38% and acid regurgitation was only 6%.

3. Are There Alarm Features?

The significance of complicated dyspepsia

Many surveys were developed in the 1970's and 1980's to distinguish patients with an organic cause for their dyspepsia from those with a non-organic cause. While the surveys were not particularly effective in this regard, the concept of complicated dyspepsia was developed. Individuals with complicated dyspepsia had a clinical picture including "alarm" features indicating a greater likelihood of organic pathology being present. No prospective evaluation of the predictive capability of alarm features has been performed. The retrospective studies available from large endoscopy practices indicate an approximately two-fold greater yield at the time of endoscopy in those with alarm features including anemia/GI bleeding, dysphagia/odynophagia, involuntary weight loss, severe pain, or persistent vomiting. Because of the setting of these studies, the significance of alarm features may be overstated.

Adang RP, Vismans JF, Talmon JL, et al. "Appropriateness of indications for diagnostic upper gastrointestinal endoscopy: association with relevant endoscopic disease." *Gastrointest Endosc* 42:390-97, 1995. (Class D)

4. Endoscopy for Alarm Features/Out of Guideline

Imaging test of choice in dyspepsia

If specialty radiologic expertise with multiphase barium UGI is available, UGI study should be viewed as an alternative to endoscopy. Otherwise, endoscopy provides greater sensitivity for the diagnosis of peptic ulcer disease. *[Conclusion Grade III: See Conclusion Grading Worksheet – Appendix A – Annotation #4 (Endoscopy)]*

There is no prospective controlled trial of the effectiveness of x-ray vs. endoscopic examination of the upper gastrointestinal tract in outpatients with dyspepsia. A number of studies over the years have compared

barium upper gastrointestinal examinations to upper gastrointestinal endoscopy for evaluation of patients. These studies generally differ in many ways including the skill and training of the endoscopists and radiologists performing the exams, the patient base (i.e. tertiary vs. primary care center, inpatient vs. outpatient), whether the study is prospective, resolution of differences between the examinations, and the type of x-ray study performed (i.e. single vs. double contrast). Not surprisingly, the results of these studies vary logically according to the variables (e.g. barium upper GI performed by radiologists completing a fellowship is more accurate than endoscopy performed by first-year GI fellows.)

Upper endoscopy is recommended based on the study of Dooley, et al. A comparison of predictive values from that study demonstrates the following:

	Positive predictive value	**Negative predictive value**
Endoscopy	1.00	0.89
Upper GI	0.94	0.52

Given that the majority of people with dyspepsia will have negative imaging studies, a test with a low negative predictive value is of minimal value. The strengths of this study are that the patients were randomized and that double contrast UGI was performed by general radiologists or the endoscopy by specialty trained gastroenterologists comparable to the local situation. In addition, disagreement in diagnosis was settled, where necessary, by a repeat examination.

Dooley CP, Larson AW, Stace NH, et al. "Double-contrast barium meal and upper gastrointestinal endoscopy." *Ann Intern Med* 101:538-45, 1984. (Class C)

In the United States as of 1995, barium upper GI studies are performed with equal frequency as esophagogastroduodenoscopy in patients with dyspepsia. Unfortunately, the majority of these upper GI studies are single contrast. Experts in endoscopy and radiology agree that single contrast studies are inadequate to evaluate the dyspeptic patient.

A number of studies have compared the sensitivity and specificity of multiphase barium UGI studies (performed by experienced radiologists with advanced training in gastrointestinal radiology) to esophagogastroduodenoscopy. In the hands of these specialized radiologists, the radiologic and endoscopic approaches are equally accurate. If this specialty expertise is available, multiple phase UGI study should be viewed as an alternative to endoscopy.

Longstreth GF. "Long-term care costs after gastroenterology consultation with endoscopy versus radiography in dyspepsia." *Gastrointest Endosc* 38:23-26, 1992. (Class A)

Shaw PC, van Romunde LKJ, Griffioen G, et al. "Peptic ulcer and gastric carcinoma: diagnosis with biphasic radiography compared with fiberoptic endoscopy." *Radiology* 163:39-42, 1987. (Class C)

6. *H. pylori* Testing, Eradication/Case Management

Case management of patients with recurrent dyspepsia and with documentation of peptic ulcer disease (PUD) on prior endoscopy or barium UGI focuses attention on the likelihood of recurrent PUD, etiology of the ulcer, and maintenance treatment.

Various studies of symptomatic patients with dyspepsia demonstrate that prior documentation of PUD is a significant predictor of recurrent ulcer. The likelihood of an ulcer being present is at least doubled. Thus proceeding as if an ulcer is present is rational.

Mann J, Holdstock G, Harman M, et al. "Scoring system to improve cost-effectiveness of open access endoscopy." *BMJ* 287:937-40, 1983. (Class C)

Recurrence is the rule with PUD. Consequently, with recurrent symptoms and no alarm features, vigorous pursuit of etiology is appropriate. The percentage of patients with PUD due to *H. pylori* depends on socio-economic status and ulcer type, but will range from 30% to 95% of affected people. *H. pylori* testing should be performed and those infected appropriately treated.

Graham DY, Lew GM, Klein PD, et al. "Effect of treatment of *Helicobacter pylori* infection on the long-term recurrence of gastric and duodenal ulcer: a randomized, controlled study." *Ann Intern Med* 116:705-08, 1992. (Class A)

Graham DY, Malaty HM, Evans DG, et al. "Epidemiology of *Helicobacter pylori* in an asymptomatic population in the United States: effect of age, race, and socioeconomic status." *Gastroenterology* 100:1495-1501, 1991. (Class D)

Tytgat GNJ, Rauws EAJ. "Campylobacter pylori and its role in peptic ulcer disease." *Gastroenterol Clin North Am* 19:183-97, 1990. (Class R)

Etiologic considerations in those negative for *H. pylori* include NSAIDs, smoking, and Zollinger-Ellison syndrome. NSAID use alone is undoubtedly the most common cause and some users will deny use of these products on detailed questioning. The reported frequency of NSAID use in PUD shows great variability ranging from 30% to 80%. Smoking is a promoter of PUD. The recurrence rate in those with no other etiology drops to less than 10% with discontinuation of smoking. Zollinger-Ellison is a rare condition. However, in those with no history of NSAID use it should be excluded by obtaining a fasting serum gastrin.

Crean GP, Holden RJ, Knill-Jones RP, et al. "A database on dyspepsia." *Gut* 35:191-202, 1994. (Class D)

Friedman GD, Siegelaub AB, Seltze CC. "Cigarettes, alcohol, coffee and peptic ulcer." *N Engl J Med* 290:469-73, 1974. (Class D)

Lanas A, Sekar MC, Hirschowitz BI. "Objective evidence of aspirin use in both ulcer and nonulcer upper and lower gastrointestinal bleeding." *Gastroenterology* 103:862-69, 1992. (Class C)

Soll AH, Weinstein WM, Kurata J, et al. "Nonsteroidal anti-inflammatory drugs and peptic ulcer disease." *Ann Intern Med* 114:307-19, 1991. (Class R)

Sontag S, Graham DY, Belsito A, et al. "Cimetidine, cigarette smoking, and recurrence of duodenal ulcer." *N Engl J Med* 311:689-93, 1984. (Class A)

A number of studies have looked at maintenance treatment for PUD. Elimination of the cause is the best "maintenance." European data indicate that the eradication of *H. pylori* in those with complicated peptic ulcer disease is effective at preventing recurrence without the need for maintenance. In the absence of U.S. data, opinion in the U.S. is divided about the need for maintenance treatment after *H. pylori* eradication in those with complicated peptic ulcer disease. For those with frequent recurrences, (< 3 year intervals between symptomatic episodes) and no identified cause for peptic ulcer disease, maintenance treatment is appropriate.

Jensen DM, Cheng S, Kovacs TOG, et al. "A controlled study of ranitidine for the prevention of recurrent hemorrhage from duodenal ulcer." *N Engl J Med* 330:382-86, 1994. (Class A)

Kovacs TOG, Campbell D, Haber M, et al. "Double-blind comparison of lansoprazole 15 mg qd, lansoprazole 30 mg qd and placebo in the maintenance of healed gastric ulcer." *Dig Dis Sci* 43:779-85, 1998. (Class A)

Palmer RH, Frank WO, Karlstadt R. "Maintenance therapy of duodenal ulcer with H2A-receptor antagonists–a meta-analysis." *Aliment Pharmacol Ther* 4:283-94, 1990. (Class M)

Pym B, Sandstad J, Seville P, et al. "Cost-effectiveness of cimetidine maintenance therapy in chronic gastric and duodenal ulcer." *Gastroenterology* 99:27-35, 1990. (Class A)

8. Is Patient Age 50 or Older, or at Increased Risk of Gastric Cancer?

Esophagogastroduodenoscopy, performed within 4 weeks, may be appropriate in patients age 50 or over because the incidence of gastric cancer is increased, but no study to date has shown improved outcomes. *[Conclusion Grade II: See Conclusion Grading Worksheet – Appendix B – Annotation #8 (Esophagogastroduodenoscopy)]*

Bytzer P, Hansen JM, Schaffalitzky de Muckadell OB, et al. "Predicting endoscopic diagnosis in the dyspeptic patient: the value of predictive score models." *Scand J Gastroenterol* 32:118-25, 1997. (Class D)

Christie J, Shepherd NA, Codling BW, et al. "Gastric cancer below the age of 55: implications for screening patients with uncomplicated dyspepsia." *Gut* 41:513-17, 1997. (Class C)

Gillen D, McColl KE. "Does Concern About Missing Malignancy Justify Endoscopy in Uncomplicated Dyspepsia in Patients Aged Less Than 55?" *Am J Gastroenterol* 94:75-78, 1999. (Class C)

Vaira D, Stanghellini V, Menegatti M, et al. "Prospective screening of dyspeptic patients by Helicobacter pylori serology: a safe policy?" *Endoscopy* 29:595-601, 1997. (Class C)

Williams B, Luckas M, Ellingham JHM. "Do young patients with dyspepsia need investigation?" *Lancet* 1349-51, 1988. (Class D)

Gastric cancer shows considerable variation in incidence on the basis of geography. Worldwide, the lowest rates are in the United States. The highest rates are three-fold higher, and are seen in East Asian residents. Rates are nearly as high for East European residents. When treating an immigrant population from these areas, the higher risk of gastric cancer may be considered an alarm feature prompting early endoscopy.

