AGA INSTITUTE

American Gastroenterological Association Medical Position Statement on the Management of Gastroesophageal Reflux Disease

The American Gastroenterological Association (AGA) Institute Medical Position Panel consisted of the authors of the technical review, a community-based gastroenterologist (Stephen W. Hiltz, MD, MBA, AGAF), an insurance provider representative (Edgar Black, MD, Medical Director, Policy Resources Technology Evaluation Center, BlueCross BlueShield Association), a general surgeon (Irvin M. Modlin, MD), a patient advocate (Gregory Lane), a primary care physician (Steve P. Johnson, MD), a gastroenterologist with expertise in health services research (Philip S. Schoenfeld, MD), the Chair of the AGA Institute Clinical Practice and Quality Management Committee (John Allen, MD, MBA, AGAF), and the Chair of the AGA Institute Practice Management and Economics Committee and the AGA Institute CPT Advisor (Joel V. Brill, MD, AGAF).

In the development of this medical position statement, 12 broad questions pertinent to diagnostic and management strategies for patients with gastroesophageal reflux disease (GERD) were developed by interaction among the authors of the technical review,[1] representatives from the American Gastroenterological Association (AGA) Institute Council, and the AGA Institute Clinical Practice and Quality Management Committee. The questions were designed to encapsulate the major management issues encountered in patients with GERD in current clinical practice. The issue of management of Barrett's esophagus was intentionally excluded, because this will be the focus of a subsequent medical position statement. For each question, a comprehensive literature search was conducted, pertinent evidence reviewed, and the quality of relevant data evaluated. The details of development methodology, literature search methodology, and literature search yield associated with each of the questions are available on the AGA Institute Web site as a separate document.[2] The resultant conclusions were based on the best available evidence or, in the absence of quality evidence, expert opinion. The strength of these conclusions was weighed using US Preventive Services Task Force (USPSTF) grades. Of note, none of the formulated practice recommendations were judged to be sufficiently unequivocal to be proposed as performance measures for gauging quality of care.

Diagnosis and Initial Therapy

1. What Is an Operational Definition of GERD? What Is the Distinction Between GERD and Episodic Heartburn?

There can be no criterion standard definition of GERD because the threshold distinction between physiologic reflux and reflux disease is ultimately arbitrary. Hence, these questions can only be answered by opinion (USPSTF grade not applicable). Fortuitously, a recent consensus in defining GERD (the Montreal consensus) emanated from a panel of world experts. The Montreal definition was adopted in the technical review as a suitable framework upon which to build management recommendations. The Montreal consensus defined GERD as "a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications." Symptoms are "troublesome" if they adversely affect an individual's well-being. Esophageal GERD syndromes are categorized as those that are symptom based and those that are defined by tissue injury, while the extraesophageal syndromes are classified as of established or proposed association with GERD, acknowledging that while the evidence on hand is sufficient to link these syndromes to reflux, it is insufficient to establish causation.

A distinguishing feature of the Montreal definition is that it does not use the term "nonerosive reflux disease" but rather subdivides esophageal syndromes into symptomatic syndromes and syndromes with esophageal injury. Hence, functional heartburn does not fit the Montreal definition of GERD, whereas it is included under the umbrella of nonerosive reflux disease. The distinction between GERD and episodic heartburn in the Montreal definition is in the word "troublesome." In the absence of esophageal injury, heartburn symptoms of insufficient frequency or severity to be perceived as troublesome by the patient (after assurance of their benign nature) do not meet the Montreal definition of a symptomatic esophageal GERD syndrome.

2. What Is the Efficacy of Lifestyle Modifications for GERD? Which Elements Should Be Recommended and in Which Circumstances?

Grade B: recommended with fair evidence that it improves important outcomes

I. Weight loss should be advised for overweight or obese patients with esophageal GERD syndromes.

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II. Elevation of the head of the bed for selected patients who are troubled with heartburn or regurgitation when recumbent. Other lifestyle modifications including, but not limited to, avoiding late meals, avoiding specific foods, or avoiding specific activities should be tailored to the circumstances of the individual patient.

Grade Insuff: no recommendation, insufficient evidence to recommend for or against

I. Broadly advocating lifestyle changes for all (as opposed to selected) patients with GERD.

Broadly speaking, lifestyle modifications recommended for GERD fall into 3 categories: (1) avoidance of foods that may precipitate reflux (eg, coffee, alcohol, chocolate, fatty foods), (2) avoidance of acidic foods that may precipitate heartburn (eg, citrus, carbonated drinks, spicy foods), and (3) adoption of behaviors that may reduce esophageal acid exposure (weight loss, smoking cessation, raising the head of the bed, and avoiding recumbency for 2–3 hours after meals). The problem with these is that there are simply too many recommendations and each is too narrowly applicable to enforce the whole set on every patient. However, it is also clear that there are subsets of patients who may benefit from specific lifestyle modifications, and it is good practice to make those recommendations to those patients based on their specific history. A patient with symptoms of nighttime heartburn or regurgitation of sufficient severity to disturb his or her sleep despite acid suppressive therapy may benefit from elevation of the head of the bed. Similarly, a patient who consistently experiences troublesome heartburn after ingestion of alcohol, coffee, or spicy foods will benefit from avoidance of these. Finally, if a patient is overweight or obese, it is reasonable to suggest weight loss as an intervention that may prevent, or at least postpone, the need for acid suppression.

