Improving the Management of

GERD

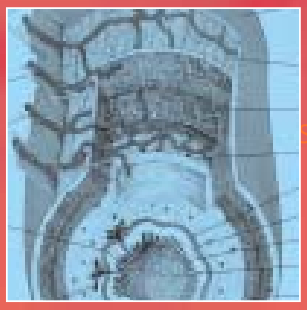
evidence-based therapeutic strategies

Walter L. Peterson, MD

Chair

American Gastroenterological Association

Consensus Development Panel



Continuing Medical Education:

Consensus Opinion in Gastroenterology

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Purpose

The management of gastroesophageal reflux disease (GERD) is controversial due in part to the paucity of high-quality evidence-based guidelines and recommendations for GERD diagnosis and treatment. To develop consensus recommendations for therapeutic approaches, a faculty of experts in the field of gastroenterology was convened under the auspices of the American Gastroenterological Association (AGA). The panel critically examined the current evidence in support of medical and surgical treatment of GERD. This educational monograph summarizes those findings and sets recommendations for the diagnosis and treatment of GERD.

Intended Audience

This program has been specifically developed to update and educate gastroenterologists, primary care physicians, and pharmacists who provide clinical advice and care for patients with acid reflux or GERD.

Learning Objectives

Upon completion of this activity, the participant will be able to:

- Define the pathophysiology of GERD, its burden of illness, and the goals of therapy
- Assess clinical trial evidence supporting medical and surgical treatment modalities for GERD
- Discuss sequelae of GERD and Barrett's esophagus
- Describe and evaluate the evidence for the role of gastroesophageal reflux in pulmonary disorders
- Evaluate and discuss the evidence for the effectiveness of over-the-counter medications in the management of acid reflux and GERD
- Outline the risks and benefits associated with use of proton pump inhibitors
- Differentiate the basis for referral of GERD patients for consultation, endoscopy, or surgery
- Formulate treatment approaches for acid reflux and GERD that incorporate the safest, most effective, and when possible, the most cost-effective modalities

The views expressed herein, while consistent with current medical literature, are solely those of the faculty.

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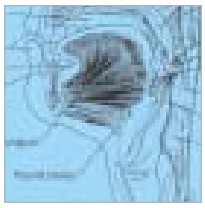
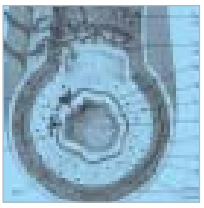
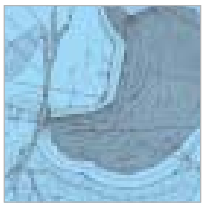

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Introduction

Overview of the Consensus Development Panel Meeting

To address the need for a comprehensive evaluation of clinical evidence and to respond to controversies in the diagnosis and treatment of GERD, a panel of 8 practicing expert gastroenterologists devoted to the investigation and treatment of GERD and GERD-related illness was convened. The genesis of the panel reflects the growing recognition that specialists have an obligation to disseminate the most current, accurate, and relevant guidelines to their peers.

The panel identified the following areas of most pressing educational need:

- What is the role of over-the-counter medications in the management of GERD?
- What is the risk of adenocarcinoma in patients with Barrett's esophagus (BE)?
- What are the implications of surgical fundoplication on future need of medical therapy and for influencing the risk of esophageal adenocarcinoma?
- When should patients with GERD be referred for consultation, endoscopy, or surgery?
- What is the evidence that endoscopic therapy of GERD is effective?
- Are there clinically important differences in proton pump inhibitors?
- What is the relation of GERD to extraesophageal pulmonary symptoms?

The panel compiled and evaluated the available evidence and reached consensus on recommendations to be shared with colleagues and the public. These are presented following individual sections and also in the "At-a-Glance Summary" found inside the back cover of this monograph.

Features of GERD

GERD is a highly prevalent gastrointestinal (GI) disorder and is one of the most common GI illnesses encountered in clinical practice. The diagnosis of GERD refers to a variable clinical picture that results from the reflux of stomach and duodenal contents into the esophagus, manifesting as a combination of symptoms and signs.[1] Heartburn (HB) is the hallmark symptom of GERD; other manifestations include acid regurgitation and dysphagia.[2] Some patients with GERD have no symptoms while others may have atypical symptoms including angina-like pain or airway induced symptoms. While transient or occasional HB is common, individuals with GERD have frequent, recurring, and prolonged episodes of reflux, usually at night.[1]

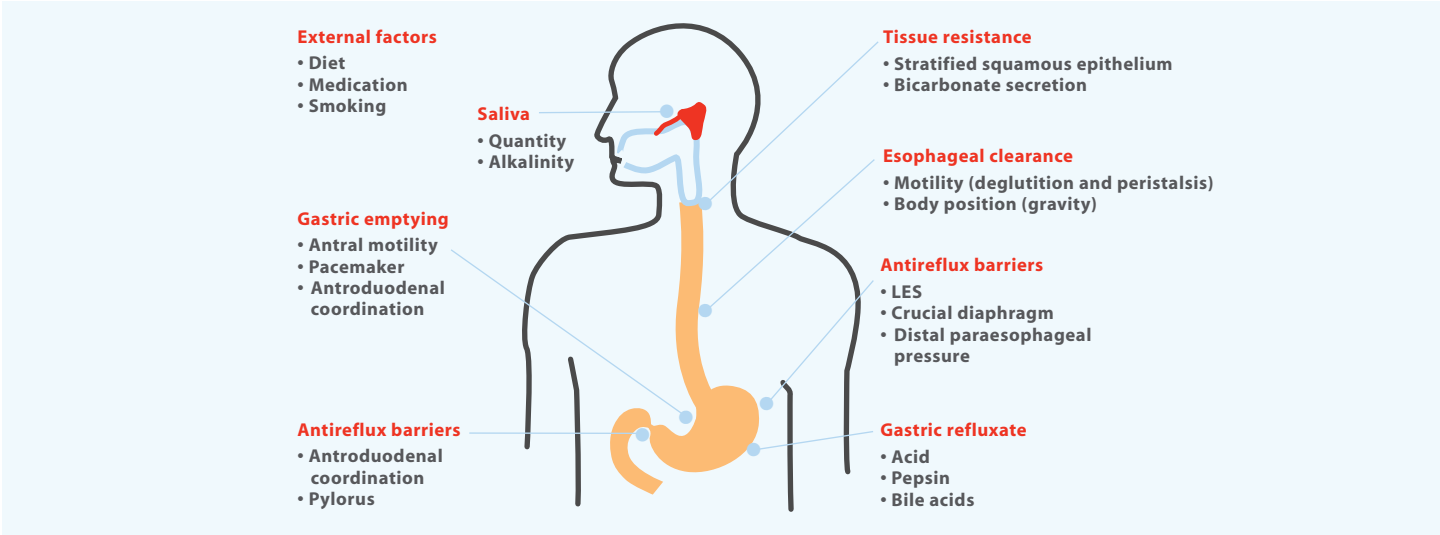

FIGURE 1.
Factors in the pathogenesis of GERD.[1-4]

Pathophysiology

The pathophysiologic basis for the differences in individuals with transient HB—such as postprandial HB—and patients with GERD are unclear, but include multiple factors (Figure 1). Reflux can occur due to transient relaxation of the lower esophageal sphincter (LES), reduced LES pressure allowing spontaneous reflux, or increased abdominal pressure.[2] Mean LES pressure is slightly higher in healthy individuals than in those with GERD, but this measure alone is an inadequate predictor of GERD.[1] Factors important in removing refluxed material (peristalsis), resisting acid (salivary pH, esophageal epithelium and bicarbonate secretion), and the characteristics and quantity of gastric fluids produced are thought to play a role in pathogenesis of GERD.[1-3] External factors that may contribute to reflux include diet, smoking, and certain medications.[4]

Complications of GERD are variable and include erosive esophagitis, esophageal stricture, esophageal ulcer, Barrett's esophagus (intestinal metaplasia of the esophagus), pulmonary aspiration, and adenocarcinoma of the esophagus.[2]

Burden of Illness

GERD affects all age groups, although older adults most often seek treatment. Certain complications vary by gender, race, and ethnicity. For instance, men are about twice as likely to be affected by esophagitis and nearly 10 times more likely to be affected by Barrett's esophagus.[2,5] Similarly, Caucasians are several times more likely to be affected by Barrett's esophagus and esophageal adenocarcinoma compared with non-Caucasians.

The epidemiologic assessment of GERD uses HB as a surrogate measure of prevalence.[2] A cross-sectional survey conducted in the United States in 1976 among healthy adults found that 7% of individuals experienced HB daily, 14% experienced HB weekly, and 15% experienced HB monthly.[6] Pregnant women have among the highest incidences of HB. A systematic review of population studies of GERD symptoms showed that HB and/or regurgitation prevalence ranged from 10%-48%.[7] A more recent survey found that over 61 million individuals in the United States experience HB at least once monthly. Further evidence for the extent of GERD is the fact that 18 million adults in the United States take indigestion aids at least twice weekly (Figure 2). A 2000 survey of 1000 adults who reported experiencing HB at least once a week found that 65% experience both daytime and nighttime HB.[8]

Quality of Life

GERD has a significant negative impact on health-related quality of life (HR-QOL). Patients with GERD report frequent interruptions during sleep, work, and social events. In a study of patients with symptoms of at least 3 months' duration, low baseline HR-QOL was demonstrated by measures of GI symptoms, general well-being, general health, vitality, and depression.[9] In a more recent study of 533 individuals with GERD symptoms of 6 months' duration, patients with GERD reported worse emotional well-being than those with diabetes or hypertension.[10] In both studies HR-QOL improved rapidly after successful treatment.[9,10]

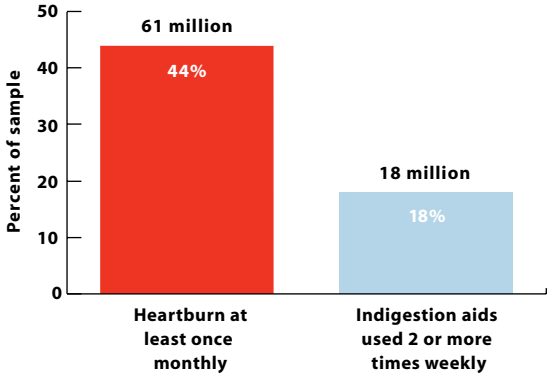

FIGURE 2.
Prevalence of HB in the United States.

Gallup Organization. HB Across America.1988, 2000.[8]

Diagnosis

A thorough and accurate history is the cornerstone of GERD diagnosis. While symptoms (HB or regurgitation) will provide the basis for diagnosis in most patients, GERD symptoms in some patients must be differentiated from those related to gastric disorders, infectious and motor disorders of the esophagus, and biliary tract disease.[2] Coronary artery disease should be considered early in individuals with a compatible history and presentation. In general, if history is sufficiently typical for uncomplicated GERD, alleviation of symptoms with a trial of empiric therapy may serve as an adequate diagnosis.[4]

Reflux can be documented with a barium esophagram (Table 1). Note that the absence of radiographic evidence of reflux during a barium swallow does not rule out GERD and the presence of reflux does not establish the diagnosis.[1] Ambulatory 24-hour esophageal pH can be monitored for values of pH ≤4; when these values are linked to symptoms, causation can be established.[1] Another approach toestablishing the relation of reflux with symptoms is the Bernstein test. A drip infusion of saline is introduced mid-esophagus, which is changed to 0.1 N hydrochloric acid. Discomfort within 4 to 5 minutes of acid exposure and rapid amelioration of symptoms by saline infusion suggest reflux as the cause of pain.[1]

While a barium esophagram will identify stricture formation or a deep esophageal ulcer, this test is insensitive to erosions. Endoscopy can detect the shallow ulcerations and erosions common to GERD. Other endoscopic observations such as erythema, edema, and friability may be too subjective to be useful in the diagnosis of GERD. Furthermore, the esophagus will appear normal in about half the patients with GERD. Manometry of LES pressure is not sensitive as a diagnostic test for GERD. Fewer than 25% of patients with GERD have a low resting pressure (<10 mm Hg). Esophageal manometry should only be used for the placement of ambulatory probes and as a guide to surgery.[11]

TABLE 1.