Hoel DG, Davis DL, Miller AB, et al. "Trends in cancer mortality in 15 industrialized countries, 1969-86." *J Nat Cancer Inst* 84:313-20, 1992. (Class D)

Initial endoscopy may be cost-effective in this age group, however, sensitivity analysis shows the cost-effectiveness is driven by the cost of endoscopy and so will vary.

Delaney BC, Wilson S, Roalfe A, et al. "Cost-effectiveness of initial endoscopy for dyspepsia in patients over age 50 years: a randomised controlled trial in primary care." *Lancet* 356:1965-69, 2000. (Class A)

10. Is *H. pylori* Testing Positive?

Clinical practice in the United States for dyspepsia has widely adopted the American College of Physicians guidelines which recommend 6 to 8 weeks of empirical antisecretory therapy for the initial management of dyspepsia without alarm features.

Kahn K, Greenfield S. "Endoscopy in the evaluation of dyspepsia." *Ann Intern Med* 102:266-69, 1985. (Class M)

This approach antedates much of the work on the role of *Helicobacter pylori*. This agent has been shown to be associated with chronic superficial gastritis (90%-100%), duodenal ulcer (80%-95%) and gastric ulcer (70%-90%) not caused by nonsteroidal anti-inflammatory agents. Moreover, its elimination decreases the risk of recurrence.

Graham DY, Lew GM, Klein PD, et al. "Effect of treatment of *Helicobacter pylori* infection on the long-term recurrence of gastric and duodenal ulcer: a randomized, controlled study." *Ann Intern Med* 116:705-08, 1992. (Class A)

Sipponen P, Hyvärinen H. "Role of *Helicobacter pylori* in the pathogenesis of gastritis, peptic ulcer and gastric cancer." *Scand J Gastroenterol* 28(Suppl 196):3-6, 1993. (Class R)

The World Health Organization has declared *Helicobacter pylori* to be a Class I carcinogen due to its role in gastric cancer worldwide. The approach to dyspepsia should reflect this change in ulcer treatment.

> World Health Organization/International Agency for Research on Cancer. "IARC monographs on the evaluation of carcinogenic risks to humans." Volume 61, 1994, Geneva, Switzerland. ISBN 92-832-12614. (Class R)

Helicobacter pylori testing appears to be a cost-effective approach for long-term dyspepsia management. *[Conclusion Grade II: See Conclusion Grading Worksheet – Appendix C – Annotation #10 (H. pylori Testing)]*

A decision-analytic model shows that an approach utilizing a combination of empiric therapy for *Helicobacter pylori* and antisecretory therapy was superior to antisecretory therapy alone. In addition, initial therapy for *Helicobacter pylori* guided by serological testing was the most cost-effective option. When endoscopy can be provided for less than $500 including all fees, immediate endoscopy is more cost-effective.

> Fendrick AM, Chernew ME, Hirth RA, et al. "Alternative management strategies for patients with suspected peptic ulcer disease." *Ann Intern Med* 123:260-68, 1995. (Class M)

> Silverstein MD, Petterson T, Talley NJ. "Initial endoscopy or empirical therapy with or without testing for *Helicobacter pylori* for dyspepsia: a decision analysis." *Gastroenterology* 110:72-83, 1996. (Class M)

A second decision analysis comparing the costs and outcomes of initial anti-*Helicobacter pylori* treatment to initial endoscopy among those who are *Helicobacter pylori* antibody positive shows initial therapy as the most cost-effective management strategy.

> Ofman JJ, Etchason J, Fullerton S, et al. "Management strategies for *Helicobacter pylori*-seropositive patients with dyspepsia: clinical and economic consequences." *Ann Intern Med* 126:280-91, 1997. (Class M)

Additional cost-benefit analyses have been performed.

> Ebell MH, Warbasse L, Brenner C. "Evaluation of the dyspeptic patient: a cost-utility study." *J Fam Pract* 44:545-55, 1997. (Class M)

> Sonnenberg A. "Cost-benefit analysis of testing for *helicobacter pylori* in dyspeptic subjects." *AJG* 91:1773-77, 1996. (Class M)

Serological testing is available that permits accurate diagnosis of *Helicobacter pylori*. Two products are available for point-of-care use and have good operating characteristics. FlexSure HP (SmithKline Diagnostics) has a calculated sensitivity of 94.4% and specificity of 87.6%. Quickvue HP (Quidel) has similar operating characteristics reported by the manufacturer with sensitivity of 96% and specificity of 92%. Both are CLIA 88 waived and are appropriate for point-of-care testing. The reagent cost of each is in the $7.00 to $8.00 range with approximately one minute of labor required for each test with the test taking 5 to 10 minutes total. The tests can be performed on whole blood, serum or plasma. Sensitivity and specificity are compared to standard serological testing.

> Graham DY, Evans DJ, Peacock J, et al. "Comparison of rapid serological tests (FlexSure HP and QuickVue) with conventional ELISA for detection of *Helicobacter pylori* infection." *AJG* 91:942-48, 1996. (Class C)

H. pylori urea breath test (UBT) is similarly sensitive at 90.2% vs. 91.3% in a direct comparison of the two methods by Cutler. The UBT was more specific than serology testing in the same trial at 95.8% vs. 91.6% for the serological test. Although these results differ arithmetically, they do not differ to a clinically significant extent. In the past, the UBT has been more expensive and less widely available than serology. If this situation changed and the price and availability of UBT was comparable to serology, it would be the preferred test.

The UBT is the test of choice in those situations where post-treatment testing is required. Post-treatment testing is not generally recommended. This testing may however be indicated in selected patients with complicated ulcer disease, low-grade gastric mucosa associated lymphoid tissue (MALT) lymphoma and following resection of early gastric cancer.

If testing is performed for eradication, it should be delayed at least 4 weeks after the completion of therapy and/or the use of proton pump inhibitors. This permits a differentiation between suppression and eradication of *Helicobacter pylori*. Serology is not useful in this situation as antibody levels commonly remain elevated for months to years after successful treatment.

11. Treatment for *H. pylori*

Helicobacter pylori infection has been associated with chronic superficial gastritis (90-100%), duodenal ulcer (80-95%), and gastric ulcer (70-90%) not caused by nonsteroidal anti-inflammatory agents. Moreover, its elimination decreases the risk of recurrence.

Graham DY, Lew GM, Klein PD, et al. "Effect of treatment of Helicobacter pylori infection on the long-term recurrence of gastric and duodenal ulcer: a randomized, controlled study." *Ann Intern Med* 116:705-08, 1992. (Class A)

Sipponen P, Hyvärinen H. "Role of Helicobacter pylori in the pathogenesis of gastritis, peptic ulcer and gastric cancer." *Scand J Gastroenterol* 28(Suppl 196):3-6, 1993. (Class R)

The World Health Organization has declared *Helicobacter pylori* to be a Class I carcinogen due to its role in gastric cancer worldwide. The approach to dyspepsia should reflect this change in ulcer treatment.

World Health Organization/International Agency for Research on Cancer. "IARC monographs on the evaluation of carcinogenic risks to humans." Volume 61, 1994, Geneva, Switzerland. ISBN 92-832-12614. (Class R)

A decision-analytic model shows that an approach utilizing a combination of empiric therapy for *Helicobacter pylori* and antisecretory therapy was superior to antisecretory therapy alone.

Fendrick AM, Chernew ME, Hirth RA, et al. "Alternative management strategies for patients with suspected peptic ulcer disease." *Ann Intern Med* 123:260-68, 1995. (Class M)

Silverstein MD, Petterson T, Talley NJ. "Initial endoscopy or empirical therapy with or without testing for Helicobacter pylori for dyspepsia: a decision analysis." *Gastroenterology* 110:72-83, 1996. (Class M)

The Cochran Library review of published trials through January 13, 2003, concluded that "*H. pylori* test and eradicate may be as effective as endoscopy-based management and reduces costs, by decreasing the proportion of patients that are endoscoped. 'Test and Treat' may be more effective then acid suppression alone, RR 0.59 (10.42-0.83)."

Delaney BC, Moayyedi P, Forman D. "Initial management strategies for dyspepsia." (Cochrane Review). In the Cochran Library, Issue 4, 2003, Chichester, UK, John Wiley & Sons, Ltd.

12. Empiric Trial of Full Dose PPI/Address NSAID Use

Empiric Trial

The proton pump inhibitors have been compared to H_2RAs for treatment of dyspepsia. There are a total of 3 trials with a total of 1,267 patients. All 3 studies show global improvement scores favoring PPIs. The advent of generic PPIs improves the cost-benefit considerations for this application.

Jones RH, Baxter G. "Lansoprazole 30 mg daily versus ranitidine 150 mg bid in the treatment of acid-related dyspepsia in general practice." *Aliment Pharmacol Ther* 11:541-46, 1997. (Class A)

Mason I, Millear LJ, Sheikh RR, et al. "The management of acid-related dyspepsia in general practice: a comparison of an omeprazole versus an antacid-alginate/ranitidine management strategy." *Aliment Pharmacol Ther* 12:263-71, 1998. (Class A)

Meiniche-Schmidt V, Krag E. "Antisecretory therapy in 1017 patients with ulcer like or reflux like dyspepsia in general practice. *European Journal of General Practice* 3:125-130, 1997. (Class A)

The choice of PPI is largely dictated by cost. There are modest differences in the drug interaction profile between the PPI agents. The PPIs are metabolized via hepatic cytochrome P450 enzymes, with CYP2C19 having the dominant role.