3. How Do Antisecretory Therapies Compare in Efficacy and Under What Circumstances Might One Be Preferable to Another? What Is an Acceptable Upper Limit of Empirical Therapy in Patients With Suspected Typical Esophageal GERD Syndromes Before Performing Esophagogastroduodenoscopy?

Grade A: strongly recommended based on good evidence that it improves important health outcomes

I. Antisecretory drugs for the treatment of patients with esophageal GERD syndromes (healing esophagitis and symptomatic relief). In these uses, proton pump inhibitors (PPIs) are more effective than histamine$_2$ receptor antagonists (H_2RAs), which are more effective than placebo.

Grade B: recommended with fair evidence that it improves important outcomes

I. Twice-daily PPI therapy for patients with an esophageal syndrome with an inadequate symptom response to once-daily PPI therapy.

II. A short course or as-needed use of antisecretory drugs in patients with a symptomatic esophageal syndrome without esophagitis when symptom control is the primary objective. For a short course of therapy, PPIs are more effective than H_2RAs, which are more effective than placebo.

Grade D: recommend against, fair evidence that it is ineffective or harms outweigh benefits

I. Metoclopramide as monotherapy or adjunctive therapy in patients with esophageal or suspected extraesophageal GERD syndromes.

The current consensus is that empirical therapy is appropriate initial management for patients with uncomplicated heartburn. Abundant data support treating patients with esophageal GERD syndromes with antisecretory drugs, and there is ample evidence that, as a drug class, PPIs are more effective in these patients than are H_2RAs, which are in turn more effective than placebo. However, the data supporting the use of PPIs (or H_2RAs) in doses higher than the standard are weak. Similarly, there is no evidence of improved efficacy by adding a nocturnal dose of an H_2RA to twice-daily PPI therapy. A notable disconnect between clinical trial data and clinical practice is in the use of PPIs twice daily. Almost all efficacy data on these medications are from once-daily dosing studies, even though the pharmacodynamics of the drugs logically supports twice-daily dosing. Hence, guidance on this issue comes primarily from expert opinion, which is essentially unanimous in recommending twice-daily dosing of PPIs to improve symptom relief in patients with an esophageal GERD syndrome with an unsatisfactory response to once-daily dosing. Patients whose heartburn has not adequately responded to twice-daily PPI therapy should be considered treatment failures, making that a reasonable upper limit for empirical therapy.

Circumstances in which one antisecretory drug might be preferable to another primarily relate to side effects or when the onset of effect is a prime consideration. The most common side effects of PPIs are headache, diarrhea, constipation, and abdominal pain. Switching among alternative PPI drugs or to a lower dose can usually circumvent these side effects. As for the issue of onset of action, this primarily pertains to on-demand therapy. If a patient intends to take a drug only in response to symptoms, then it should be a rapidly acting drug. The most rapidly acting agents are antacids, the efficacy of which can be sustained by combining them with an H_2RA or a PPI.

4. What Is the Role and Priority of Diagnostic Tests (Endoscopy With or Without Biopsy, Esophageal Manometry, Ambulatory pH Monitoring, Impedance-pH Monitoring) in the Evaluation of Patients With Suspected Esophageal GERD Syndromes?

Grade B: recommended with fair evidence that it improves important outcomes

I. Endoscopy with biopsy for patients with an esophageal GERD syndrome with troublesome dysphagia. Biopsies should target any areas of suspected metaplasia, dysplasia, or in the absence of visual abnormalities, normal mucosa (at least 5 samples to evaluate for eosinophilic esophagitis).
II. Endoscopy to evaluate patients with a suspected esophageal GERD syndrome who have not responded to an empirical trial of twice-daily PPI therapy. Biopsies should target any area of suspected metaplasia, dysplasia, or malignancy.
III. Manometry to evaluate patients with a suspected esophageal GERD syndrome who have not responded to an empirical trial of twice-daily PPI therapy and have normal findings on endoscopy. Manometry will serve to localize the lower esophageal sphincter for potential subsequent pH monitoring, to evaluate peristaltic function preoperatively, and to diagnose subtle presentations of the major motor disorders. Evolving information suggests that high-resolution manometry has superior sensitivity to conventional manometry in recognizing atypical cases of achalasia and distal esophageal spasm.
IV. Ambulatory impedance-pH, catheter pH, or wireless pH monitoring (PPI therapy withheld for 7 days) to evaluate patients with a suspected esophageal GERD syndrome who have not responded to an empirical trial of PPI therapy, have normal findings on endoscopy, and have no major abnormality on manometry. Wireless pH monitoring has superior sensitivity to catheter studies for detecting pathological esophageal acid exposure because of the extended period of recording (48 hours) and has also shown superior recording accuracy compared with some catheter designs.