Assessments in the Diagnosis of GERD[1-3]

Documentation of reflux
- **Barium esophagram**
- **Ambulatory 24-hr pH test**

Establishing GERD as cause of symptoms
- **Bernstein test**
- **Symptom correlation with 24-hr pH test**

Damage to esophagus
- **Barium esophagram**
- **Endoscopy**

GERD Therapy

The goals of treatment are to relieve and prevent symptoms and complications.[2,3] Treatment includes medical, surgical, and endoscopic therapies that modify lifestyle, increase gastric pH, increase esophageal clearance, decrease gastric volume and increase gastric emptying, and in some patients, increase LES tone.[2,4] From the perspective of the specialist, lifestyle modifications are often less effective since at that point of consultation, the patient may have advanced disease and treatment experience. Patient readiness is an important factor in successful therapy; an individual seeking care for GERD symptoms may be already prepared for more aggressive approaches. Primary care physicians can play a critical role in helping patients find the best approach for their GERD or GERD-related symptoms.

Evidence for Efficacy of Over-the-Counter Medications for GERD in Patients With Mild-to-Moderate Symptoms

Efficacy Studies of Over-the-Counter Medications for GERD

Over-the-counter (OTC) medications commonly employed in GERD therapy include antacids, alginate/antacid combination, H_2 receptor antagonists (H_2RAs), and H_2RA/antacid combinations. To assess clinical evidence for efficacy of these medications, randomized, placebo controlled clinical trials were reviewed that examined clinical end points (ie, GERD, GERD-related signs). Studies reporting physiologic or intermediate end points such as gastric pH and gastric secretion were not included.

Antacids

Few clinical trials have evaluated antacid efficacy. Three clinical trials that examined antacids in randomized, double-blind, placebo-controlled studies are summarized in Table 2.[12-14]

Only 1 of the 3 studies showed positive evidence for antacid efficacy. Two studies unable to detect a statistically significant difference between antacid and placebo in severity and frequency of HB did show that antacids improved global scores and regurgitation.[12,14] The studies were limited, however, by small sample sizes and a lack of intent-to-treat analysis.

TABLE 2.

Clinical Trials of Antacids[12-14]

Authors and Design	N	Groups	End Points	Results
Graham et al, 1983 R,PC,DB,PG	**32**	**Liquid antacid (15 mL) 7 times daily vs placebo for 5 weeks**	**Frequency and severity of HB, Bernstein test results, erosive esophagitis**	**No statistically significant difference**
Weberg et al, 1989 R,PC,DB,CR	**47**	**Chewable antacid tablet (1) QID vs placebo for 2 weeks**	**HB, dysphagia, regurgitation, global scores**	**No statistically significant difference in HB; antacids superior for regurgitation (P<0.05)**
Grove et al, 1985 R,PC,DB,CR	**57**	**Liquid antacid (10 mL) 7 times daily vs ranitidine 150 mg BID vs placebo**	**Pain, regurgitation, dysphagia, endoscopic findings**	**Antacid was significantly superior to placebo in pain reduction but not other measures**

R=randomized; PC=placebo controlled; DB=double blind; PG=parallel group; CR=crossover; BID=twice daily; QID=4 times daily.

Overcoming some of the limmitations was a recent randomized, placebo-controlled clinical trial of 1640 GERD patients that compared an H_2RA/antacid combination treatment with monotherapy using either famotidine or antacid. In the arm where patients received antacid, significantly better global symptom relief was achieved compared with the control arm.[15] (This study will be discussed in more depth in a subsequent section.)

Alginate/Antacid Combinations

Studies of alginate in combination with low-dose antacid showed a statistically significant benefit compared with placebo for relief of mild-to-moderate GERD symptoms (Table 3).[12,16-22] Clinical studies showed that active treatment with alginate plus antacid is superior to placebo in the ability to relieve GERD symptoms such as HB and pain as well as in the prevention of HB and healing of esophagitis. Most studies compared the alginate/antacid combination to antacid alone or to placebo; no study was able to demonstrate superiority of alginate/antacid to antacid alone.

One randomized, double-blind trial compared alginate/antacid with sucralfate. Sucralfate resulted in a higher rate of complete esophageal healing compared with alginate/antacid (53% vs 34%, respectively) but the difference did not reach statistical significance.[18] No placebo-controlled trials of sucralfate were identified.

H_2 Receptor Antagonists

Clinical trials of OTC H_2RAs examined the efficacy of famotidine, cimetidine, nizatidine, and ranitidine.[15,23-31] In at least ten, well-designed trials, H_2 blockers were shown to be significantly more effective than placebo for relief of mild-to-moderate GERD symptoms (Table 4). Efficacy was demonstrated in short-term trials of up to 4 weeks with an H_2RA taken once or twice daily. In addition, H_2RAs were superior to placebo in the prevention of postprandial symptoms when taken 30-60 minutes before a meal. H_2RAs demonstrated efficacy of 50% to 70% with significant symptom relief. In general, small differences in efficacy were observed when equipotent doses of H_2RAs were compared.

Trials of H_2RAs were of a higher quality than those of antacids and antacids/alginates. Studies had larger patient populations, and used well-defined clinical end points. As with other OTC trials, the placebo effect was substantial, but results of H_2RA trials provided stronger evidence as a result of improved statistical power and higher quality. These studies showed that episodic HB and postprandial HB are effectively treated with H_2RAs compared with placebo.

Despite statistically significant differences between OTC H_2RAs and placebo, several limitations among these studies are notable. Only moderate symptomatic response rates were observed (60% to 70%), and, in most studies, it was not known whether erosive esophagitis was present. This is an important consideration as erosive esophagitis correlates with symptom recurrence. Also, the use of H_2RAs for "breakthrough symptoms" in patients using normal doses of H_2RAs and proton-pump inhibitors (PPIs) was not specifically studied. Finally, almost all studies of antacids and H_2RAs were short-term (4-week) trials; while these agents are approved for short-term use, GERD is a chronic disease.

The FACT study is distinguished from these studies by its large number of patients and improved efficacy results. For example, in the H_2RA arm, 72% reported an "excellent/good response."[15]

TABLE 3.

Clinical Trials of Alginate in Combination With Antacid[12,16-22]

Authors and Design	N	Groups	End Points	Results
Beeley and Warner, 1972 R, PC, DB, CR	28	Alginate/antacid vs alginate vs placebo (2 tablets QID) for 2 weeks	Relief of regurgitation, HB	HB relief in 79% (alginate/antacid), 57% (alginate only), 25% (placebo)
Stanciu, 1974 R, PC, PG	60	Alginate/antacid vs antacid only, vs placebo (2 tablets QID) for 2 weeks	Intraesophageal pH on day 1, repeated 2 weeks, pain during the second pH recording	Alginate/antacid significantly decreased number of reflux episodes, and time at pH <4 Alginate/antacid and antacid significanty decreased symptoms during test
Barnardo et al, 1975 R, PC, CR	42	Alginate/antacid vs placebo (QID) for two 6-week periods	Mean Ridit scores for pain, Mean reflux ratings	Alginate/antacid significantly decreased pain after meal and at night and mean reflux rating after meal at night
Lanza et al, 1986 R, DB, PC, CR	60	Alginate/antacid vs placebo (2 tablets following provocative meal)	Marked relief within 15 minutes	Alginate/antacid significantly superior to placebo
Chevrel, 1980 R, CR	44	Alginate/antacid vs placebo (2 tablets following provocative meal)	Relief of symptoms	Alginate/antacid significantly superior to placebo
McHardy G, 1978 R, DB, MC	133	Alginate/antacid vs antacid only, (2 tablets QID) for 4 weeks	Daily assessments of HB attacks and intensity	No significant difference between two groups
Graham DY R, DB	41	Alginate/antacid vs antacid only, (2 tablets QID) for 4 weeks	Complete healing	75% achieved complete healing, no significant difference between groups
Laitinen R, DB	68	2 g alginate/antacid (QID) vs 1 g sucralfate for 6 weeks	Heartburn, regurgitation, endoscopy grade	70% of patients symptom-free or improved at study end, sucralfate significantly superior to alginate/antacid on esophagitis healing

R=randomized; PC=placebo controlled; DB=double blind; CR=crossover; QID=4 times daily; PG=parallel group; MC=multicenter.

H_2RA/Antacid Combination vs Antacid or H_2RA as Monotherapy

FACT Study

This recent controlled clinical trial evaluated 1640 patients who were randomly assigned to receive H_2RA famotidine 10 mg/antacid combination tablet (FACT) (n=410), famotidine alone (n=411), antacid alone (n=411), or placebo (n=115).[15] Patients were instructed to take the assigned medication when experiencing an episode of postcibal HB and to rate HB relief at 5-minute intervals for 1 hour, then hourly for 8 hours.[15]

Efficacy results were based on 6281 HB episodes, 90% of which occurred during "waking hours"—0701 to 2300. Onset of relief was significantly faster for those in the FACT group compared with either the H_2RA (P=0.001; OR=1.42; 95% CI=1.17-1.73) or placebo groups (P< 0.001; OR=1.59; 95% CI=1.31-1.94) but not significantly different from those taking antacid. Remarkably, those treated with FACT experienced a significantly longer duration of relief than those who received any other treatment, that is, H_2RA, antacid or placebo: P<0.05 for the H_2RA comparison; P<0.001 for the antacid and placebo comparisons. The odds ratios for these comparisons indicated that those in the FACT arm were 1.57-1.60, or 2.15 times more likely to maintain adequate relief compared with those taking H_2RA (95% CI=1.26-1.92), antacid (95% CI=1.31-1.95) or placebo (95% CI=1.77-2.62), respectively.

Overall symptom response was excellent or good in more patients receiving FACT than in other groups (P=0.004 for all comparisons) (Figure 3). This combination of an H_2RA plus antacid combines the rapid onset of symptom relief of antacids with the sustained duration of H_2RAs. Additional benefits of FACT were the reduced need for rescue medication (antacid) during the 8-hour post-dose period compared with those in all 3 of the other treatment arms and a significantly increased time to rescue medication (P<0.001 for all comparisons); odds ratios were 1.70, 1.80, and 2.34 for the FACT versus H_2RA, antacid, and placebo arms, respectively.

Individual results from the FACT study treatment arms may be compared with the individual treatment comparisons from the appropriate studies cited above. For example, those in the antacid arm of the FACT trial had significantly better overall symptom response than those taking placebo: 72% reported an "excellent/good" response with antacid versus 65% with placebo (P≤0.004). Antacid was signifi-

TABLE 4.