However, the dominance of this route varies significantly among the PPIs. The specific P450 enzymes involved in PPI metabolism and the potential for interactions among these agents shows variation. Omeprazole is metabolized largely via CYP2C19, and the potential for interactions thus appears to be the greatest among the PPIs. If this metabolic pathway becomes saturated, there is the possibility for interactions with many drugs, including warfarin, diazepam, and phenytoin. While rabeprazole is also metabolized by this isoenzyme, it apparently possesses significant affinity for CYP3A4; very few interactions have been documented with rabeprazole. Lansoprazole is metabolized principally via CYP3A4, and interactions with theophylline have been reported. As the metabolism of pantoprazole primarily involves CYP2C19 O-demethylation, significant CYP3A4 and CYP1A induction is not seen. This agent has the lowest potential for P450 metabolism and drug interactions.

Diaz D, Fabre I, Daujat M, et al. "Omeprazole is an aryl hydrocarbon-like inducer of human hepatic cytochrome P450." *Gastroenterology* 99:737-47, 1990. (Class D)

Gugler R, Jensen JC. "Omeprazole inhibits oxidative drug metabolism: studies with diazepam and phenytoin in vivo and 7-ethoxycoumarin in vitro." *Gastroenterology* 89:1235-41, 1985. (Class D)

Meyer UA. "Metabolic interactions of the proton-pump inhibitors lansoprazole, omeprazole and pantoprazole with other drugs." *Eur J Gastroenterol Hepatol* 8:S21-S25, 1996. (Class R)

Parsons ME. "Pantoprazole, a new proton-pump inhibitor, has a precise and predictable profile of activity." *Eur J Gastroenterol Hepatol* 8:S15-S20, 1996. (Class R)

NSAIDs

Patients on NSAIDs should have these discontinued, if possible.

The risk of gastrointestinal lesions in patients on NSAIDs is considerable, with one survey showing 68% with evidence of upper tract injury, although only 9% of those with such injury had dyspepsia. Among those with evidence of injury, the distribution of lesions included ulcers in 15%. Other lesions included mucosal injury in 45%, erosions in 53% and both in 34%.

Larkai EN, Smith JL, Lidsky MD, et al. "Gastroduodenal mucosa and dyspeptic symptoms in arthritic patients during chronic nonsteroidal anti-inflammatory drug use." *Am J Gastroenterol* 82:1153-58, 1987. (Class D)

A community survey study in Olmsted County, Minnesota showed 26% prevalence of non-aspirin NSAID use by those over 65. A logistic regression was performed and revealed a significant association between dyspepsia and/or heartburn with a relative risk of 1.8 (95% confidence interval of 1.3-2.6) among NSAID users.

Talley NJ, Evans JM, Fleming KC, et al. "Nonsteroidal anti-inflammatory drugs and dyspepsia in the elderly." *Dig Dis Sci* 40:1345-50, 1995. (Class C)

When assessing patients for complicated dyspepsia, NSAIDs do not appear to mask alarm symptoms. In three studies of patients with bleeding upper gastrointestinal lesions, there were no differences in presenting symptoms between NSAID users and non-users.

Aabakken L, Weberg R, Lygren I, et al. "Gastrointestinal bleeding: dyspeptic symptoms and clinical course in relation to use of non-steroidal anti-inflammatory drugs." *Scand J Rheumatol* 20:366-69, 1991. (Class C)

Jorde R, Burhol PG, Johnson JA. "Peptic ulcer bleeding in patients with and without dyspepsia." *Scand J Gastroenterol* 23:213-16, 1987. (Class C)

Wilcox CM, Clark WS. "Features associated with painless ulcer bleeding." *Am J Gastroenterol* 92:1289-92, 1997. (Class C)

Preventive co-therapy with NSAIDs is not necessary for all patients but may be appropriate in patients with a definite history of peptic ulcer, patients using both NSAIDs and corticosteroids, NSAIDs and warfarin, and patients with serious comorbid conditions that would compromise tolerance of ulcer complications.

Misoprostol is approved for prevention of NSAID-induced ulcer but is poorly tolerated due to diarrhea at full doses, with a 40% withdrawal rate seen due to diarrhea.

Raskin JB, White RH, Jackson JE, et al. "Misoprostol dosage in the prevention of nonsteroidal anti-inflammatory drug-induced gastric and duodenal ulcers: a comparison of three regimens." *Ann Intern Med* 123:344-50, 1995. (Class A)

Comparable efficacy to misoprostol in healing gastric ulcers or more than 10 gastric erosions was seen with the use of Omeprazole 20 mg qd. Treatment was successful in 76% of omeprazole patients and 71% given misoprostol 200 micrograms qid. More patients remained in remission during maintenance treatment with omeprazole 20 mg qd (61%) than with misoprostol (48%, $p < 0.001$).

Hawkey CJ, Karrasch JA, Szczepanski L, et al. "Omeprazole compared with misoprostol for ulcers associated with nonsteroidal antiinflammatory drugs." *N Engl J Med* 339:727-34, 1998. (Class A)

A prospective trial comparing the efficacy of omeprazole and ranitidine for ulcers associated with nonsteroidal anti-inflammatory drugs demonstrated 80% success at 8 weeks with 20 mg omeprazole qd compared to 63% with those given ranitidine 150 mg bid ($p < 0.001$). The maintenance phase demonstrated remission in 72% of those in the omeprazole group and 59% in the ranitidine group ($p < 0.004$).

Yeomans ND, Tulassay T, Juhász L, et al. "A comparison with ranitidine for ulcers associated with nonsteroidal anti-inflammatory drugs." *N Engl J Med* 338:719-25, 1998. (Class A)

COX2 inhibitors have been shown in prospective randomized controlled trials to produce significantly fewer endoscopically determined gastroduodenal ulcers than standard NSAIDs. Representative studies with celecoxib show a 4% ulcer rate compared to 26% seen with Naprosyn.

Simon LS, Weaver AL, Graham DY, et al. "Anti-inflammatory and upper gastrointestinal effects of celecoxib in rheumatoid arthritis: a randomized controlled trial." *JAMA* 282:1921-28, 1999. (Class A)

Statistically significant but much smaller decreases have also been shown for the risk of clinical events of perforation, bleeding and symptomatic ulcers. In a prospective study of 5435 patients with osteoarthritis, a 12-month cumulative incidence of these events was 1.3% in the rofecoxib group versus 1.8% in the nonselective NSAID group.

Langman MJ, Jensen DM, Watson DJ, et al. "Adverse upper gastrointestinal effects of rofecoxib compared with NSAIDs." *JAMA* 282:1929-33, 1999. (Class M)

A recent research trial selected a patient group for study with a history of prior gastric ulcer. This study compared placebo, misoprostol and lansoprazole and demonstrated that ulcer healing was superior to placebo in both the PPI and misoprostol groups but the PPI was better tolerated.

Graham DY, Agrawal NM, Campbell DR, et al. "Ulcer prevention in long-term users of nonsteroidal anti-inflammatory drugs: results of a double-blind, randomized, multicenter, active- and placebo-controlled study of misoprostol vs lansoprazole." *Arch Intern Med* 162:169-75, 2002. (Class A)

We are unable to find any studies comparing COX2 agents versus nonselective NSAIDs plus either misoprostol, PPIs or H_2RAs.

At this time, patients with a history of acid peptic disease and requirement for NSAIDs benefit from a combination of nonselective NSAID and a PPI. Whether this is superior or inferior to the use of a COX2 agent is unclear based on studies published to this point.

13. Symptoms Persist > 4 Weeks?

Although ulcer healing may take 8 weeks or more, the majority of patients with gastric or duodenal ulcer have improved symptoms at 4 weeks. Moreover, study shows that the yield of esophagogastroduodenoscopy is improved by limiting evaluation to those with symptoms persisting despite a short course of therapy.

Adang RP, Vismans JF, Talmon JL, et al. "Appropriateness of indications for diagnostic upper gastrointestinal endoscopy: association with relevant endoscopic disease." *Gastrointest Endosc* 42:390-97, 1995. (Class D)

This delay in evaluation is limited due to concern that a gastric neoplasm may progress from a resectable to an unresectable stage. One prospective study of 208 patients receiving endoscopy only if symptoms persisted or returned after a four week therapeutic trial detected both of the gastric cancers in the study population at the four week follow-up due to persisting symptoms.

Bytzer P, Hansen JM, Schaffalitzky de Muckadell OB. "Empirical H2 blocker therapy or prompt endoscopy in the management of dyspepsia." *Lancet* 343:811-16, 1994. (Class A)

16. Case Management

With identification of an ulcer, determination of etiology is essential. Serologic assays have a true sensitivity and true specificity in the mid-80% range. Consequently, with identification of an ulcer, either multiple biopsies of the stomach followed by examination of formalin-fixed specimens with special stains or the carbon 14 breath test should be performed, given accuracies in excess of 95%.

Cutler AF, Havstad S, Ma CK, et al. "Accuracy of invasive and noninvasive tests to diagnose *Helicobacter pylori* infection." *Gastroenterology* 109:136-41, 1995. (Class C)

Also refer to Discussion and References #6, "*H. pylori* Testing, Eradication/Case Management."

17. Continue Treatment for 8 Weeks Total Course and Then Stop

The proton pump inhibitors have been compared to H2RAs for treatment of dyspepsia. There are a total of 3 trials with a total of 1267 patients. All 3 studies show global improvement scores favoring PPIs. The advent of generic PPIs improves the cost-benefit considerations for this application.

Jones RH, Baxter G. "Lansoprazole 30 mg daily versus ranitidine 150 mg bid in the treatment of acid-related dyspepsia in general practice." *Aliment Pharmacol Ther* 11:541-46, 1997. (Class A)

Mason I, Millear LJ, Sheikh RR, et al. "The management of acid-related dyspepsia in general practice: a comparison of an omeprazole versus an antacid-alginate/ranitidine management strategy." *Aliment Pharmacol Ther* 12:263-71, 1998. (Class A)

Meiniche-Schmidt V, Krag E. "Antisecretory therapy in 1017 patients with ulcer like or reflux like dyspepsia in general practice." *European Journal of General Practice* 3:125-30, 2749, 1997. (Class A)

For further dicussion, please refer to Discussion and References #12, "Empiric Trial of Full Dose PPI/Address NSAID Use."