Grade Insuff: no recommendation, insufficient evidence to recommend for or against

I. Using alarm symptoms (other than troublesome dysphagia) as a screening tool to identify patients with GERD at risk for esophageal adenocarcinoma.
II. Combined impedance-pH, catheter pH, or wireless pH monitoring studies to distinguish hypersensitivity syndromes from functional syndromes, the distinction being that in hypersensitivity syndromes symptoms are attributable to reflux events, whereas in functional syndromes they are not.
III. Combined impedance-pH, catheter pH, or wireless pH esophageal monitoring studies performed while taking PPIs.

Diagnostic testing for esophageal GERD syndromes is invoked in 3 broad scenarios: (1) to avert misdiagnosis, (2) to identify complications of reflux disease, and (3) in the evaluation of empirical treatment failures. The discussion of misdiagnosis and identifying complications of reflux disease usually revolves around the concept of "alarm features" that are suggestive of an alternative diagnosis. Important alternative diagnoses include coronary artery disease, gallbladder disease, gastric or esophageal malignancy, peptic ulcer disease, and eosinophilic, infectious, or caustic esophagitis. High-quality evidence supporting the broad utility of alarm features as a diagnostic tool is quite limited. However, individual alarm features with the best performance for identifying esophageal or gastric malignancies are weight loss, dysphagia, and epigastric mass on examination, making it appropriate to evaluate these with endoscopy. A caveat in the endoscopic evaluation of dysphagia is that the endoscopist should have a low threshold for obtaining multiple (preferably at least 5) esophageal mucosal biopsy specimens to evaluate for eosinophilic esophagitis.

The other broad scenario under which diagnostic testing is performed is in the evaluation of troublesome symptoms that have not adequately responded to empirical twice-daily PPI therapy. Did therapy fail because of troublesome symptoms attributable to reflux that did not resolve with PPI therapy or because the symptoms under consideration are not attributable to reflux? Endoscopy is again the first diagnostic test to consider because it may demonstrate Barrett's metaplasia, stricture, or an alternative upper gastrointestinal diagnosis. After a normal endoscopy, priority should be given to identifying conditions for which an effective alternative therapy exists. In the case of GERD, the only alternative, potentially more effective, therapy is antireflux surgery. High-quality evidence on the efficacy of antireflux surgery exists only for esophagitis and/or excessive distal esophageal acid exposure when PPI therapy is withheld. Another requirement for antireflux surgery is that some peristaltic function be preserved. Finally, it is important to identify alternative diagnoses that may masquerade as GERD: functional heartburn, atypical cases of achalasia, or distal esophageal spasm. Given these priorities, the second diagnostic evaluation should be esophageal manometry and the third should then be to ascertain whether or not there is excessive esophageal acid exposure when PPI therapy is withheld. Whether this examination should be performed with the patient on acid suppressive therapy is debated. The unclear relevance of "normative" data for impedance-pH studies performed on PPI therapy makes it difficult to interpret such studies. If normal values are not adjusted, then such an on-PPI study could show an unequivocal PPI nonresponse. That, however, rarely occurs. At this point in the diagnostic algorithm, troublesome symptoms of heartburn, chest pain, regurgitation, or dysphagia persist despite normal findings on endoscopy (including mucosal biopsy in the case of dysphagia), normal esophageal acid exposure, and a manometry study that ruled out a

major motor disorder. Current thinking is that the major remaining possibilities are a hypersensitivity syndrome or a functional syndrome, the distinction being that in the case of a hypersensitivity syndrome symptoms are attributable to reflux events, whereas in the case of a functional syndrome they are not. This is a subtle distinction and a domain in which there is currently no high-quality evidence supporting one management approach or another.

5. What Are the Unique Management Considerations in Patients With Suspected Reflux Chest Pain Syndrome?

Grade A: strongly recommended based on good evidence that it improves important health outcomes

I. Twice-daily PPI therapy as an empirical trial for patients with suspected reflux chest pain syndrome after a cardiac etiology has been carefully considered.