Clinical Trials of H_2 Receptor Antagonists as Monotherapy[23-31]

Authors and Design	N	Groups	End Points	Results
Paul et al, 2001 R, PC, PG	994	Nizatidine vs placebo (75 mg BID) for 2 weeks	HB relief for 3 hours posttreatment	Nizatidine significantly superior to placebo
Spiegel et al, 1997 R, DB, PC, PG	413	Nizatidine (25, 75, or 225 mg given 30 min before meal) vs placebo	HB presence or absence or HB severity (VAS 3.5 hr)	Nizatidine (75 mg or 225 mg) significantly superior to placebo in preventing HB; all nizatidine dosages superior to placebo in reducing average and peak HB severity
Pappa et al, 1999 R, DB, PC, PG	284	Ranitidine (75 mg) vs placebo 30 min prior to provocative meal	HB over 4.5 hours (15 min intervals)	Ranitidine significantly superior to placebo in prevention of HB and HB severity
Pappa et al, 1998 R, PC, DB, PG	296	Ranitidine (75 mg) 1 hour before provocative meals	HB severity (VAS)	Ranitidine significantly superior to placebo in mean HB severity
Pappa et al, 1999 R, DB, PG, PC	1439	Ranitidine (25 mg or 75 mg) vs placebo PRN up to 4 per day for 2 weeks	HB over 3 hours, adequate relief within 1 hour that is sustained through the 3 hours (>10% improvement)	Ranitidine (75 mg) significantly superior to placebo in all episodes
Ciociola et al, 2001 R, DB, PG	1620	Ranitidine (25 mg or 75 mg) vs placebo PRN up to 4 per day for 2 weeks	HB over 3 hours, adequate relief within 1 hour that is sustained through the 3 hours (>10% improvement)	Ranitidine (75 mg) significantly more effective than placebo in all episodes
Gottlieb et al, 1995 R, DB, PC, CR	121	Famotidine (5, 10, or 20 mg) vs antacid vs placebo in single doses 1 hour before standard meal	HB severity (5-point scale over 5 hours)	Famotidine significantly superior to placebo
Simon et al, 1995 R, DB, PC, CR	565	Famotidine (5, 10, 20 mg) vs antacid vs placebo, self-directed up to twice daily for 4 weeks; open-label antacid as a rescue medication	Complete relief not requiring rescue antacid	Famotidine significantly superior than placebo, no difference between famotidine and antacid; antacid significantly superior to placebo
Galmiche et al, 1998 R, PC, DB	1336	Ranitidine (75 mg) vs cimetidine (200 mg) vs placebo PRN up to three per day for 15 days	Proportion of patients with >75% relief of HB	Ranitidine and cimetidine significantly superior to placebo; no significant difference between ranitidine and cimetidine groups
FACT study R, PC	1640	Famotidine 10 mg as monotherapy vs antacid as monotherapy vs famotidine 10 mg/antacid combination	Global symptom improvement; Onset and duration of symptom improvement	Famotidine as monotherapy more effective than placebo

R=randomized; PC=placebo controlled; DB=double blind; PG=parallel group; CR=crossover; BID=twice daily; PRN=as needed; VAS=visual analog scale.

cantly better than placebo for rapidity of relief, duration of relief, and overall global assessment and provided significantly better overall global assessment than placebo. In the 3 randomized clinical trials previously described (Table 2), there was only a trend toward improvement in measurements of global symptom scores with antacids. These trials may have been inadequately powered to detect a significant difference, while a similar arm of the FACT study included over 800 patients and demonstrated antacid superiority to placebo. In the H_2RA treatment arm of FACT, patients experienced efficacy comparable to those receiving antacid: 72% reported an "excellent/good" response with famotidine, versus 65% with placebo ($P \leq 0.004$).[15]

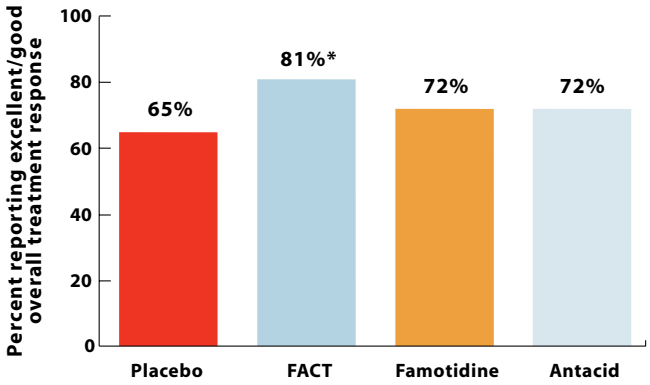

FIGURE 3.
Patients with an overall symptom response of excellent/good in FACT.[15]

*$P \leq 0.004$

OTC Medications and GERD: Conclusions and Recommendations

Randomized clinical studies showed that 60% to 70% of patients studied responded to acid neutralization or acid inhibition by OTC medications.

Selection of the appropriate end point is essential to the quality of clinical studies measuring efficacy in OTC agents used to treat GERD. For example, early studies found global scores of "healed esophagitis" with antacids to be similar to those of placebo.[12-13] However, more recent studies were able to demonstrate the superiority of antacids alone, or in combination with an H_2RA using symptom relief as a clinical end point.[14,15,30] Some of these results with combination agents may rest in their ability to better control gastric output.[32]

A cardinal feature of early antacid trials was the small sample sizes employed, suggesting they were likely underpowered to discern any differences in efficacy. The substantial placebo effect seen in these trials further supports that notion. The larger studies of FACT (n=1640) and Simon et al (n=565) were able to demonstrate a difference between antacid and placebo.[15,30]

The best available evidence suggests that OTC medications have a clinically meaningful role in treating GERD symptoms (Table 5). For those experiencing episodic HB for periods not exceeding 4 weeks, OTC agents provide rapid, effective, and safe relief.

Based on the FACT study, antacids or H_2RAs provide a 7% absolute benefit increase (ABI) in overall symptom response compared with placebo (NNT=14). Notably the combination of antacid and H_2RA provides another 9% ABI (NNT compared with placebo=6).

Trials enrolling an adequate sample size show antacids, low-dose H_2RAs, and alginate/antacid provide significantly greater symptom relief than placebo. The absolute benefit from these agents, however, is relatively small. Antacids offer a more rapid response than H_2RAs, but relief from H_2RAs has a longer duration. Combination of these two agents (antacid/H_2RA) provides an incremental improvement in efficacy, compared with the individual agents.

The efficacy of OTC medications for breakthrough symptoms on proton pump inhibitors (PPIs) has not been demonstrated in clinical trials. One study of 12 normal volunteers taking omeprazole (20 mg BID for 7 days) did show that an OTC H_2RA was significantly more effective for nocturnal acid breakthrough than bedtime omeprazole or placebo.[33]

It is the physician's role to establish the severity and clinical implications of each patient's symptoms. OTCs can be given for meal-stimulated, infrequent episodic HB. Referral from the primary care physician to a gastroenterologist may be indicated if HB is frequent or alarm symptoms are present.

TABLE 5.
OTC Medications Are Effective for GERD Symptoms

- **Prevention and rapid relief of symptoms**
- **Reduction of frequency and severity of symptoms**
- **Role in therapy**
  - **— Primary treatment (approved indication, evidence-based)**
  - **— Breakthrough symptoms in patients taking PPIs (no evidence)**
- **Limitations**
  - **— 60% to 70% efficacious for the above**
  - **— Unclear role in erosive esophagitis**
  - **— Approved and tested for short-term use (2 to 4 weeks)**

Risk of Adenocarcinoma in Patients With Barrett's Esophagus

A common and potentially serious consequence of chronic gastroesophageal reflux (GER) is the replacement of native squamous epithelium of the esophagus by a proliferation of metaplastic columnar epithelium, a condition known as Barrett's esophagus (BE).[2] This metaplastic epithelium may progress to esophageal adenocarcinoma, a tumor whose reported incidence has increased dramatically in industrialized countries over the past 3 decades, especially in white men.[34,35]

Early studies documented a moderate association between Barrett's esophagus and adenocarcinoma.[36] A recent, highly publicized study of esophageal cancer in patients with GERD showed that occurrence of HB, regurgitation, or both at frequency greater than once weekly was associated with a 7.7-fold increase in risk of adenocarcinoma. The study showed that increased frequency and severity of these symptoms over 20 years increases this risk to 43.5-fold. These data escalated concern about risk of cancer with GERD.[37]

The development of cancer in BE is thought to begin with GER (Figure 4). Acid damage to the squamous epithelium initiates a pathway that will lead to regenerative healing with squamous epithelium or to replacement with metaplastic epithelium. The role of acid reflux beyond these events is not certain. What is known about the role of reflux in carcinogenesis, however, suggests that to prevent severe clinical sequelae GER should be viewed as potentially etiologic and treated aggressively and as early as possible.

The risk of cancer in BE may vary with the extent of columnar-lined esophagus. Short segment BE is defined as less than 3 cm in length of columnar-lined esophagus; traditional BE is defined as equal to 3 cm in length. The risk of progression from BE to cancer was assessed in a prospective study in 235 patients with metaplasia.[38] The study showed an increase in the incidence of adenocarcinoma as the extent of metaplasia increased, but the difference in cancer incidence among groups was not statistically significant (Table 6). In the absence of more definitive studies, the approach to management of patients with both short- and long-segment BE should be the same.

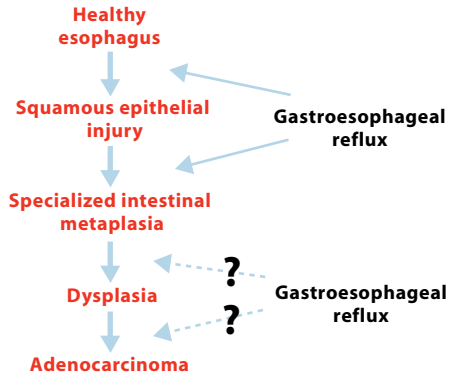

FIGURE 4.
Pathogenesis of esophageal adenocarcinoma.

TABLE 6.
Risk of Adenocarcinoma Associated With Barrett's Metaplasia[38]

Extent of Metaplasia	Number of Patients	Cancer Incidence (per 100 Patient-Years)	Relative Risk (95% CI)
<3 cm	69	0.4	1.0 (referent)
3-6 cm	84	0.6	1.5 (0.1-16)
7-10 cm	62	0.9	1.8 (0.2-18)
>10 cm	20	1.8	3.7 (0.3-45)

The annual incidence of esophageal cancer in BE patients had been estimated to be approximately 1%.[3] Recent evidence, however, suggests that risk of cancer associated with BE has been overestimated owing to publication bias, the systematic publication of studies that have positive or extreme results. Figure 5 shows a funnel diagram—the epidemiologic method used to measure publication bias—of data obtained from BE publications. If unbiased, published risk ratios would be evenly distributed on either side of the "true" risk. That published risk for cancer in patients with BE is distinctly skewed to the right is strongly suggestive of bias toward publication of studies demonstrating positive results. In addition, increased risk strongly correlated with smaller study size, further evidence of publication bias.[39]

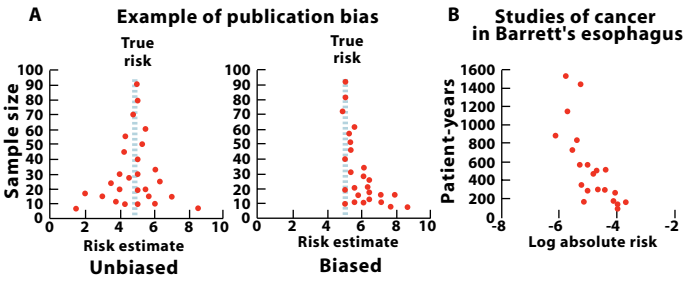

FIGURE 5.
Publication bias in studies of cancer incidence in patients with BE.

Adapted with permission from Shaheen et al, 2000.[39]

Epidemiologic data suggest the true incidence of cancer in patients with BE is much lower than formerly believed, closer to 0.4% than the commonly reported 1% to 2%.[40] If correct, this difference is significant in terms of clinical decision making. Computer models suggest that cancer risk above 1% warrants endoscopic surveillance at a frequency of once a year.[40] A risk of 0.5% would indicate surveillance every 4 to 5 years. If the rate of cancer falls below 0.2%, no endoscopic surveillance would be warranted.[40]

Inflated assessments of cancer risk may also be reflected by the prevalence of BE, which is about 10-times higher than the incidence. Therefore, most patients with Barrett's metaplasia who develop cancer present for the first time with both findings, potentially biasing perceptions toward a stronger association.[3]

Based on annual cancer risk of 0.5% and a hypothesized risk reduction of 50% with screening, the number needed to treat (NNT) to detect and theoretically prevent cancer in patients with BE would be 400. To be clinically effective, such a treatment in patients with BE would need to be convenient, inexpensive, and entail very low risk.

Dysplasia is a histologic diagnosis and is classified as low- or high-grade. Few prospective data exist on low-grade dysplasia, and there is significant subjectivity in the interpretation of its histopathology.

Patients with high-grade dysplasia in BE have a substantially increased risk of cancer. A study of 76 patients with high-grade dysplasia found a 59% 5-year cumulative incidence (Figure 6).[41] Another study found a 7.3-year cancer incidence of 16% among 75 patients: this study lacked external validation for the diagnosis of high-grade dysplasia.[42] A Mayo Clinic study found an intermediate 5-year cumulative incidence—32%—highlighting the variability among these studies.[43]

Historically, treatment for esophageal dysplasia has been the same as that for GERD. As shown in the previous section of this monograph, symptom control—a poor predictor of reflux control—has been the most common end point in clinical studies. As a result these studies were not adequately controlled to assess the influence of acid control on progression of BE.[3] A recent study, however, has shown that normalization of acid in the esophagus decreases cell proliferation in BE. Interestingly, this study showed that use of a PPI does not

guarantee adequate pH normalization for diminished proliferation, despite resolving symptoms.[44] How much acid control is needed and for how long are questions that await results of large clinical trials.