Duodenal Ulcer

Combined analyses of gastric acid secretion studies and meta-analysis of multiple clinical trials using regression analysis have demonstrated that healing rates in duodenal ulcer are related to degree of acid suppression, duration of acid suppression, duration of acid suppression over a 24-hour period, and duration of therapy. These analyses apply to agents that suppress acid, i.e., H_2RA (ranitidine, cimetidine, nizatidine, famotidine), proton pump inhibitors (lansoprazole, omeprazole, rabeprazole, pantoprazole, esomeprazole), as well as antacids. Healing rates for duodenal ulcers with H_2RAs are approximately 70 percent at four weeks and 90 percent at eight weeks. With omeprazole 20 mg a day healing rates of 90 to 100 percent have been demonstrated within one month. Placebo healing rates are significant at approximately 40 percent at four weeks but may vary between 20 and 60 percent at four weeks. The influence of pharmacologic therapy to induce healing at significant rates above placebo may vary, but is consistently significant between two and eight weeks. However, pharmacologic effects tend to reach a plateau in the range of four to six weeks.

Gastric Ulcer Healing

In studies of gastric ulcer healing with pharmacologic agents the degree of acid inhibition, the duration of acid suppression during a 24-hour period and the duration of treatment are the most important variables. However, the association of healing in gastric ulcer with acid suppression is less strong than in duodenal ulcer. The predominant variable is the duration of treatment. Healing rates progressively increase with time such that healing rates of 52 to 81 percent at four weeks, 63 to 86 percent at six weeks and 82 to 95 percent at eight weeks are reported for the antisecretory agents. Although statistically significant, the pharmacologic effects on gastric ulcer healing are less pronounced than that on duodenal ulcer. Placebo healing rates in gastric ulcer are greater than with duodenal ulcer and these rates increase progressively with time; 33 percent at four weeks, 42 percent at 6 weeks, 53 percent at eight weeks and 63 percent at 12 weeks. Extending the duration of treatment to 12 weeks heals nearly all benign gastric ulcers.

Omeprazole produces numerically greater healing rates than H_2RA but the healing rate is not as accelerated as duodenal ulcers and probably does not have clinical significance in the ordinary patient. Misoprostol was not significantly better than placebo. Antacids produce healing that is somewhat less effective than antisecretory agents.

NSAID Use

Continued NSAID use decreases the rate of healing of gastric and duodenal ulcers with either H_2RAs or PPIs. Cessation of NSAID use during ulcer treatment results in healing rates comparable to those in patients who have not had NSAIDs. For gastric ulcers, a healing rate of 71% was noted after 4 weeks in those receiving an H_2RA, compared to 54% in those continuing on an NSAID during their H_2RA treatment. At 8 weeks, the comparable values were 95% and 63%. Finally, at 12 weeks of treatment, the two groups showed healing rates of 100% vs. 79%.

Lancaster-Smith MJ, Jaderberg ME, Jackson DA. "Ranitidine in the treatment of non-steroidal anti-inflammatory drug associated gastric and duodenal ulcers." *Gut* 32:252-55, 1991. (Class A)

For duodenal ulcers, the rate of healing at 4 weeks was 74% on H2RAs for those stopping NSAIDs compared to 57% for those continuing to use NSAIDs. The comparable rates after 8 weeks were 100% and 92%. Thus, for a patient not able to discontinue NSAIDs during treatment, a course of treatment of 12 weeks with proton pump inhibitors is recommended.

Soll AH. "Chapter 30: Gastric, duodenal, and stress ulcer." *In* Gastrointestinal Disease, 5th ed. Sleisenger MH, Fordtran JS, eds. Philadelphia: Saunders, 580-657, 1993. (Class R)

18. Functional Dyspepsia

Patients presenting with dyspepsia will frequently have no identifiable abnormalities on endoscopy. When no structural or biochemical abnormalities are identified to explain their symptoms, these patients may be given a diagnosis of functional or non-ulcer dyspepsia. Such patients require reassurance, and further diagnostic testing should be kept to a minimum. H_2RAs, PPIs, prokinetics, mucosal protectants, *Helicobacter pylori* eradication regimens, low-dose tricyclic antidepressants, and psychodynamic therapies have all been evaluated in clinical trials. The placebo response rate in these trials has been quite high (often greater than 30 percent), and thus it has been difficult to demonstrate differences because of the number of potential therapies available and the fact that none has been demonstrated superior to the others. In particular, the role of *Helicobacter pylori* in non-ulcer dyspepsia has been assessed in four separate large, randomized clinical trials. Three showed no benefit beyond placebo, and the fourth showed a benefit in only a quarter of the patients. At present, no firm recommendations can be made regarding the management of non-ulcer dyspepsia. Further care for functional dyspepsia should be done on a case by case basis.

Blum AL, Talley NJ, O'Moráin C, et al. "Lack of effect of treating *helicobacter pylori* infection in patients with nonulcer dyspepsia." *N Engl J Med* 339:1875-81, 1998. (Class A)

Locke GR III. "Nonulcer dyspepsia: what it is and what it is not." *Mayo Clin Proc* 94:1011-15, 1999. (Class R)

McColl K, Murray L, El-Omar E, et al. "Symptomatic benefit from eradicating *helicobacter pylori* infection in patients with nonulcer dyspepsia." *N Engl J Med* 339:1869-74, 1998. (Class A)

Talley NJ, Vakil N, Ballard ED II, et al. "Absence of benefit of eradicating *helicobacter pylori* in patients with nonulcer dyspepsia." *N Engl J Med* 341:1106-11, 1999. (Class A)

Talley NJ, Janssens J, Lauritsen K, et al. "Eradication of *helicobacter pylori* in functional dyspepsia: randomised double blind placebo controlled trial with 12 months' follow up." *BMJ* 318:833-37, 1999. (Class A)

Talley NJ, Phillips SF. "Non-ulcer dyspepsia: potential causes and pathophysiology." *Ann Intern Med* 108:865-79, 1988. (Class R)

GERD Algorithm Discussion and References

24. Initial Management (8 weeks)

The availability of over-the-counter (OTC) PPI and associated cost reduction permits the use of this therapy for initial management of GERD. The use of initial PPI has been shown to reduce heartburn severity and duration compared to the use of H_2RA. This was the case when H_2RA was used alone, used in a program that permitted use of PPI either initially followed by PPI ("step down") or after a failed trail of H_2RA ("step up").

Howden CW, Henning JM, Huang B, et al. "Management of heartburn in a large, randomized community based study: comparison of four therapeutic strategies." *Am J of Gastro* 96:1704-10, 2001. (Class R)

26. Endoscopy

Flexible endoscopy is the preferred test to establish esophagitis in patients with typical reflux symptoms or extra-esophageal symptoms and in patients with atypical symptoms suggesting possible reflux. The standard barium esophagram is insensitive in the mild stages of esophagitis: 14% in grade 1, 16% in grade 2, and 50% in grade 3.

Chen MYM, Ott DJ, Sinclair JW, et al. "Gastroesophageal reflux disease: correlation of esophageal pH testing and radiographic findings." *Radiology* 185:483-86, 1992. (Class D)

Adding a double contrast examination to the single contrast study increases this sensitivity to 70-80 percent in grades 2 and 3; however, the overall accuracy of the combined studies is not enhanced because the false positive rate significantly increases to 14%.

Koehler RE, Weyman PJ, Oakley HF. "Single- and double-contrast techniques in esophagitis." *AJR* 135:15-19, 1980. (Class C)

27. Positive?

Esophagitis as seen at endoscopy is thought to be highly specific for the diagnosis of GERD. Although infectious, caustic and pill-induced esophagitis occurs, the vast majority of patients with linear erosions in their distal esophagus will have gastroesophageal reflux. Esophagitis is graded on a continuum from mild to severe. Mild, non-erosive esophagitis is common at endoscopy and may not correlate well with the patient's symptoms. For this reason, esophagitis of moderate severity is recommended before making a positive diagnosis of GERD.

Behar J, Biancani P, Sheahan DG. "Evaluation of esophageal tests in the diagnosis of reflux esophagitis." *Gastroenterology* 71:9-14, 1976. (Class C)

Johnsson F, Joelsson B, Gudmundsson K, et al. "Symptoms and endoscopic findings in the diagnosis of gastroesophageal reflux disease." *Scand J Gastroenterol* 22:714-18, 1987. (Class C)

28. Case Management for Negative Endoscopy

Many diagnostic tests to find pathological reflux have been developed. Few of them have withstood rigorous scientific testing and some lack relevance to clinical management. Manometry defines lower esophageal sphincter pressure accurately but does not identify the presence of significant reflux. The water siphon test (sipping water in supine position during a barium esophagram) has a sensitivity of only 60% and a false positive rate of 30%.

Battle WS, Nyhus LM, Bombeck CT. "Gastroesophageal reflux: diagnosis and treatment." *Ann Surg* 177:560-65, 1973. (Class C)

Spot esophageal pH measurements are only 58% sensitive in esophagitis patients and measure esophageal pH only briefly. The standard esophagram also performs poorly in esophagitis patients (sensitivities range from 5% in grade 1 and 18% in grade 2 to 60% in grade 4.) Gastroesophageal reflux scintiscanning has been reported to be 90% sensitive by one medical center; however, this result has not been readily reproducible, remains quite expensive, and has not been widely accepted as clinically useful.

Fisher RS, Malmud LS, Roberts GS, et al. "Gastroesophageal (GE) scintiscanning to detect and quantitate GE reflux." *Gastroenterology* 70:301-08, 1976. (Class C)

Therefore, 24-hour pH monitoring has been adopted as the diagnostic standard. 24-hour pH monitoring measures longer periods, captures transient pH changes not associated with symptoms, and can be coded into a scientific scoring system yielding acceptable sensitivities. These strengths make it the most useful test in patients with surreptitious disease and normal endoscopy. However, pH monitoring does not provide evidence of causality.