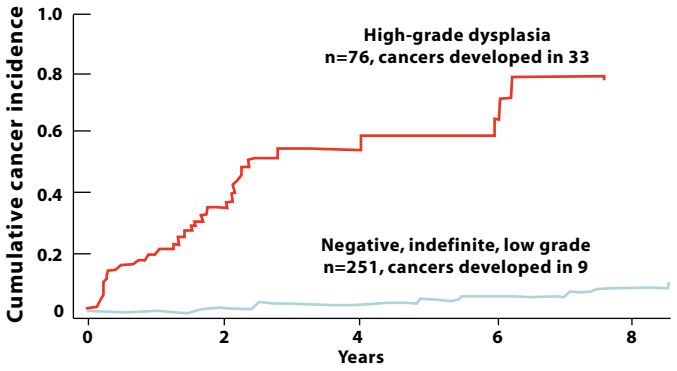

FIGURE 6.
Incident cancer in patients with BE-associated high-grade dysplasia.

Adapted with permission from Reid et al, 1999.[41]

Adenocarcinoma Risk With Barrett's Esophagus: Conclusions and Recommendations

Estimation of the risk of cancer in BE remains controversial, although it is clear that the risk is smaller than had been assumed and that death from esophageal cancer is uncommon in patients with BE. Furthermore, no therapy has been shown to prevent cancer. Expectations on the part of patient and physician alike may lead to unnecessary endoscopic procedures in a large percentage of patients. Primary care physicians and specialists need to recognize the relatively low risk of adenocarcinoma in this patient population. Efforts should be made to inform the lay and professional populations that GERD does not necessarily lead to cancer.

Management guidelines for BE patients have been redeveloped to reflect the lower risk estimates for cancer in these patients (Figure 7). It should be noted that no management strategy for BE has been validated by studies demonstrating that the strategy prolonged survival or enhanced quality of life.

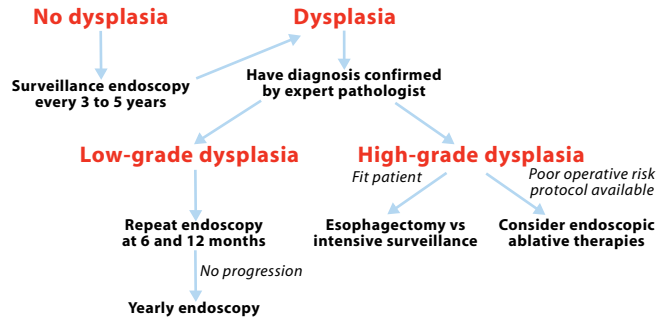

FIGURE 7.
Management of Barrett's esophagus.

Adapted with permission from Spechler et al, 2002.[36]

Effect of Surgical Fundoplication on the Need for Medical Therapy and the Risk of Esophageal Adenocarcinoma

Antireflux surgery attempts to restore sphincter competence by wrapping the gastric fundus around the esophagus, called fundoplication. When performed skillfully, this procedure will restore LES, reduce reflux, heal peptic esophagitis and may lead to reversal of peptic stricture.

The role of surgery in reducing the risk of cancer associated with BE is in debate. The mechanism by which fundoplication is believed to prevent cancer is by blocking acid to the distal esophagus, also the goal of medical therapy. Acid and bile salts may act synergistically in the development of BE, potentially inducing carcinogenesis (Table 7).[45] While prolonged acid exposure increases differentiation in Barrett's epithelium, pulses of acid and bile salts increase proliferation without altering differentiation.[46,47] Normalization of acid in the distal esophagus decreases proliferation and increases differentiation.[44]

In contrast to studies suggesting a protective role for fundoplication, others infer that surgery may not prevent adenocarcinoma. For example, proliferation of esophageal epithelium may remain unchanged after surgery.[48] Also, inhibition of apoptosis, a mechanism of proliferation, is unchanged after antireflux surgery.[49] While bile salts and acid may promote proliferation, the effects of bile salts on proliferation are blocked by acid.[47] Indeed, a study of patients with gastrectomy showed that reflux of bile without acid did not increase incidence of the long- or short-segment BE.[50]

Unfortunately, the ability of fundoplication to prevent adenocarcinoma in patients with BE has not been well studied. A study in 113 patients who underwent antireflux surgery at the Mayo Clinic showed that at a mean follow-up time of 6.5 years, the incidence of esophageal carcinoma was similar to nonsurgical populations. The population was selected nonrandomly and there was no control group. Notably, there was a high morbidity (36%) and mortality (0.9%) resulting from surgery.[51]

TABLE 7.
Potential Beneficial or Neutral Outcomes of Surgery for Barrett's Esophagus[44-50]

Evidence for and against a role for surgery in reduction of cancer risk in patients with Barrett's esophagus	
Why Surgery Might Prevent Cancer	**Why Surgery Might Not Prevent Cancer**
• Acid and bile salts are synergistic in the development of Barrett's esophagus and could induce carcinogenesis	• Inhibition of apoptosis is unchanged after anti-reflux surgery
• Pulses of acid increase proliferation without altering differentiation	• Proliferation in Barrett's epithelium is unchanged after surgery
• Bile salts induce cell proliferation in Barrett's esophagus	• Bile salts and acid block each other's effects on Barrett's epithelium and decrease proliferation
• Normalization of acid in the distal esophagus decreases proliferation & increases differentiation	• Human studies in patients with gastrectomy (and bile reflux) do not show an increased risk of esophageal cancer

In a prospective study, 59 individuals with BE were assigned randomly to medical (PPI) or surgical treatment and followed for 1 to 11 months. Five patients in the medical arm developed dysplasia, and 1 patient in each arm progressed to carcinoma *in situ*. The study was underpowered and no statistical difference between the groups could be demonstrated.[52]

A large retrospective cohort analysis included nearly all patients undergoing antireflux surgery in Sweden for 32 years (n=66,965). The incidence of esophageal adenocarcinoma in those not undergoing surgery (treatment unknown), was about 6 times that of the general population and increased with time, while in those undergoing surgery, the incidence was about 14 times that of the general population. There was a trend toward higher cancer rates in those receiving surgery; however, this group would likely be biased toward those with more severe disease. Despite this shortcoming, these results show that the risk of adenocarcinoma remains unchanged after surgery.[53]

Whether surgery is capable of eliminating the need for medical therapy is also a matter of debate. A reduction in the need for medication must be balanced against the substantial risks of morbidity and mortality from surgery. Uncontrolled data from surgical trials report patient relief rates as high as 92% to 97%.[54-57] Larger controlled trials comparing surgery with PPIs found equivalent rates of relief. In a 5-year follow-up of 310 patients with erosive esophagitis randomly assigned to omeprazole or open fundoplication, the rate of remission was significantly higher in the surgery arm of the study if dose adjustment was not allowed in the medical treatment group. If adjustment of the PPI dose was permitted in the medically treated group, the efficacy in the medical and surgical arms was statistically indistinguishable.[58]

In a short-term trial of 80 patients undergoing fundoplication in a community practice setting, 32% returned to OTC and prescription medical therapies.[59] In a 5-year follow-up study, 62% of patients randomized to surgery were using medical therapy for control of their symptoms.[60]

In another 5-year study in 500 patients treated by an expert surgical group, 11% were on regular medical therapy; 3.9% of the patients had a second operation for dysphagia.[61] Another study evaluated 198 patients treated with fundoplication for 32 months. Patients had moderate symptoms after the surgery including bloating (12%), diarrhea (9%), nausea (5%), and dysphagia (6%).[62]

A similar study reported long-term (median 77 months) endoscopic follow-up in 127 consecutive patients receiving antireflux surgery. This study revealed even higher rates of side effects, notably, 31% with long-term dysphagia. In this study, 13% of patients required a PPI or H_2RA postsurgically.[63]

The results of these studies demonstrate a spectrum of side effects and a continuing need for medication in patients undergoing antireflux surgery. Bloating, dysphagia, and flatulence that develop in approximately one third of patients after surgery have been shown to have a meaningful impact on quality of life in surgical patients.

An additional large study examined VA databases to assess outcomes of 1147 patients with erosive esophagitis who underwent Nissen fundoplication:[64] 605 patients with erosive esophagitis (53%) and 542 who had esophageal ulcers or peptic strictures (47%). This cohort was compared with 34,578 subjects with erosive esophagitis who did not receive fundoplication. Patients who underwent fundoplication had greater frequency of dysphagia, postsurgical syndromes, as well as more outpatient visits and procedures. Moreover, there was not significant reduction in esophageal adenocardinoma or prevention of strictures in those who did not have these lesions already.

Surgical Fundoplication Impact on Cancer Risk and Medical Therapy: Conclusions and Recommendations

The best data indicate that approximately 40% of patients undergoing fundoplication are free of heartburn and do not require medical therapy after prolonged follow-up. The proportion of patients returning to medical therapy is substantial (11% to 32% in studies extending to 5 years and >60% at 10 years).

Review of data available on cancer outcomes does not support the use of surgery to prevent esophageal adenocarcinoma. Recent

TABLE 8.
Guidelines for Endoscopy in Patients With GERD[11,65,66]

American Society for Gastrointestinal Endoscopy	American College of Gastroenterology	Canadian Consensus Conference
Clinical suggestions of severe reflux or other disease	**Further diagnostic testing if**	**General recommendations**
• Dysphagia	• Empiric therapy failure	• Dysphagia
• Odynophagia	• Symptoms of complicated disease	• Odynophagia
• Persistent/progressive symptoms on therapy	• Dysphagia	• Bleeding
• Extraesophageal symptoms	• Bleeding	• Weight loss
• Mass/stricture/ulcer on esophagram	• Weight loss	• Noncardiac chest pain
• Esophageal symptoms in immunosuppressed patients	• Choking	• Failure to respond to 4-8 weeks of therapy
• GI bleeding or iron deficiency	• Chest pain	• Once in a lifetime if requiring chronic therapy
• Preoperative evaluation	• Selected individuals with long standing symptoms	
	• Require continuous therapy	
	• Screening for Barrett's esophagus	

epidemiologic data suggest that the rate of cancer development is similar in patients treated surgically and those who are not.

The mortality and morbidity of fundoplication is substantially higher than the risk of developing adenocarcinoma in uncomplicated GERD. In light of this risk/benefit balance, the use of surgery to prevent further medical therapy or to reduce the incidence of adenocarcinoma cannot be recommended.

Surgery may be offered as a treatment alternative to certain patients with GERD, but concerted efforts are needed to educate physicians about the potential benefits and risks of laparoscopic fundoplication. Patients should be informed to *not* expect they will no longer need medication or experience GERD symptoms.[60] Anticipation of cancer risk may motivate GERD patients to seek surgery, but "prevention of cancer" is not an acceptable indication for surgery.

Referral for Endoscopy, Consultation, and Antireflux Surgery

Several consensus groups have formulated recommendations for endoscopy in GERD (Table 8).[11,65,66] Most guidelines propose use of endoscopy for the assessment of esophageal mucosa in cases of prolonged reflux or failure of pharmacologic therapy. The role of endoscopy in primary practice centers on three areas: 1) assessing the presence and severity of symptoms; 2) tailoring therapy to severity of GERD; 3) establishing prognosis.

The use of endoscopy in detection and assessment of disease has been evaluated in several studies. Data from these studies conflict, however, and symptoms are not predictive of erosive esophagitis; esophagogastro-duodenoscopy (EGD) results are negative in about half of patients with GERD symptoms.[67]

In a study of data collected from 46 endoscopists, grading correlated significantly with HB severity. But, considerable overlap was noted.[68] Another efficacy study found that severity of HB did not correlate with erosive esophagitis, as 68% of patients had nonerosive reflux disease.[69]

While tailoring treatment to the severity of GERD is a goal of therapy, endoscopy has limited utility in this regard. One prospective study of 598 patients with GERD who were referred to a specialist showed that medical therapy was increased in 74% of patients who had EGD findings of BE or erosive esophagitis while medical therapy increased in 35% with normal findings on EGD.[70] Another prospective study in 742 patients with GERD showed that most patients were switched to a PPI after EGD, regardless of findings.[71]

There are several drawbacks in the use of endoscopy to tailor therapy in GERD. It is more difficult to heal severe grades of esophagitis. PPIs, however, result in healing rates of 80% to 90%.[72] High-grade lesions, however, are rare in the community setting, suggesting that endoscopic evaluation in most cases will not provide useful information. Symptom relief is a central goal of therapy. As a trial of a PPI is recommended before endoscopy and symptoms of nonerosive and erosive reflux disease are treated similarly, endoscopy contributes little to management.

The prognostic value of endoscopy for relapse was shown in the study of Lundell and colleagues cited above. In 2 separate studies in a total of 455 patients, relapse after discontinuation of a PPI was significantly correlated with endoscopic severity grade.[68] These data, however, should be considered in the light of the fact that patients with nonerosive disease relapse at a similar rate, and both groups are treated symptomatically.

Those at highest risk for BE and adenocarcinoma (white males ≥50 years of age with chronic GERD symptoms), should undergo screening by endoscopy.[36] A case-control study compared 79 patients with BE to non-BE patients with GERD and with controls undergoing endoscopy for other reasons. The study showed that patients with BE developed reflux symptoms at an earlier age than control groups and had more severe symptoms of longer duration.[73] A community-based observational study found that the odds ratio of developing BE was significantly correlated with duration of symptoms.[74] This study was limited, however, as determination of presumed BE was based on endoscopy rather than histologic findings. A nationwide case-control study in Sweden showed that persons with recurrent symptoms of reflux, compared with those without symptoms, were much more likely to develop adenocarcinoma and that risk escalated with the length of symptoms.[37] These studies offer compelling evidence for a relation between long-term, severe symptoms and the onset of BE and adenocarcinoma. It is important to note, however, that the majority of patients with BE will not progress to cancer. A recent study showed that only less than 5% of 1503 patients with resected esophageal carcinoma had a previous diagnosis of BE.[75]

There are no studies to guide when a patient with GERD should be referred to a gastroenterologist. Recommendations are based on an appraisal of the role of the specialist from perspectives of the patient, practitioner and healthcare delivery system (Table 9).[67]

TABLE 9.

Recommendations for Referral of Patients With GERD to a Gastroenterologist[67]

- **Endoscopy**
- **Specialized testing**
  - **— 24-hr pH**
  - **— Manometry**
  - **— Impedance**
- **Failure of PPI therapy**
- **Long-term management strategy**

Guidelines governing referral for antireflux surgery vary. ACG guidelines categorize antireflux surgery as a maintenance option for well-documented GERD if performed by an experienced surgeon.[11] The Genval Conference guidelines suggest it is a matter of patient preference based on informed consent.[76] Guidelines from the Society of American Gastrointestinal Endoscopic Surgeons (SAGES) cite failure of medical therapy as the primary reason to choose surgery.[77] One caveat is that failed therapy may stem from an incorrect diagnosis. Other factors include continuous medical therapy, increasing dose of medication, age of the patient and adherence to therapy.[78]

Other indications for laparoscopic antireflux surgery include symptom relapse after discontinuing therapy, volume of reflux, complications

(strictures, BE), and respiratory complications.[79] In patients who continue to experience GERD symptoms despite aggressive antisecretory therapy, reconsideration of diagnosis, therapy, or both should precede surgical intervention.[11] GERD refractory to therapy, however, is rare.

There is no clear proof that surgery is superior to PPI therapies. In a 5-year study comparing omeprazole therapy vs open fundoplication, significant superiority of surgery was shown only when PPI dose escalation was considered therapy failure.[58] This study showed the lack of difference between PPI and surgery when based on symptom resolution. A recent study evaluating satisfaction with treatment among those who initially received medical or surgical therapy, found a majority who received surgery continued taking antireflux medication despite reporting satisfaction with their initial treatment (Figure 8).[60]

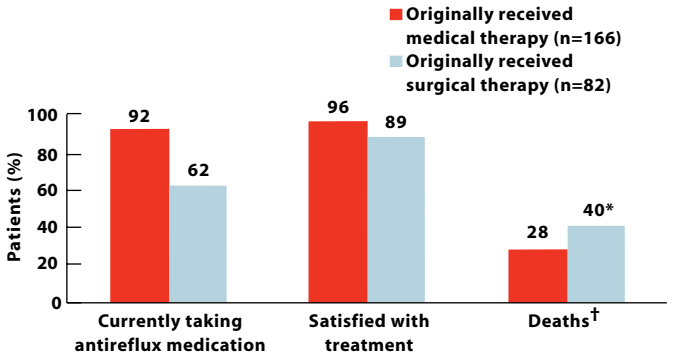

FIGURE 8.
Long-term follow-up of GERD therapy.

Adapted with permission from Spechler et al, 2001.[60]
*P=0.047.
†Deaths due to all cancers and cardiac and pulmonary diseases similar in both arms.

A review of laparoscopic fundoplication found several disturbing trends reflecting lack of clinical knowledge and risk of complications.[80] Reports of surgical outcomes are selective, originating primarily from specialized centers versus the community. Studies have found a subset of patients experience operative complications, especially dysphagia. The long-term durability of fundoplication wrap is questionable. Currently, about 5% to 10% of patients undergoing this procedure will have complications.

Patient Referral for Endoscopy, Consultation, and Surgery: Conclusions and Recommendations

Lack of data as well as conflicting results leave unresolved the question as to whether and when patients should be referred for endoscopy. It is incumbent upon specialists, therefore, to assume a more active role before endoscopy and assist in making decisions for surgery and for long-term management issues.

The question of whether the benefits of endoscopy and/or surgery outweigh the risks is one that deserves more attention. There is no evidence to support the use of routine endoscopy in patients with HB who respond to medical therapy and for whom there is no concern about other diagnoses. While it is tempting to seek information by endoscopy, only trials designed to identify the high-risk population who will benefit from endoscopic surveillance can settle these issues.

Effect of Endoscopic Therapy for GERD on the Need for Medical Therapy

Endoscopic therapies for GERD include two techniques approved by the US Food and Drug Administration (FDA): Radiofrequency energy delivery (Stretta) and endoscopic suturing. While Stretta and endoscopic suturing are FDA-approved for safety, they are not approved for efficacy.

The Stretta procedure delivers radiofrequency energy to create a lesion, the healing of which results in stenosis. Stretta also is thought to interfere with the neural mechanism of transient lower esophageal sphincter relaxations (tLESRs).

Evidence for efficacy of the Stretta procedure comes from a multicenter, prospective 12-month uncontrolled study in 118 patients with chronic HB and/or regurgitation.[81] Patients had a mean duration of symptoms of 9.5 years and 88% were currently taking PPIs. At 12 months, 94/118 patients were available for follow-up. The Stretta procedure was associated with significant improvements in HB when compared with baseline without medication. However, symptoms after the Stretta procedure were comparable to baseline symptoms with medication (Figure 9). Compared with baseline, GERD symptoms were significantly diminished after treatment, independent of medication use. Esophageal time at pH below 4 was significantly decreased at study end (P<0.05). Mental and physical findings using SF-36 showed that, compared with baseline without medication, improvements in QOL with medication at baseline and with endoscopy at 6 months were comparable. While these data suggest that Stretta results in improvements for patients with GERD, there are several important caveats. This was an uncontrolled trial, and while PPI use declined after surgery, use of H_2RAs and OTC medications was comparable after endoscopy. In addition, these results cannot be generalized to patients with esophagitis; 70% of participants were endoscopy-negative. Finally, the benefits may take as long as 6 months to accrue.

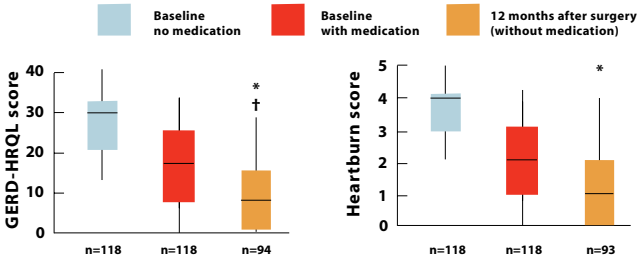

FIGURE 9.
Efficacy of the Stretta procedure in GERD symptoms 12 months after endoscopy.

*P<0.05 vs baseline off medication.
†P<0.05 vs baseline on medication.
Adapted with permission from Triadafilopoulos et al, 2002.[81]

Another pilot physiological study examined the efficacy of Stretta in 15 patients.[82] Six months after the procedure, tLESRs, time at pH below 4, and GERD symptoms were all significantly decreased compared with baseline.

Endoscopic suturing creates a plication by intraluminally suturing the distal esophagus. A multicenter trial in 64 patients randomized to two suturing methods examined manometry, endoscopy, 24-hour pH, and symptom severity before and 6 months after endoscopic plication.[83] HB severity and frequency as well as regurgitation were significantly improved (all $P<0.05$) compared with baseline off medication, but were comparable to baseline measures with medication. In comparison with baseline, the decrease in number of reflux episodes at pH below 4 was not significant at 3 months but reached significance at month 6. At 6 months after the procedure, 62% of patients were taking fewer than 4 doses per month of a medication for GERD.

In addition to the two FDA-approved procedures, at least 2 unapproved endoscopic methods are being evaluated in clinical trials. Subcutaneous injection of polymethylmethacrylate (PMMA) microspheres is used to augment thickness of the lower esophageal folds. One small prospective trial examined 10 patients with GERD refractory to medical treatment who underwent PMMA implantation.[84] Five to eleven months after implantation, 7/10 patients were taking no medication. GERD symptom score and time at pH below 4 were significantly decreased.

Enteryx is another endoscopic method in which ethylene-vinyl-alcohol is injected into the gastric cardia. In an uncontrolled pilot study in 15 patients, LES pressure, HB score, and GERD symptom score ($P<0.05$ vs baseline) all improved significantly.[85]

Endoscopic Therapy for GERD: Conclusions and Recommendations

Current evidence for endoscopic GERD procedures is limited to pilot studies and small trials lacking controls. Consequently, the clinical utility of these procedures is uncertain at this time.

Endoscopic procedures have largely been examined in patients without erosive esophagitis. It is likely that these procedures will be of little therapeutic value for management of erosive esophagitis as the central pathogenic mechanisms for this condition are dominated by acid clearance rather than reflux.

It should be stressed that these novel procedures, although approved for safety, remain investigational. No recommendations for use of endoscopic therapies currently should be made; in fact, it is important that patients are made fully aware of risks associated with unproven therapies.

The Search for Clinically Significant Differences Among Proton Pump Inhibitors

To determine the comparative clinical efficacy of PPIs, two independent literature searches were conducted to identify randomized clinical trials comparing two or more PPIs in esophagitis, or endoscopy-negative GERD. Studies published in 1985-2002 were identified using databases including MEDLINE®, EMBASE®, and others.

Evidence from randomized, controlled trials showed that PPIs were superior to placebo for relief of GERD symptoms in patients with erosive esophagitis. Standard doses of the PPIs omeprazole, lansoprazole, pantoprazole, and rabeprazole resulted in comparable rates of healing and remission in erosive esophagitis[86-92] For time-to-healing, esomeprazole (40 mg/day) was found to be superior to omeprazole (20 mg/day) or lansoprazole (30 mg/day) for healing erosive esophagitis within 8 weeks, but only in some of the comparative trials; these results were not consistently found.[89,90] Any advantage of esomeprazole over omeprazole or lansoprazole in erosive esophagitis is largely confined to Los Angeles esophagitis grades C and D.[89]

There have been several potential concerns related to the long-term use of PPIs in patients with GERD (Table 10). Little is known about long-term use of PPIs in endoscopy-negative GERD, and no trials were identified that compared PPIs in these patients. PPIs have demonstrated superiority compared with placebo or H_2RAs in endoscopy-negative patients, though symptom relief afforded by these agents was not as great as found for erosive esophagitis. There is no reason, however, to suggest that there are differences in efficacy among PPIs in endoscopy-negative patients.