Proton pump inhibitors (PPIs) are capable of marked acid suppression and may allow a simultaneous empiric, therapeutic, and diagnostic trial. In the only study to be fully published, Schindlbeck, et al demonstrated an 83.3% sensitivity of omeprazole (40 mg bid for seven days) in reducing symptoms in 75% of patients with GERD symptoms, normal endoscopy, and abnormal pH monitoring studies. Omeprazole in a dose of 20 mg bid was not effective.

Schindlbeck NE, Klauser AG, Voderholzer WA, et al. "Empiric therapy for gastroesophageal reflux disease." *Arch Int Med* 155:1808-12, 1995. (Class C)

Therefore, the administration of high-dose PPI appears useful as a diagnostic and therapeutic trial in selected groups of patients with non-cardiac chest pain, atypical symptoms, or a normal endoscopy.

29. Case Management for Refractory Reflux

Essential elements in case management of esophagitis that is erosive or worse (moderate or worse) include selection of cost-effective treatment, the need for maintenance treatment, consideration of surgical treatment, and the need for referral to gastroenterology.

Relief of symptoms and healing of esophagitis are dependent on the degree and duration of acid suppression. Routine therapeutic doses of PPI are only fair at best in treating this minority subset of patients at the more severe end of the disease spectrum. For acute healing, a two-month course of standard dose PPIs (lansoprazole, omeprazole, rabeprazole, pantoprazole, esomeprazole) is recommended. Cost analyses are limited to decision models but suggest that PPIs are cost-effective compared to branded H_2RA. When compared to generic cimetidine, PPIs are of equivalent cost-effectiveness; consequently, the clinically superior treatment (i.e., PPIs) should be favored.

Bloom BS, Hillman AL, LaMont B, et al. "Omeprazole or ranitidine plus metoclopramide for patients with severe erosive oesophagitis: a cost-effectiveness analysis." *PharmacoEconomics* 8:343-49, 1995. (Class A)

Hillman AL, Bloom BS, Fendrick AM, et al. "Cost and quality effects of alternative treatments for persistent gastroesophageal reflux disease." *Arch Intern Med* 152:467-72, 1992. (Class M)

Robinson M, Decktor DL, Maton PN, et al. "Omeprazole is superior to ranitidine plus metoclopramide in the short-term treatment of erosive oesophagitis." *Aliment Pharmacol Ther* 7:67-73, 1993. (Class A)

Sontag SJ. "The medical management of reflux esophagitis: role of antacids and acid inhibition." *Gastroenterol Clin North Am* 19:683-712, 1990. (Class R)

The challenge of treating erosive or more severe esophagitis is the very high rate of relapse with discontinuation of treatment or with step down treatment. The relapse rate is greater than 90% at 6 months. Because of that, ongoing support for lifestyle modifications is essential. However, present evidence from clinical trials would suggest that the treatment providing symptom relief and healing should be continued long-term. The most cost-effective approach is established for those with peptic ulcers. Long-term PPIs are superior. For those with less severe esophagitis, decision models are divided on the preferred approach: continuation of PPIs, or PPIs only after failure of one trial of step down therapy.

Harris RA, Kuppermann M, Richter JE. "Prevention of recurrences of erosive reflux esophagitis: a cost-effectiveness analysis of maintenance proton pump inhibition." *Am J Med* 102:78-88, 1997. (Class M)

Hetzel DJ, Dent J, Reed WD, et al. "Healing and relapse of severe peptic esophagitis after treatment with omeprazole." *Gastroenterology* 95:903-12, 1988. (Class A)

Hillman AL, Bloom BS, Fendrick AM, et al. "Cost and quality effects of alternative treatments for persistent gastroesophageal reflux disease." *Arch Intern Med* 152:467-72, 1992. (Class M)

Lundell L, Backman L, Ekström P, et al. "Prevention of relapse of reflux esophagitis after endoscopic healing: the efficacy and safety of omeprazole compared with ranitidine." *Scand J Gastroenterol* 26:248-56, 1991. (Class A)

Marks RD, Richter JE, Rizzo J, et al. "Omeprazole versus H2-receptor antagonists in treating patients with peptic stricture and esophagitis." *Gastroenterology* 106:907-15, 1994. (Class A)

Decisions regarding referral to gastroenterology and surgery should be at the discretion of patient and physician. Long-term use of PPIs is established as safe. For those on a usual dose of PPIs with good symptom control, this is acceptable long-term treatment. For those not controlled or requiring a double dose of PPIs, referral to gastroenterology or surgery should be considered. Decision modeling of laparoscopic fundoplication versus long-term PPIs does not establish a preferred cost-effective option. Controlled studies of this question are underway.

Heudebert GR, Marks R, Wilcox CM, et al. "Choice of long-term strategy for the management of patients with severe esophagitis: a cost-utility analysis." *Gastroenterology* 112:1078-86, 1997. (Class M)

Spechler SJ, Department of Veterans Affairs Gastroesophageal Reflux Disease Study Group, The. "Comparison of medical and surgical therapy for complicated gastroesophageal reflux disease in veterans." *N Engl J Med* 326:786-92, 1992. (Class A)

30. Encourage Single Trial Step-Down Therapy

The availability of OTC PPI and associated cost reduction permits the use of this therapy for initial management of GERD. The use of initial PPI has been shown to reduce heartburn severity and duration compared to the use of H_2RA. This was the case when H_2RA was used alone, used in a program that permitted use of PPI either initially, followed by PPI ("step down"), or after a failed trial of H_2RA ("step up").

Howden CW, Henning JM, Huang B, et al. "Management of heartburn in a large, randomized community based study: comparison of four therapeutic strategies." *Am J of Gastro* 96:1704-10, 2001. (Class R)

In a follow-up study of six years' duration, 80% of patients whose initial symptoms were controlled by lifestyle modifications alone required ongoing lifestyle measures and only occasional H_2RAs for symptom relief. Of patients initially requiring H_2RAs, 67% were controlled with lifestyle measures and intermittent H_2RAs.

Kuster E, Ros E, Toledo-Pimentel V, et al. "Predictive factors of the long-term outcome in gastroesophageal reflux disease: six year follow-up of 107 patients." *Gut* 35:8-14, 1994. (Class D)

Empiric Trial

The proton pump inhibitors have been compared to H_2RAs for treatment of dyspepsia. There are a total of 3 trials with a total of 1,267 patients. All 3 studies show global improvement scores favoring PPIs. The advent of generic PPIs improves the cost-benefit considerations for this application.

Jones RH, Baxter G. "Lansoprazole 30 mg daily versus ranitidine 150 mg bid in the treatment of acid-related dyspepsia in general practice." *Aliment Pharmacol Ther* 11:541-46, 1997. (Class A)

Mason I, Millear LJ, Sheikh RR, et al. "The management of acid-related dyspepsia in general practice: a comparison of an omeprazole versus an antacid-alginate/ranitidine management strategy." *Aliment Pharmacol Ther* 12:263-71, 1998. (Class A)

Meiniche-Schmidt V, Krag E. "Antisecretory therapy in 1017 patients with ulcer like or reflux like dyspepsia in general practice." *European Journal of General Practice* 3:125-130, 1997. (Class A)

33. Return to Chronic PPI Therapy

Most patients with typical reflux symptoms will respond to acid suppressive therapy. This guideline encourages trying to reduce the therapy over time but many patients will stay on such therapy for months if not years. As outlined in this guideline, as long as these patients are not symptomatic they do not require an endoscopy.

Some groups have suggested, however, that patients with reflux should have an endoscopy to screen for Barrett's esophagus (BE). BE is a change in the lining of the esophagus from the normal squamous mucosa to a metaplastic intestinal columnar mucosa. Patients with BE are at increased risk of adenocarcinoma of the esophagus and thus patients with BE are placed into endoscopic surveillance programs.

The American College of Gastroenterology recommends: "Patients with chronic GERD symptoms are those most likely to have Barrett's esophagus and should undergo endoscopy."

Sampliner RE, Practice Parameters Committee of the American College of Gastroenterology, The. "Updated guidelines for the diagnosis, surveillance and therapy of Barrett's esophagus." *Am J Gastroenterol* 97:1888-95, 2002. (Class R)

At present there are no data to demonstrate the cost-effectiveness of such a strategy. Patients with longer duration of symptoms (> 10 years) are more likely to have BE. White men are at increased risk. Selecting patients on the basis of risk would improve the cost-effectiveness but has not been incorporated into guidelines. Given the absence of clear evidence of benefit, screening for Barrett's esophagus in patients with GERD cannot be advocated in all patients.

Conclusion Grading Worksheet – Appendix A – Annotation #4 (Endoscopy)

Work Group's Conclusion: If specialty radiologic expertise with multiphase barium UGI is available, UGI study should be viewed as an alternative to endoscopy. Otherwise, endoscopy provides greater sensitivity for the diagnosis of peptic ulcer disease.