Studies showed that PPI therapy may reduce serum cobalamin (B_{12}) levels. Serial measurement of B_{12} in 111 patients using a PPI for a mean of 4.5 years showed significant reduction of 30% among 68 patients treated for more than 5 years.[94] Another study in 49 patients using omeprazole for a mean of 61 months found significant reduction in B_{12} only among 15 patients with atrophic gastritis.[93]

Hypersecretion of acid has been observed following discontinuation of PPIs. Three studies revealed significant increase in basal and maximal acid output in a small number of volunteers.[97-99] Increased acid was observed for up to 8 weeks after discontinuing PPIs. While two of these studies were conducted in individuals negative for *Helicobacter pylori* infection, the third showed that acid hypersecretion was seen in previously infected individuals whose *H pylori* had been successfully eradicated. There is no evidence that the increased acid secretion observed in these studies is of clinical significance.

H pylori is associated with atrophic gastritis and an early study showed that the risk of corpus glandular atrophy was increased in those *H pylori*–infected patients taking a PPI, compared with those undergoing surgery.[95] A multicenter, randomized trial comparing PPI therapy with antireflux surgery showed atrophic gastritis prevalence was comparable in both groups. In a 3-year follow-up of 87 *H pylori*–infected patients, levels of atrophic gastritis were comparable among patients in the surgical and medical arms of the study.[96] A study of long-term PPI use found that atrophic gastritis increased with time in patients with and without *H pylori* infection, although the prevalence of atrophic gastritis was greater in the infected group.[103]

In a prospective case control study, patients treated with a PPI were randomized to PPI alone or PPI with antimicrobial therapy for eradication of *H pylori*.[100] In the persistently infected group, inflammation was found to increase in the corpus and decrease in the antrum. These data demonstrate that the distribution of *H pylori*–related gastritis changes during PPI treatment. This is of no clinical consequence.

The use of PPIs is potentially linked to an increased risk of enteric infection.[101] One case control study showed that risk of confirmed enteric infection with *Campylobacter* was significantly higher in patients who had used omeprazole in the month before infection (Odds ratio [OR]=10.0; 95% confidence interval [CI], 2.2-46). A similar association was not seen with H_2RAs (OR=1.8; 95% CI, 0.8-3.9).

Clinical Trial Comparison of PPIs: Conclusions and Recommendations

No clinical evidence exists to support differences between available PPIs for treatment of endoscopy-negative GERD. For erosive esophagitis, esomeprazole has been inconsistently found to have higher esophagitis healing rates than omeprazole and lansoprazole; the clinical significance of this is not substantiated. In the light of comparable safety and efficacy, cost may be a factor in choosing PPIs.

Long-term use of PPIs has been postulated to have potentially adverse effects, but evidence of this is insubstantial. Clinical pharmacological studies have demonstrated acid hypersecretion after discontinuation of PPI treatment, an effect not shown to be clinically significant. While an increased risk of enteric infections has been shown in a single study, lack of corroborating evidence from substantial clinical experience suggests that this observation be viewed cautiously. Tachyphylaxis to the antisecretory effect of PPIs has not been shown, although it may occur with H_2RAs.

Evidence for a Role of Gastroesophageal Reflux in Pulmonary Symptoms

It has been speculated that GERD is a risk factor for extraesophageal pulmonary complications. The relation between GERD and asthma, cough, and other pulmonary diseases is unclear. Original research and expert opinion on the causative relation of GERD with pulmonary disease is summarized here.

Causation has not been established for pulmonary extraesophageal manifestations of GERD. From the standpoint of evidence-based medicine, classic epidemiologic criteria of causation are used to evaluate published data (Table 11).

TABLE 11.

Evidence-Based Diagnostic Criteria for the Establishment of Causation

- **Temporal relation between exposure (GERD) and outcome (asthma/cough) (eg, exposure precedes outcome)**
- **Dose-response gradient**
- **Treatment or elimination of exposure decreases or eliminates outcome**
- **Association consistent from study to study**
- **Association makes biologic sense**

Epidemiologic studies show a moderate association between GERD and a range of pulmonary symptoms. A cross-sectional study of HB prevalence in 2200 participants showed that incidence of pulmonary symptoms (eg, asthma, bronchitis, pneumonia) were slightly elevated among those with frequent GERD compared with those without GERD.[104] Only bronchitis was significantly more prevalent in individuals with GERD. A case-control study including over 100,000 cases compared rates of pulmonary disease among patients with erosive esophagitis and/or esophageal stricture.[105] Increased risk for several extraesophageal conditions was significantly associated with esophagitis, including asthma (OR=1.5; 95% CI, 1.4-1.6), chronic

TABLE 10.

Possible Concerns Associated With the Use of PPIs[93-101]

	Potential Drawbacks of PPI Therapy		
Potential Concern	**Level of Evidence***	**Grade†**	**Comments**
There are no studies comparing PPIs in endoscopy-negative GERD	**3**	**D**	**There is no *a priori* reason to believe that any PPI will be superior to others in endoscopy-negative GERD**
Long-term PPI treatment may lead to reduced serum cobalamin levels	**2b**	**B**	**This is most likely to occur in individuals with atrophic gastritis**
Increased acid output has been seen after stopping a PPI	**2b**	**B**	**This is of no proven clinical significance**
The distribution of *Helicobacter pylori*–related gastritis changes during PPI treatment, with increased corpus inflammation and reduced antral inflammation	**2b**	**B**	**Effects of PPI treatment on corpus glandular atrophy in *H pylori*–infected individuals are difficult to interpret due to possible sampling error and short study duration**
PPI treatment may predispose to bacterial enteric infection	**3**	**B**	**Only shown in a single case control study**

*Level of evidence: 1, Evidence for and/or general agreement that treatment is useful and effective: 1a, Systematic review with homogeneity of RTCs; 1b, Individual RTC (with narrow confidence interval); 2, Conflicting evidence and/or divergent opinion about efficacy and use; 2a, Evidence or opinion is in favor of treatment; 2b, Use and efficacy is less well established by evidence or opinion; 3, Evidence and/or general agreement that treatment is not useful or effective and may be harmful in some cases.
†Quality grading: A, Well-designed, clinical trials; B, Well-designed cohort or case-control studies; C, Case reports, flawed trials; D, Personal clinical experience; E, Insufficient evidence to form opinion.[102]

obstructive pulmonary disease (COPD)(OR=1.2; 95% CI, 1.2-1.3), bronchiectasis (OR=1.3; 95% CI, 1.1-1.5), and pneumonia (OR=1.2; 95% CI, 1.1-1.2). An international cross-sectional study in 2661 individuals found that, compared with those without GERD, individuals with GERD had increased risk of pulmonary conditions like wheezing, nocturnal cough, and chest tightness.[110] In this study, association of GERD with physician-diagnosed asthma was marginally significant (OR=2.2; 95% CI, 1.04-4.70). A cross-sectional hospital-based prospective study found that a greater proportion of COPD patients had significant GERD symptoms, including HB/regurgitation greater than once weekly (P<0.001), chronic cough (P<0.03), and dysphagia compared with controls (P<0.02).[107]

Other studies have demonstrated that GERD is highly prevalent in patients with asthma and that asthma symptoms correlate with severity of GERD.[108,109] In addition, a study attributed chronic cough to GERD in 21% of patients with a normal chest x-ray.[110] While these studies show consistent association, they do not reveal a temporal relation of GERD and pulmonary symptoms. Furthermore, these studies show that pulmonary symptoms are frequent in the absence of GERD; therefore, GERD may be sufficient but not necessary to cause (or exacerbate) pulmonary symptoms.

Several mechanisms have been proposed to explain a potential etiologic role of GERD in pulmonary diseases (Table 12).[111-114] The vagal reflex model has purported that a vagal reflex is triggered by chemoreceptors in the trachea and esophagus, resulting in bronchospasm.[114] Evidence for this model is provided in studies showing that infusion of acid increases airway resistance and bronchospasm.[112,113] Furthermore, increased airway resistance correlates temporally with GERD symptoms and is reversed by GERD symptom treatment.[111]

TABLE 12.

Proposed GERD-Related Pathophysiologic Mechanisms Related to Pulmonary Symptoms[111-114]

Proposed Mechanism	Evidence
Vagus nerve-mediated reflex	**Esophageal acid infusion increases airway flow resistance**
	Airway resistance correlates with duration of gastroesophageal reflux
	Bronchospasms clinically detectable
Direct acid-peptide injury	**Low concentration of inhaled acid causes profound bronchoconstriction**

A second potential mechanism is that of the direct contact of refluxate resulting from micro-aspiration of refluxate. This is supported by the observation that induction of a low concentration of acid inhalation leads to profound bronchoconstriction.[111]

Medical treatment of GERD in patients with pulmonary manifestations has provided little insight into a causal relation for these two conditions. A meta-analysis of 8 randomized, placebo-controlled clinical trials found that treatment of GERD symptoms was associated with improvement in asthma symptoms and decreased asthma medication use consistently across studies (Figure 10).[115] Treatment of GERD did not, however, result in improved lung function.

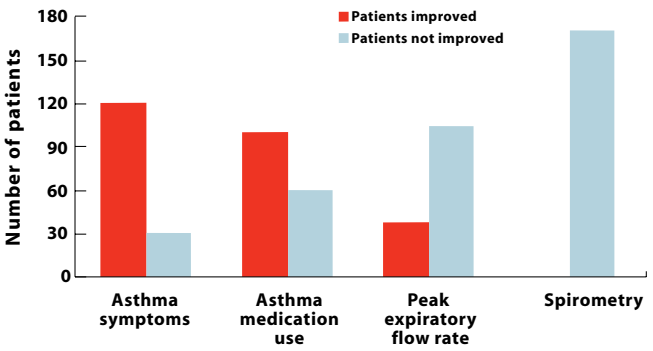

FIGURE 10.

Results of meta-analysis of medical antireflux trials.

Adapted with permission from Field et al, 1998.[115]

Effect of antireflux surgery on pulmonary symptoms has been examined in clinical studies. A retrospective analysis of patients undergoing surgery for GERD identified 39 individuals with asthma as the primary indication for surgery.[116] In these patients, postoperative improvements were seen for asthma attacks, cough, exercise tolerance, and nocturnal asthma. A study of 150 patients undergoing laparoscopic fundoplication showed that relief of atypical symptoms attributed to GERD was less predictable than relief of HB.[57] A randomized clinical trial compared antireflux surgery with medical therapy in 90 patients with pulmonary symptoms. Patients were randomized to therapy with surgery, an H_2RA, or placebo.[117] Follow-up at 6 months showed that pulmonary function improved in the H_2RA and surgery groups, but posttreatment improvement levels were not significantly different than baseline. At 6 years, the surgical group maintained clinical improvement and decreased pulmonary medication intake, while the placebo group worsened.

In another study, the rate of chronic cough before and after fundoplication in 195 patients showed that surgery significantly decreased cough prevalence (69% vs 31%; P<0.05).[54] In a systematic review of antireflux surgery reported in 24 published studies, fundoplication improved asthma symptoms and decreased medication requirements, but had little effect on pulmonary function.[118]

Several clinical studies of medical and surgical treatment for GERD suggest that patients with pulmonary symptoms experience some improvement. The majority of these studies suffer from absence of blinding, placebo control, and a lack of adequate follow-up. Most studies were conducted in small groups of patients and medical treatment was of short duration. Further, there is no gold standard for diagnosis of GERD-related pulmonary symptoms, and, therefore, inclusion and exclusion criteria may be invalid.

Clinical studies are unable to provide insight into a causative relation, if any, between GERD and pulmonary illnesses. GERD is more common in patients with pulmonary symptoms but this observation is not evidence of causation.

GERD and Extra-esophageal Symptoms: Conclusions and Recommendations

Studies demonstrate an association between GERD and pulmonary symptoms such as asthma and cough. Additionally, data show that reflux (defined by symptoms or pH measurements) is more frequent in patients with these pulmonary problems compared with controls.

There are no data to answer the question of whether or not reflux precedes onset of cough/asthma. Better-designed prospective cohort studies may provide further insight. In the absence of a "gold standard" diagnostic measure on which to base inclusion in studies, clinical trials will continue to suffer from a lack of validity.

In the light of the lack of data to support a causal relation between GERD and pulmonary illnesses, it is surprising that "GERD-associated asthma" and other similar entities appear commonly in the medical literature. As a result, PPIs are sometimes administered based on the presence of pulmonary conditions such as asthma/cough, a therapeutic approach currently *not* demonstrated by consistent clinical evidence to benefit patients.

Summary

Controversies remain across the spectrum of GERD management. The Consensus Development Panel on GERD Diagnosis and Treatment identified and investigated the most noteworthy issues facing primary physicians, pharmacists, and specialists who treat patients with GERD. The extent and quality of scientific and clinical evidence that can guide decision making in the management of GERD was determined. A pharmacist was also asked to provide input and perspective into the panel's findings. The findings on the potential benefits and limitation of treatment modalities are summarized in the "At-a-Glance Summary."

A goal of the Consensus Development Panel, is to disseminate accurate, evidence-based information that can guide rational decision making; 2 treatment algorithms are presented in Figures 11 and 12.

The data presented in this monograph represent areas where divergence exists between the implementation of therapeutic and diagnostic strategies and clinical evidence to support their safety and efficacy. The identification of these gaps in knowledge and the increased awareness of those limitations will hopefully lead to improvements in the quality of patient care. In addition, recognizing the need for information about current therapies for GERD should help to drive clinical studies designed to answer questions most relevant to diagnosis and treatment.

Appendix: The Role of the Pharmacist in the Management of GERD

This monograph reviews the evidence surrounding key issues in the treatment of GERD and its manifestations. People with reflux disease often seek the advice of pharmacists because they frequently self-treat with over-the-counter medications, and reflux may require chronic treatment with prescription drugs. Thus, pharmacists will find the information in this publication relevant and timely and it will help them appropriately counsel patients with GERD. Specific recommendations for pharmacists are provided in this appendix.

GERD is a chronic and frequently relapsing illness. Patients often need long-term treatment to prevent symptoms and achieve the goals of the therapy. Maintaining medical therapy is essential to esophageal healing and the avoidance of relapse. If adherence is poor or medications are discontinued, about 90% of patents will experience a recurrence within 6 months.[119]

The pharmacist plays a central role in the successful management of GERD by acting as a member of the therapeutic team, helping in the development, implementation, and evaluation of GERD care plans. Pharmacists can assist patients by encouraging them to record symptom frequency and intensity in a journal, and to include a record of relief of symptoms by medication. Assessment of the patients' medication schedule can help identify potential problems with adherence to complex treatment regimens. Pharmacists can recommend appropriate times to take medications and assist with alternative forms of oral dosing. Adverse effects of medication are another potential cause of noncompliance. Finally, potential drug-drug interactions should be identified.

Pharmacists are likely to be the first healthcare providers consulted by patients with GERD; this offers several opportunities to help patients with information and guidance. Education of patients about GERD causes and therapies and advice about lifestyle changes are valuable resources. Pharmacists can guide individuals in selection of an appropriate OTC medication and should screen patients to determine whether the patient requires further medical evaluation. For those with diagnosed GERD, pharmacists should be alert to recognition of alarm symptoms of GERD that suggest serious complications (Table 13).[11] Other circumstances in which pharmacists may want to refer patients to a primary care physician or specialist include extended use of OTC H_2RAs or extended PPI use outside the regular care of a physician; regularly recurring HB or HB that is severe and/or long-lasting; severe HB with NSAID use; concurrent use of H_2RAs and PPIs; individuals using higher doses of OTCs drugs for GERD than is recommended; and pregnant or nursing women with HB who are seeking OTC treatment.

TABLE 13.

Alarm Symptoms That Signal Potential GERD Complications[11]

- **Dysphagia**
- **Bleeding**
- **Weight loss**
- **Choking (acid causing coughing, shortness of breath, or hoarseness)**
- **Chest pain**

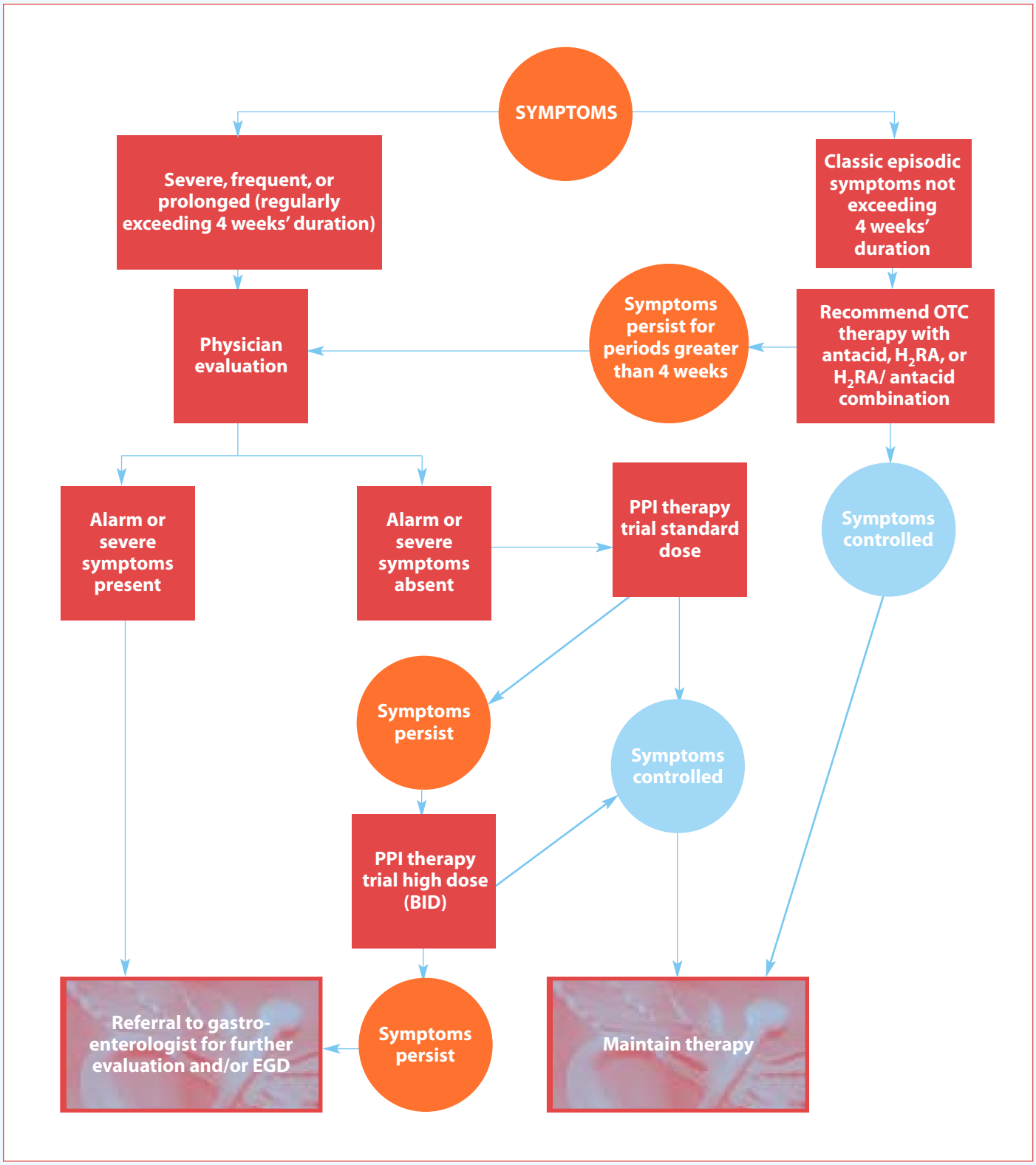

FIGURE 11.
Algorithm for the treatment of patients with GERD.

Adapted from Vivian et al, 2000[119] and Fendrick, 2001.[120,121]
GERD=gastresophageal reflux disease; OTC=over-the-counter medication; EGD=esophagogastroduodenoscopy; H_2RA=histamine-2–receptor antagonist; PPI=proton pump inhibitor.

Based on the proceedings of an AGA Consensus Development Panel.

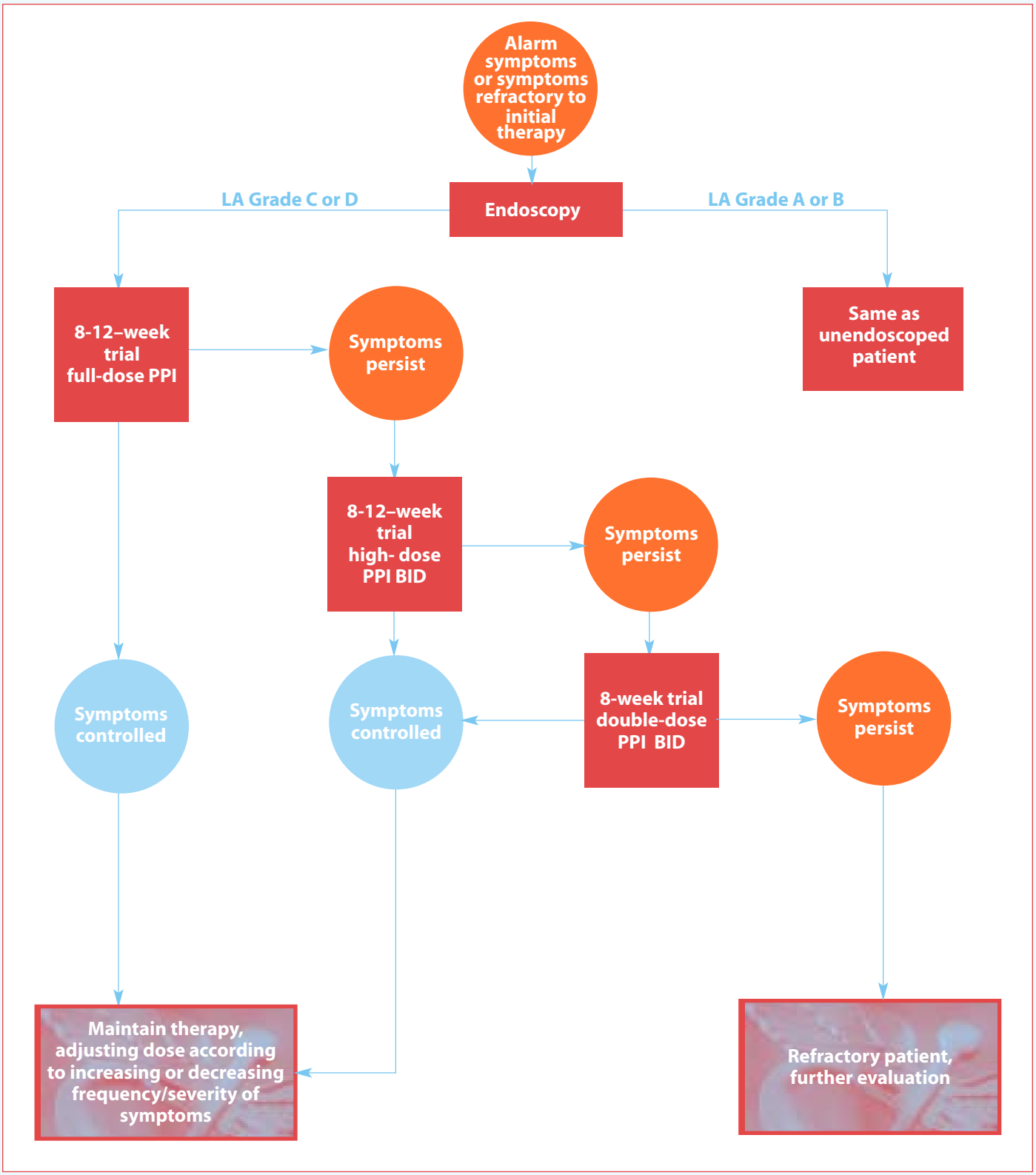

FIGURE 12.
Algorithm for the treatment of patients with GERD undergoing endoscopy.