Conclusion Grade: III

Author/Year	Design Type	Class	Quality +, –, ø	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Dooley, Larson, Stace, et al. (1984)	Sensitivity and specificity of a diagnostic test	C	–	-Inpatients routinely scheduled to receive barium meal; asked to have endoscopy within 3 days; 132 agreed, 100 completed both -Excluded if they had either procedure within last 6 months, if endoscopy was contraindicated, or if they had upper GI hemorrhage within 7 days of selection -Barium meal was double-contrast technique; 2nd staff radiologist did blind reading -Endoscopist was blinded to results of barium meal -Neither the barium meal or endoscopy were considered "gold standard" - "correct" diagnosis was determined at weekly conference with both reports and clinical follow-up information; disagreements were resolved by repeating the tests (n=3)	-98 of 100 had complete agreement on "correct" diagnosis; 2 that did not agree (and had no follow-up studies) were excluded from further analysis -53% had some lesion of the upper GI tract -Endoscopy resulted in 4 false-negative errors (failure to diagnose duodenal ulceration); barium meal resulted in 4 false-positive errors and 30 false-negative errors (both primarily for gastric lesions) -Endoscopy provided accurate diagnosis in 96% of patients; barium meal was 70% accurate ($p<0.001$) Procedure — Sensitivity — Specificity Endoscopy — 92% — 100% Barium Meal — 54% — 91% ($p<0.001$) — ($p<0.05$) -Second radiologist agreed with first in 85% of patients (94 of 98 had 2nd review) -In 39 of 98 (40%) the initial clinical diagnosis was subsequently shown to be correct; in 29 of the 59 (60%) that were incorrect additional information from barium meal increased clinician's accuracy to 65%; in the remaining 30 the clinical diagnosis remained incorrect after barium meal; endoscopy subsequently provided the correct diagnosis for 19 - Overall, after endoscopy the correct diagnosis was made in 88%; in the rest, correct diagnosis required further studies -Clinician placed 47 patients (48%) on correct tx before both procedures; in 51 (52%) the initial management was found later to be incorrect; 23 of the 51 were placed on correct tx after barium meal; of the remaining 28, 17 were placed on appropriate treatment after endoscopy for an overall appropriate treatment in 87 (88%); after both procedures 11 lacked final diagnosis and definite tx regimen -30% of radiologic errors were attributed to poor patient cooperation	-Endoscopy was significantly more sensitive and specific than the double-contrast barium meal in diagnosing lesions of the upper GI tract providing the correct diagnosis in 96% compared to 70% for the barium meal -Radiographic study is not a prerequisite to a safe and adequate endoscopy -Results indicated that review by more than one radiologist can provide for more accurate final diagnosis NOTES: patient population was less cooperative (in undergoing procedures, especially endoscopy); inpatients are likely different from outpatients in degree of illness etc. *Work Group's Comments* *-Authors were not looking for gastric cancer specifically; may do better with different technique*

Author/Year	Design Type	Class	Quality +,−,ø	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Shaw, van Romunde, Griffioen et al. (1987)	Sensitivity and specificity of a diagnostic test	C	–	-385 outpatients; no obvious GI bleeding or history of gastric surgery -Referring physician requested both a barium study and a fiberoptic endoscopic exam (no clinical information to either radiologist or endoscopist) -Biphasic radiographic exam of stomach and duodenum (all done by one radiologist) -Endoscopy within one week; exam done in presence of the radiologist; findings were compared immediately and endoscopy repeated if disagreement -Biopsy result did not provide absolute standard for peptic ulcers so kappa statistic was used (in absence of an absolute standard); kappa statistic measures agreement with a correction for chance -Also estimated sensitivity and specificity	-Compared findings for two conditions: gastric malignancy and peptic ulcer; -385 had radiographic exam, 374 had endoscopy **Peptic Ulcer** -Detected in 50 patients (16 gastric, 27 duodenal, 7 with both or 23 with gastric and 34 with duodenal) -In 12 of 23 (52%) with gastric ulcer there was full agreement between investigators; 4 of the remaining 11 were discovered only by radiologic exam and 7 were discovered endoscopically -In 22 of 34 (65%) with duodenal ulcer there was full agreement; 4 of remaining 12 were identified by radiologist and 8 by endoscopist -Kappa index for gastric ulcers was 0.67 -Kappa index for duodenal ulcers was 0.77 -Better agreement if location of ulcer is not considered; Lesion Method Sensitivity Specificity Gastric Radiographic 0.91 0.99 Endoscopic 0.85 0.98 Duodenal Radiographic 0.50 0.99 Endoscopic 0.99 1.0 **Gastric Carcinoma** -Cancer was diagnosed in 6 patients; all six on radiographic exam and 5 with endoscopy -Kappa index for gastric cancer was 0.91	-Kappa values of 0.67 and 0.77 (for gastric and duodenal ulcers, respectively) represent a substantial agreement beyond chance between radiographic and endoscopic findings -Kappa value of 0.91 for cancer represents almost perfect agreement beyond chance -Biphasic radiographic examination of the stomach and duodenum compared favorably with endoscopy in the detection of peptic ulcers and gastric carcinoma and the choice of initial procedure can be made based on other considerations *Work Group's Comments* *-Lower sensitivity for duodenal ulcer with double-contrast study*

Author/Year	Design Type	Class	Quality +,−,ø	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Longstreth (1992)	RCT	A	–	-Adult outpatients whose dyspepsia met the ACP criteria for diagnostic endoscopy and who had drug coverage as part of their HMO benefit; excluded patients with previous gastric or esophageal surgery or peptic ulcer, or upper GI endoscopy or radiography within previous 6 months -90 were eligible, 8 refused; after entry 9 endoscopy and 7 radiography patients were excluded (no drug coverage, left HMO, did not complete tests, etc.) -Randomly assigned to either gastroenterology consultation and endoscopy or barium UGI x-ray; gastroenterologists knew patients were part of study; radiologists were not told about study -Recorded data on all physician visits during 6 months before randomization and on dyspepsia-related visits and radiologic and endoscopic exams during the subsequent 6 months; use of dyspepsia drugs was obtained from pharmacy records -Cost assigned to physician visits, diagnostic tests, and drugs	-32 had consultation/endoscopy and 34 had barium radiography -2 groups were similar with regard to age, gender, 6-month physician utilization, dyspepsia drug cost, and diagnostic evaluation criteria; none had complications of peptic disease or signs of severe systemic illness -Findings (numbers of patients): -Six month follow-up: -Of the 6 endoscopies performed in patients from radiography group, no abnomalities were found	-Most of the patients (94%) had nonulcer dyspepsia -Higher long-term costs in radiography group were due to greater costs for visits, drugs, and alternative testing *Work Group's Comments* *-Type of barium radiography study was not reported* *-Focus of study was on what happened after evaluation rather than the accuracy of the evaluation - major benefit of endoscopy is perceived higher accuracy of negative study leading to lower costs* *-Most patients don't get double-contrast, biphasic radiography and specially trained radiologists would be needed for this; if these options are not available, the evaluation is likely better done with endoscopy* *-Cost analysis does not include consult costs or procedure costs*

Findings	Endoscopy	Radiography
Normal or hiatial hernia	27	32
Duodenal ulcer	2	2
Mild esophageal erythema	2	0
Focal duodenal erythema	1	0

Variable	Endoscopy	Radiography	
Physician visits*	$33.1	$114	(p<0.005)
Radiologic procedures*	$70.5	$67.6	(p>0.30)
All dyspepsia drugs*	$30.4	$100.1	(p=0.08)
H2 blockers*	$25.4	$96.0	(p=0.06)
Alternative test for dyspepsia (%)	0	6	(p<0.025)
Total 6-month cost	$134.0	$435.3	(p=0.006)
Dyspepsia self-rating	1.41	1.41	(p>0.30)

*6-month cost

Conclusion Grading Worksheet – Appendix B – Annotation #8 (Esophagogastroduodenoscopy)

Work Group's Conclusion: Esophagogastroduodenoscopy, performed within 4 weeks, may be appropriate in patients age 50 or over because the incidence of gastric cancer is increased, but no study to date has shown improved outcomes.

Conclusion Grade: II

Author/Year	Design Type	Class	Quality +,–,ø	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Williams, Luckas, Ellingham, Dain, & Wicks (1988)	Case Series	D	ø	-Reviewed data from dyspeptic patients who underwent endoscopy (n=686) or double-contrast barium meal (n=700) at the request of a general practitioner (1 year period) -Also reviewed all cases of gastric malignant disorders over previous 6 years	-Of 626 endoscopies, 271 (40%) were in those <45 years of age; there were no cases of esophageal or stomach carcinoma among those <45 and 17 cases in those >age 45 -Of 700 barium meal studies, 347 (57%) were in those <45 years of age; there were no cases of esophageal or stomach carcinoma in those < age 45 and 10 cases in those >age 45 -In a 6 year period 13 of 707 (1.8%) cases of gastric malignant disorders were in patients ≤ age 45	-Too many young patients with simple dyspepsia are being investigated; young dyspeptic patients should be treated symptomatically; failure to respond to treatment should then be referred for prompt evaluation NOTE: after 8 years and 16,000 endoscopies only 4 cases of early gastric cancer had been diagnosed at the hospital studied
Vaira, Stanghellini, Menegatti, et al. (1997)	Non-random trial	C	+	-1638 patients from a referral center (*H. pylori* is a primary focus) and 3281 patients from 93 nonreferral hospitals -Included those ≥18 years; previously uninvestigated upper abdominal pain (≥ 1 month); no prior upper GI endoscopy; no history of major abdominal surgery or organic, systemic, or metabolic disease; no intake of antibiotics, antisecretory drugs, bismuth-containing compounds or NSAIDs during the 4 wks preceeding the study; no presence of alarm symptoms -Tests included: serology (IgG specific to *H. pylori*), endoscopy, histology (for *H. pylori*)	**Nonreferral Hospitals:** -Seroprevalence of *H. pylori* was 59.1% for those under age 45 and 80.5% for those over age 45; avoidance of endoscopy if under 45 would have reduced endoscopy workload by 17.5% (557 cases); in 35 of those cases (6.3%) ulcers would have been missed, in 2 cases (0.3%) cancer would have been missed **Referral Hospitals:** -Seroprevalence was 58.6% for those under age 45 and 72.1% for those over age 45; avoidance of endoscopy if under 45 would have reduced workload by 19% (304 cases); in 6 cases (2%) ulcers would have been missed; no cancers would have been missed	-Safety of a pre-endoscopic screening policy based on age is questionable when used by medical centers without a specific interest in the field; policy needs to be further refined before adopted on a large scale -Overall prevalence of gastric cancer was 0.7%; 2 of 36 gastric cancers were in the 2096 patients under age 45 (0.09%)

Author/Year	Design Type	Class	Quality +,–,ø	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Bytzer, Hansen, Schaffalitzky de Muckadell, Malchow-Møller (1997)	Cross-Sectional Study	D	+	-Endoscopy group consisted of 1026 outpatients referred for diagnostic endoscopy; dyspeptic symptoms at the time of presentation; no prior surgery and no signs of GI bleeding -Empirically managed group; 207 patients referred to participate in clinical trial of either empirical treatment with H_2 blocker or management based on endoscopy; all had dyspeptic symptoms without previously documented peptic ulcer or esophagitis severe enough to justify treatment -Endoscopy group divided to test group (n=539) and validation group (n=487) -3 models (logistic regression)	**MODEL A** (prediction of organic dyspepsia–defined as peptic ulceration, esophagitis, or cancer (n=357) vs. non-organic dyspepsia (NOD, n=669) -Identified 5 predictors in favor of (vomiting, retrosternal pain, age ≥ 40 yrs, heavy smoker, dysphagia) and 1 in disfavor of (irritable bowel symptoms) organic dyspepsia; subset of variables explained 10.1% of the log likelihood **MODEL B** (prediction of major dyspepsia–defined as cancer, peptic ulceration, or complicated esophagitis (n=183) vs. uncomplicated esophagitis (n=843) -Identified 6 predictors in favor of (previous peptic ulcer, NSAID user, episodic pain, age ≥ 40 yrs, vomiting, heavy smoker) and 2 in disfavor of (symptoms provoked by bending/lying down, irritable bowel symptoms) major dyspepsia; model accounted for 18.4% of log likelihood **MODEL C** (prediction of peptic ulceration (n=146) vs. NOD, cancer, or esophagitis (n=880) -Identified 6 predictors in favor of (previous peptic ulcer, NSAID user, episodic pain, vomiting, heavy smoker, age ≥ 40 yrs) and 1 in disfavor of (symptoms provoked by bending/lying down) peptic ulcer; model accounted for 22.4% of log likelihood	-Score models to predict endoscopic diagnosis have not proved their value in the management of patients with dypepsia referred for endoscopy and score models developed in these patients cannot be trusted in patients who are potential candidates for endoscopy; future models should be constructed and validated in such populations *Work Group's Comments* *-Didn't model cancer specifically* *-Addresses question of probability of pathology not risk of undiagnosed cancer*

Author/Year	Design Type	Class	Quality +,–,ø	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Christie, Shepherd, Codling, & Valori (1997)	Population based descriptive study	C	+	-Cases of gastric cancer at initial presention (identified from pathology database); diagnosis on clinical and pathological basis; divided into age groups based on age at diagnosis -Clinical details for patients under age 55 determined from hospital record and GP record; pathological assessment in some cases	-Incidence of gastric cancer during 7 year period: 16.24 cases/100,000/year (319 cases); 25 (7.8%) were under age 55 at time of diagnosis -24 of the 25 under age 55 had one or more suspicious symptoms at time of diagnosis (including weight loss [14 patients], dysphagia [8], anemia [7], GI bleed [3], previous gastric surgery [3], palpable mass [3], GI perforation [1], cerebral metastases [1]) -10 of the 15 with available GP records were diagnosed within 3 months of first consultation for dyspepsia; only 2 had greater than 6 month delay -Diagnosis was histologically confirmed in all 25	-Prevalence of gastric cancer presenting with uncomplicated dyspepsia in the under 55 age group is very low -Gastric cancer below age 55 usually presents with recognizable alarm symptoms and/or signs so it should be possible to reassure patients aged less than 55 with uncomplicated dyspepsia without the need for endoscopy and without significantly affecting the detection and staging of gastric cancer *Work Group's Comments* *-Suggests age <55 is not a risk factor but doesn't settle question of whether age >55 years is an alarm/risk factor*

Conclusion Grading Worksheet – Appendix C – Annotation #10 (*H. pylori* Testing)

Work Group's Conclusion: *Helicobacter pylori* testing appears to be a cost-effective approach for long-term dyspepsia management.

Conclusion Grade: II

Author/Year	Design Type	Class	Quality +,–,ø	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Fendrick, Chernew, Hirth, & Bloom (1995)	Decision Analysis	M	**N/A**	-Computer simulation; 1000 patients; symptoms suggestive of peptic ulcer disease; not concurrently taking NSAIDs; symptoms severe enough to justify empiric course of antisecretory agents; no previously documented peptic ulcer disease -4 initial strategies: 1. immediate endoscopy and biopsy for *H. pylori* 2. immediate endoscopy only 3. qualitative serologic test for *H. pylori* 4. antisecretory therapy only 5. both antisecretory and antibiotic therapy -Subsequent intervention for recurrent symptoms, *H. pylori* infection, and active ulcer disease -Economic analysis from perspective of payer; used actual payments (not charges) -Assumptions (when used) favored initially invasive strategy	-Estimated costs (by strategy): Strategy Per ulcer cured Per patient treated 1. $8045 $1584 2. $6984 $1375 3. $4541 $894 4. $4835 $952 5. $4155 $818 -Cost-effectiveness advantage of strategies 3, 4, & 5 (noninvasive) relative to strategies 1 & 2 (invasive) was sensitive to a) cost of endoscopy (as cost decreases cost associated with immediate endoscopy approaches that of noninvasive strategies) and b) probability of recurrent symptoms if not initially treated invasively and ulcer disease was not the underlying cause of symptoms (as probability of recurrent symptoms increases the potential savings of noninvasive management diminishes as use of endoscopy increases) -Analysis of biopsy vs. no biopsy indicated no scenario in which performance of biopsy was justified for endoscopically diagnosed peptic ulcer -In no case was cost-effectiveness of empiric antisecretory therapy only (strategy 4) superior to combined empiric therapy (strategy 5) Comparison of combined empiric regimen with initial serologic testing showed no clear advantage; depended on cost of serologic test	-Results support the continued use of noninvasive treatment at first symptomatic episode, adapted to address the possibility of *H. pylori* infection NOTES: limited model to 1 year; limited to 5 treatment strategies likely in community practice; no evidence that 6- to 18-week potential delay in diagnosis of gastric cancer affects mortality and morbidity; model did not include nondrug costs related to overprescribing of antibiotics; best way to achieve benefits of *H. pylori* eradication are less clear

Author/Year	Design Type	Class	Quality +,–,ø	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Sonnenberg (1996)	Cost-benefit analysis	M	N/A	-Decision tree of testing for *H. pylori* in dyspeptic patients; 30% test positive; 60% of those are cured of *H. pylori* by anti-biotic/antisecretory therapy with resolution of dyspepsia in 10% of all patients treated, peptic ulcer cured or prevented in 10% of all patients treated, gastric cancer prevented in 0.12% of all patients treated; 78.88% have achieved little (no specific disease cured or prevented and no improvement of symptoms) -Cost benefits assigned: prevention of cancer = $30,000; prevention of peptic ulcer = $7,000; successful tx of dyspepsia = $5,000 -Multiply cost of items by their probability of occurrence	-Net benefit of *H. pylori* testing in dyspeptic patients is $112; testing is of benefit with prevalence of peptic ulcer disease between 0 and 10% and a cure rate between 60% and 80%; testing for *H. pylori* becomes more costly and less beneficial than non-testing only if benefit of ulcer prevention drops below $1000	-Cost-benefit relationship of testing for *H. pylori* in dyspeptic patients is influenced mostly by the monetary benefit of ulcer prevention, the prevalence rate of peptic ulcer disease in *H. pylori* positive patients, and the response rate of non-ulcer dyspepsia to *H. pylori* eradication; if the benefit of ulcer prevention exceeds $4000 and ulcer prevalence exceeds 10%, testing pays off -Strategy to screen all dyspeptic patients with a serological test for *H. pylori* and subject all positive patients to antibiotic therapy without further work up cannot be recommended NOTES: model does not itemize different diagnostic techniques or different treatment modalities of nonulcer dyspepsia, peptic ulcer, and gastric cancer *Work Group's Comments* *-Inadequate consideration of clinical costs and events (e.g., on-going medical costs)* *-Low cure rate for therapy*

Author/Year	Design Type	Class	Quality +,–,ø	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Silverstein, Petterson, & Talley (1996)	Decision Analysis	M	N/A	-Initial management of first episode of dyspepsia in ambulatory adult patients; 1 year tx period -All-payer perspective -Two alternative strategies: 1. initial endoscopy with medical tx based on results 2. empirical therapy -Risks of endoscopy and biopsy assumed negligible (ignored) -Recurrent episodes were assumed to be caused by same etiology that causes initial episode; treatment the same -Accounted for early (within 1 wk) and late (at end of initial 2 months) empirical tx failures; failures would have endoscopy -Arbitrarily assumed a 33% increased risk of death with a 2 month delay in gastric cancer diagnosis -Did analysis for 3 age groups (age 40, age 55, and age 75) -Prevalence and probability data from expert opinion and literature; surveyed to get pharmacy charges -Evaluated alternative strategies with maintenance therapy and with initial *H. pylori* testing	-One-year total medical care cost for initial management of episode of dyspepsia was $2122.60 for empirical therapy compared to $2162.50 for initial endoscopy ($39.90 or 1.8% difference); similar results for all ages -Alternative strategies involving maintenance therapy were evaluated for both initial strategies; the charges for empirical therapy were $2167.49 compared to $2374.59 for endoscopy ($207.10 or 8.7% difference) -Medical charges based on etiology of dyspepsia: Etiology / Prevalence (%) / Endos. / Initial Therapy / Empirical Therapy / Difference $ / Difference % GERD 20 $1284 $1179 -105 -8.2 Peptic Ulcer 20 $1292 $1402 +110 +8.6 Gastric 1 $87217 $87487 +270 +0.3 Cancer Functional 59 $1313 $1239 -74 -5.6 Dyspepsia Overall 100 $2162 $2122 -40 -1.8 -Sensitivity analysis indicated that charges for both strategies were highly sensitive to costs of endoscopy, costs of H_2 antagonist therapy, costs of initial general medical exam and return visits, and number of recurrent episodes of dyspepsia -Choice of least costly management strategy was sensitive to probabilities of peptic ulcer disease and gastric cancer; the charges for endoscopy, H_2 antagonist therapy, return visits; and the number of recurrent episodes of dyspepsia -In simulation sensitivity analyses, empirical therapy was least costly in 85.7% of the trials (but endoscopy was within $100 of empirical strategy costs in 91.5% of trials); life expectancy of patients managed by the two strategies was within 0.1 years in all trials and within 0.01 yrs in 67.7% of trials when probability of gastric cancer was est. at 1%	-Optimal strategy is a choice between two equal alternatives -Implications: 1) strategies that encourage empirical therapy will likely produce only modest savings, 2) actual savings may not be realized in individual practice settings because of variations in number of recurrent episodes, 3) failure of empirical therapy or recurrent episodes may make limiting the use of endoscopy unacceptable, 4) for individual patients, the difference in life expectancy under the 2 strategies may be 8-10 months (not the average of a few days) -Although the medical charges and life expectancy were approximately equivalent, the endoscopy first strategy provides more specific diagnosis, rules out malignancy, and reassures patients and therefore seems to be the better strategy for patients NOTES: this analysis includes an explicit statement of perspective and assumptions; variations in strategies were considered (maintenance therapy and alternate approaches); analysis was based on available information; sensitivity analyses considered wide ranges, Monte Carlo simulation reflected the simultaneous effect of uncertainty in the estimates *Work Group's Comments* *-Well-done sensitivity analysis*