Adapted from Kahrilas, 2000.[122]
GERD=gastroesophageal reflux disease; PPI=proton pump inhibitor.

Based on the proceedings of an AGA Consensus Development Panel.

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Posttest

Please mark your answers on the Posttest Answer Form on the following page.

1. The cardinal symptoms of GERD are

A. HB, chest pain, and acid regurgitation
B. HB, acid regurgitation, and intractable hiccups
C. HB, acid regurgitation, and dysphagia
D. HB, angina, and dysphagia

2. Which of the following statements is true about the diagnosis of GERD?

A. Bernstein's test can link reflux with erosions caused by GERD.
B. The 24-hour pH test is the "gold standard" test of GERD symptoms.
C. The barium esophagram is a sensitive test of gastric strictures.
D. Manometry will show a low resting LES in half of GERD patients.

3. The goals of GERD therapy are

A. Relieve LES pressure, heal esophagus, and prevent strictures
B. Reverse metaplasia, heal erosions, and prevent relapse/complications
C. Relieve symptoms, increase LES pressure, and prevent relapse/complications
D. Relieve symptoms, promote healing, and prevent relapse/complications

4. Which statement is most true about clinical trial evidence of antacid efficacy?

A. Clinical trials were unable to demonstrate antacid efficacy due to inappropriate end point selection.
B. Most clinical trials were underpowered to demonstrate efficacy, but larger trials proved antacids to be efficacious.
C. Antacids were only proved efficacious when compared with H_2RAs in crossover studies.
D. Clinical trials of antacids were not placebo controlled and only provide inferential evidence.

5. Which of the following statements about OTC medications is not true?

A. A combination antacid/H_2RA was more effective than either agent alone.
B. Randomized clinical trials of OTC agents examined only short-term treatment (4-6 weeks).
C. Randomized trials showed OTC medications are effective for erosive esophagitis.
D. Double-blind OTC trials showed symptom relief with placebo was usually around 10%-20%.

6. Which statement about the epidemiology of Barrett's esophagus is *not* true?

A. Patients with BE who lack evidence of dysplasia should have an endoscopy every 3-5 years.
B. Pregnant women have the highest incidence of BE, but the greatest prevalence is among white males.
C. Studies show that an increased extent of metaplasia is associated with a higher risk of adenocarcinoma.
D. The incidence of adenocarcinoma in patients with BE is probably closer to approximately 0.4%, rather than the previously thought 1% to 2%.

7. Which of the following is most true about clinical evidence from fundoplication outcomes studies?

A. The data indicate that approximately 40% of patients undergoing surgery will need no further therapy.
B. The morbidity and mortality of surgery are known from community-based outcomes trials.
C. The risk of surgery is less than that of long-term medical therapy.
D. Side effects of surgery are minor and do not affect the quality of life.

8. Which of the following is most true about the role of endoscopy in the management of GERD?

A. Endoscopy is important to rule out deep erosions, a common complication in the community setting.
B. For most patients with GERD, a trial of medical therapy should precede endoscopy.
C. Endoscopy grade correlates inversely with relapse potential of patients taking a PPI.
D. Annual screening by endoscopy should focus on all patients, not just those at high risk for adenocarcinoma.

9. What conclusions did the Consensus Panel reach about endoscopic therapies?

A. There is insufficient evidence to support their use at this time.
B. Stretta should be recommended for patients who cannot have surgery.
C. Physicians should only recommend FDA-approved procedures.
D. Endoscopic therapy is only for patients who fail medical therapy.

10. Which of the following best characterizes the clinical trial data on comparative efficacy of PPIs?

A. PPIs have comparable efficacy; rabeprazole is more tolerable in some studies.
B. PPIs have comparable efficacy in endoscopy-negative patients.
C. PPIs have comparable efficacy; lansoprazole is superior in time-to-healing.
D. PPIs have comparable efficacy in patients with erosive esophagitis.

11. Which of the following best characterizes risk associated with long-term use of PPIs?

A. There is little evidence of clinically meaningful long-term adverse outcomes from PPI use.
B. Patients with *H pylori* infections may develop rebound acid hypersecretion.
C. There is a risk of developing enteric infections in those with gastric atrophy.
D. There is clinical trial evidence that reduced levels of serum pyridoxine results from PPI use.

12. Which of the following best characterizes treatment of GERD in patients with pulmonary manifestations?

A. Medical treatment of GERD symptoms provides asthma relief but does not affect chronic cough.
B. Medical treatment of GERD improves pulmonary symptoms but does not improve pulmonary function.
C. Both medical and surgical treatment result in long-term improvement of pulmonary symptoms of GERD.
D. Only patients whose pulmonary symptoms are caused by GERD improve with therapy.

13. Which of the following best characterizes a patient with HB that a pharmacist should refer to a physician for further medical evaluation?

A. 50-year-old man who awakes at night with HB, coughing, and choking
B. 20-year-old student complaining of indigestion after eating pizza
C. 40-year-old woman who has HB once a month
D. 35-year-old man taking OTC H_2RAs for 1 week

14. What are the alarm symptoms of GERD that may signal potentially serious conditions?

A. Cough, dyspepsia, hemoptysis, weight loss
B. Dysphagia, night sweats, diarrhea, weight loss
C. Dysphagia, bleeding, choking, weight loss
D. Dyspnea, chest pain, tinnitus, weight loss

Posttest Answer Form

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To receive 3 hours of continuing medical education credit, participants must complete the Posttest Answer Form and Evaluation Form after reading the monograph. Please **mail** the completed CME Posttest Answer Form and this Evaluation Form, with a $15 processing fee (please make checks payable to AGA), to the attention of:

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Posttest Answers

Circle the letter that corresponds to the correct answer for each question.

1.	A	B	C	D	8.	A	B	C	D
2.	A	B	C	D	9.	A	B	C	D
3.	A	B	C	D	10.	A	B	C	D
4.	A	B	C	D	11.	A	B	C	D
5.	A	B	C	D	12.	A	B	C	D
6.	A	B	C	D	13.	A	B	C	D
7.	A	B	C	D	14.	A	B	C	D

You must complete the Evaluation Form on the back of this page.

Evaluation Form

I. Using the following scale, please indicate how well the Learning Objectives were met:
1 = Not at all 2 = Partially 3 = To a large degree 4 = Completely

After reviewing the *Improving the Management of GERD: Evidence-Based Therapeutic Strategies* monograph, I am able to

1. Define the pathophysiology of GERD, its burden of illness, and the goals of therapy.	1	2	3	4	
2. Assess clinical trial evidence supporting medical and surgical treatment modalities for GERD.	1	2	3	4	
3. Discuss sequelae of GERD and Barrett's esophagus.	1	2	3	4	
4. Describe and evaluate the evidence for the role of gastroesophageal reflux in pulmonary disorders.	1	2	3	4	
5. Evaluate and describe the evidence for the effectiveness of over-the-counter medications in the management of acid reflux and GERD.	1	2	3	4	
6. Outline the risks and benefits associated with use of proton pump inhibitors.	1	2	3	4	
7. Differentiate the basis for referral of GERD patients for consultation, endoscopy, or surgery.	1	2	3	4	
8. Discuss the role of endoscopy and fundoplication in management of GERD.	1	2	3	4	
9. Formulate treatment approaches for acid reflux and GERD that incorporate the safest, most effective, and when possible, the most cost-effective modalities.	1	2	3	4	

II. Circle the number that reflects your opinion of the effectiveness of the monograph.

	Strongly disagree to Strongly agree				
1. The material was presented in clear and forthright language.	1	2	3	4	5
2. The content was current.	1	2	3	4	5
3. The content was relevant to the learner's needs.	1	2	3	4	5
4. There was no perceived commercial bias, or the obvious appearance of skewed material which has been influenced by commercial support.	1	2	3	4	5

5. If you disagree with statement # 4, please explain why:

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	Least valuable to Most valuable				
Monograph	1	2	3	4	5
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Workshop	1	2	3	4	5
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2. How valuable would the following be for receiving CME credit:

CME on the Internet	1	2	3	4	5
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☐ National Meeting ☐ Grand Rounds Presentation ☐ By Request ☐ Mail

IV. Personal Information: To help the CME Committee interpret your answers, please supply this personal information:

1. In which city/state/county do you practice? _____

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4. What is your age:
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5. Is your primary practice arrangement (please mark 1 response):
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Thank you for your evaluation. This information will be used to plan future AGA educational offerings.

At-a-Glance Summary

Findings of the Consensus Development Panel for each area examined

Evidence for Efficacy of Over-the-counter Medications for GERD in Patients With Mild-to-Moderate Symptoms

- Randomized clinical trials' evidence for over-the-counter (OTC) medications (antacids, H_2RAs, combination alginate/antacid, combination antacid/H_2RA) demonstrate their effectiveness in patients with mild-to-moderate GERD in prevention of symptoms, providing rapid pain relief, and reduction of symptom frequency and severity
- Evidence for some agents (antacids alone) is primarily from small studies while evidence for other agents (H_2RAs and antacid/H_2RAs) comes from large, well-designed clinical trials. The FACT Trial had a large antacid monotherapy arm
- OTCs can be used for "breakthrough" GERD symptoms concurrent with H_2RA or PPI therapy, but clinical trial data on this use are not available
- Evidence is lacking for a role of OTC medications in erosive esophagitis
- Combination H_2RA/antacid is better at symptom relief than its constituent components used alone

Risk of Adenocarcinoma in Patients With Barrett's Esophagus

- The incidence of adenocarcinoma in patients with BE is probably closer to 0.5% per year, rather than the previously thought 1% to 2% per year
- While almost all esophageal adenocarcinomas occur in patients with BE, most patients with BE will never develop this tumor
- Most patients with Barrett's metaplasia who develop cancer present for the first time with both findings
- Surveillance guidelines should be modified to reflect up-to-date evidence on cancer risk

Effect of Surgical Fundoplication on the Need for Medical Therapy and the Risk of Esophageal Adenocarcinoma

- The best data indicate that only 40% of patients have complete, long-term HB relief after surgery
- Overall, 20% to 30% of patients resume medical therapy 1-3 years after antireflux surgery
- Guidelines for the use of surgery and reports of morbidity and mortality outcomes are based on studies that do not meet accepted standards for clinical evidence
- Side effects (eg, late dysphagia, lowered QOL) of antireflux surgery are more serious and widespread than currently believed
- Surgery does not prevent esophageal cancer
- Risk of morbidity and mortality of surgery probably outweighs the risk of developing esophageal cancer in GERD

Referral for Endoscopy, Consultation, and Antireflux Surgery

- There is a need for GI specialists to play an active role in decision making for antireflux surgery and long-term management issues in GERD
- Clinical evidence does not support the use of screening endoscopy in patients with HB that respond to medical therapy and for whom there is no concern about other diagnoses

Effect of Endoscopic Therapy for GERD on the Need for Medical Therapy

- Current endoscopic/intraluminal therapeutic procedures are approved for safety, not efficacy
- There is currently no adequate randomized clinical trial evidence to support endoscopic/intraluminal therapies
- The public and physicians should be educated about the risk and limitations of endoscopic/intraluminal procedures

The Search for Clinically Significant Differences Among Proton Pump Inhibitors

- Standard doses of lansoprazole, omeprazole, pantoprazole, and rabeprazole produce comparable rates of healing and remission in patients with erosive esophagitis
- Esomeprazole (40 mg) is slightly more effective than other PPIs in relieving heartburn and healing erosive esophagitis
- For endoscopy-negative GERD, randomized clinical trial evidence shows that PPIs are superior to placebo in symptom relief
- PPIs are less efficacious in providing symptom relief in the setting of erosive esophagitis than in endoscopy negative GERD
- No clinical trial evidence supports the existence of long-term negative side effects of PPIs

Evidence for a Role of Gastroesophageal Reflux in Pulmonary Symptoms

- Epidemiological studies consistently demonstrate modest but significant associations, though no causal relationships, between pulmonary manifestations and GERD
- Classic reflux symptoms, chest pain, and other ENT complications are absent in the majority of patients with pulmonary manifestations
- Randomized clinical trials provide evidence of symptom improvement with GERD therapy; lung function tests, however, do not improve

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