Author/Year	Design Type	Class	Quality +,–,ø	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Ebell, Warbasse, & Brenner (1997)	Cost-Utility	M	N/A	-Seven strategies to identify the most cost-effective strategy (in dollars per quality-adjusted life years [$/QALYs]): 1) empiric antisecretory therapy for 1 months with omeprazole; 2) empiric *H. pylori* eradication; 3) upper endoscopy, 4) upper GI, or 5) serum titer for *H. pylori* (3, 4, 5 - goal is to identify patients for *H. pylori* eradication) 6) upper endoscopy, or 7) upper GI (6, 7 - follow by serum titer for *H. pylori* if positive for ulcer) -Index patient was adult presenting to primary care physician in outpatient setting with chief complaint of dyspepsia -One year time horizon -Probabilities determined from literature -Payer perspective used to determine cost; pharmacy and medical reimbursement data -Assumed: initial cost of $0, initial QALY of 1.0; patient had either duodenal ulcer, gastric ulcer, gastric cancer, or non-ulcer dyspepsia; symptomatic recurrences resulted in endoscopy; patients with non-ulcer dyspepsia are not "cured" and require maintenance therapy	-Cost-Utility Analysis: Strategy Cost Cost-Utility ($/QALY) 1 $1286.39 1287.53 2 $1196.74 1198.25 3 $2109.92 2113.79 4 $1509.50 1512.44 5 $1213.14 1214.41 6 $2125.99 2129.87 7 $1452.39 1455.08 Strategies 1, 2, and 5 (B, A, & E in text) were roughly equal in cost per dyspeptic patient and cost-effectiveness -Strategy 2 (A) was associated with lowest probability of recurrence (1.3%) and death (2.6 per 100,000); Strategy 1 (B) had a higher rate of recurrence (3.5%) and death (7/100,000) than any other strategy -Sensitivity analysis of the sensitivity and specificity of different tests did not affect choice of optimal strategy	-Three strategies were roughly equal in cost-effectiveness: empirical *H. pylori* eradication, *H. pylori* eradication if the serum *H. pylori* titer was positive, and empirical antisecretory therapy (although this strategy was associated with greater probability of recurrence and death and is therefore not recommended) NOTES: some of the model's assumptions are quite conservative (no benefit of *H. pylori* eradication for patients with non-ulcer dyspepsia, lower rate of *H. pylori* eradication than noted in literature); limited by 1 year time frame (protection from recurrence may extend to at least 2 years); 1 year time frame probably underestimates that benefits of *H. pylori* eradication; probabilities, costs, and utilities in model may be inaccurate or may not reflect a particular patient population; baseline treatment was omeprazole, clarithromycin, and amoxicillin for 1 week; more widespread use of regimens to eradicate *H. pylori* may lead to development of antibiotic resistance *Work Group's Comments* *-Supports serology testing to decrease risk of resistance* *-Followed patients for 1 year from time of diagnosis*

Author/Year	Design Type	Class	Quality +,–,ø	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Ofman, Etchason, Fullerton, Kahn, & Soll (1997)	Decision Analysis	M	N/A	-Four strategies for initial management: 1. initial endoscopy 2. empirical anti-*H. pylori* therapy without testing 3. noninvasive testing for *H. pylori* followed by either anti-*H. pylori* therapy or endoscopy -1 year after initial management strategy -Data from published reports; chose estimates that biased model against initial anti-*H. pylori* strategy -Third-party payer perspective -Used 0.05% probability of severe endoscopic complications -3 categories of antibiotic side effects: mild, moderate, worst-case	-Base-case analysis: Variable Strategy 1 Strategy 2 Difference Cost/Patient $1276.00 $820.00 $456.00 Endoscopies per 1000 (n) 1050 492 down 53% Courses of antibiotic per 1000 (n) 314 1105 up 252% -Savings produced by initial anti-*H. pylori* therapy were robust across entire range of cost and probability estimates	-Initial anti-*H. pylori* therapy could result in substantial cost savings compared with initial endoscopy in simple, uninvestigated dyspepsia NOTES: Does not consider patients with complicated dyspepsia, history of peptic ulcer disease, previous anti-*H. pylori* therapy, use of nonsteroidal anti-inflammatory drugs within the past month, or typical symptoms of GERD; base-case analysis did not stratify by age

This section provides resources, strategies and measurement specifications for use in closing the gap between current clinical practice and the recommendations set forth in the guideline.

The subdivisions of this section are:

- Priority Aims and Suggested Measures
  - Measurement Specifications
- Recommended Website Resources

Priority Aims and Suggested Measures

1. To increase the use of recommended methods for evaluating dyspepsia.

   Possible measures of accomplishing this aim:

   a. Percentage of patients evaluated for dyspepsia with discussion regarding appropriate *H. pylori* testing.

   b. Percentage of patients evaluated for dyspepsia without standard single phase contrast studies.

   c. Percent of patients evaluated for dyspepsia with endoscopy prior to receiving a therapeutic trial who do not have an alarm feature present.

2. To increase appropriate pharmaceutical treatment of patients with dyspepsia.

   Possible measures of accomplishing this aim:

   a. Percentage of patients with dyspepsia positive for *H. pylori* who receive antibiotic therapy.

   b. Percentage of patients with dyspepsia treated with antibiotics for positive *H. pylori* who receive effective therapy.

   c. Percentage of patients with dyspepsia treated with a PPI without previous endoscopic examination.

3. To decrease complications associated with peptic ulcer disease.

   Possible measure of accomplishing this aim:

   a. Number or rate of hospital admissions for ulcer hemorrhage.

4. To improve functional outcomes and satisfaction of patients with dyspepsia.

   Possible measures of accomplishing this aim:

   a. Percentage of patients with dyspepsia with improved symptoms following treatment as measured by a dyspepsia-specific health status instrument.

   b. Percentage of patients with dyspepsia who report that they are satisfied or very satisfied following treatment for dyspepsia.

5. Increase the use of initial treatment recommendations for evaluating GERD.

   Possible measures for accomplishing this aim:

   a. Percentage of patients with GERD following behavioral modification recommendations.

   b. Percentage of patients with GERD treated with PPI for an 8 week period.

   c. Percentage of patients with GERD reporting relief of symptoms after 8 week trial of PPI.

   d. Percentage of patients with GERD and control of symptoms with a PPI who have had a trial of step down therapy.

6. To increase appropriate treatment for patients who have ongoing symptoms after initial treatment recommendations.

   Possible measures for accomplishing this aim:

   a. Percentage of patients with continued symptoms of GERD after an 8 week trial of PPI having an endoscopy.

   b. Percentage of patients age 50 (and over) who have GERD or a history of GERD for 10 years or more who have been evaluated with endoscopy.

   c. Percentage of patients with ongoing symptoms of GERD (see annotation #1) and a BMI greater than 35 referred for surgical opinion regarding fundoplication, bariatric surgery and/ or endoscopic approaches.

At this point in development for this guideline, there are no specifications written for possible measures listed above. ICSI will seek input from the medical groups on what measures are of most use as they implement the guideline. In a future revision of the guideline, measurement specifications may be included.

Recommended Website Resources

The websites were viewed by the ICSI *Dyspepsia and GERD* guideline work group as credible resources. ICSI does not have the authority to monitor the content of these sites. Any health-related information offered from these sites should not be interpreted as giving a diagnosis or treatment.

Website Sponsor	Target Audience	Description	Website Address
National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)	Patients	A division of the National Institutes of Health. Conducts and supports basic and clinical research. Answers to frequently asked questions, from specific medical questions and nutrition information to finding a support group and more.	www.digestive.niddk.nih.gov/ddiseases/pubs/gerd/index.htm
International Foundation for Functional Gastrointestinal Disorders (IFFGD)	Patients	Nonprofit education and research organization that addresses the issues surrounding life with gastrointestinal functional and motility disorders and increases the awareness of these disorders among the general public, researchers, and the clinical care community.	www.iffgd.org/GIDisorders/GIAdults.html

Criteria for Selecting Websites

The preceding websites were selected by the *Dyspepsia and GERD* guideline work group as additional resources for practitioners and the public. The following criteria were considered in selecting these sites.

- The site contains information specific to the particular disease or condition addressed in the guideline.
- The site contains information that does not conflict with the guideline's recommendations.
- The information is accurate and/or factual. The author of the material or the sponsor of the site can be contacted by means other than e-mail. For example, a nurse line or other support is provided.
- The material includes the source/author, date and whether the information has been edited in any way. The site clearly states revision dates or the date the information was placed on the internet.
- The site sponsor is an objective group without an obvious or possible bias. For example, the site does not promote a product, service or other provider.
- The coverage of the topic is appropriate for the guideline's target audience. It is clearly written, well-organized and easy to read. The site is easy to navigate.