Chest pain indistinguishable from ischemic cardiac pain can be caused by GERD. Because the morbidity and mortality associated with ischemic heart disease is substantially greater than that of GERD and because of the impressive array of available therapeutic interventions, this diagnosis must be thoroughly considered before accepting a diagnosis of reflux chest pain syndrome. Once ischemic heart disease has been adequately considered, the relative rarity of esophageal motor disorders in this group of patients, as well as results from empirical treatment trials of acid suppressive therapy, suggest that GERD may be the next most likely etiology. Meta-analyses of placebo-controlled treatment trials in patients with suspected reflux chest pain suggest benefit from a 4-week trial with twice-daily PPI therapy. If a patient continues to have chest pain despite this course of therapy, diagnostic testing with esophageal manometry and pH or impedance-pH monitoring can exclude motility disorders or refractory reflux symptoms.

6. What Is the Best Initial Management for Patients With Suspected Extraesophageal Reflux Syndromes (Asthma, Laryngitis, Cough)? What Are the Unique Management Considerations With Each? What Is the Appropriate Dose and Course of Antisecretory Therapy in Each?

Grade B: recommended with fair evidence that it improves important outcomes

I. Acute or maintenance therapy with once- or twice-daily PPIs (or H_2RAs) for patients with a suspected extraesophageal GERD syndrome (laryngitis, asthma) with a concomitant esophageal GERD syndrome.

Grade D: recommend against, fair evidence that it is ineffective or harms outweigh benefits

I. Once- or twice-daily PPIs (or H_2RAs) for acute treatment of patients with potential extraesophageal GERD syndromes (laryngitis, asthma) in the absence of a concomitant esophageal GERD syndrome.

Grade Insuff: no recommendation, insufficient evidence to recommend for or against

I. Once- or twice-daily PPIs for patients with suspected reflux cough syndrome.

Chronic cough, laryngitis, and asthma have an established association with GERD on the basis of population-based studies. However, cough, laryngitis, and asthma have a multitude of potential etiologies other than GERD, making them nonspecific for GERD. Furthermore, the causal relationship of GERD with these nonspecific syndromes in the absence of a concomitant esophageal GERD syndrome remains controversial and unproven. The only randomized controlled trials showing a treatment effect for GERD therapies in these syndromes were in patients with esophageal GERD syndromes in addition to either laryngitis or asthma. Hence, existing evidence supports the following: (1) the association between these syndromes and GERD, (2) the rarity of extraesophageal GERD syndromes without concomitant esophageal symptoms or findings, (3) that suspected extraesophageal GERD syndromes are usually multifactorial, and (4) that data substantiating benefit from the treatment of reflux for the extraesophageal syndromes are very weak. Furthermore, clinical predictors implicating GERD in the extraesophageal syndromes have proven elusive, and the premature adoption of flawed diagnostic criteria has likely resulted in the overdiagnosis of extraesophageal GERD syndromes.

Given the nonspecific nature of the extraesophageal symptoms and the poor sensitivity and specificity of diagnostic tests such as pH monitoring, laryngoscopy, or endoscopy for establishing an etiology of GERD, empirical therapy with PPIs has become common practice. Most therapeutic trials of these syndromes have used twice-daily dosing of PPIs for treatment periods of 3–4 months. The rationale for this unapproved dosing for unapproved indications comes from pH monitoring data showing that the likelihood of normalizing esophageal acid exposure with twice-daily PPIs in patients with GERD is 93%–99%, the logic then being that lesser dosing does not exclude the possibility of a poor response because of inadequate acid suppression. Having said that, there are no controlled studies investigating the optimal dosage or duration of PPI therapy in patients with extraesophageal GERD syndromes. The only supportive data for twice-daily PPI dosing are uncontrolled open-

label studies of suspected reflux laryngitis or asthma. Furthermore, despite widespread treatment with PPIs twice daily, high-quality evidence supporting treatment efficacy in these syndromes is scant.

In summary, patients with suspected extraesophageal GERD syndromes may have GERD as a contributing etiology but rarely as the sole cause. However, the increasing incrimination of GERD as an etiologic factor along with the lack of accurate confirmatory diagnostic tests has resulted in widespread overdiagnosis and overtreatment of these conditions. Nonetheless, empirical therapy with twice-daily PPIs for 2 months remains a pragmatic clinical strategy for subsets of these patients if they have a concomitant esophageal GERD syndrome. Failing such a trial, etiologies other than GERD should be explored.

Chronic Management

7. Does GERD Progress in Severity, Such That Symptomatic Patients Without Esophagitis Develop Esophagitis and Barrett's Metaplasia, or Are These Distinct Disease Manifestations That Do Not Exist Along a Continuum? If Patients Do Progress, at What Rate Does This Occur, and Does It Warrant Endoscopic Monitoring?

Grade D: recommend against, fair evidence that it is ineffective or harms outweigh benefits

I. Routine endoscopy in subjects with erosive or nonerosive reflux disease to assess for disease progression.

Two potential paradigms for viewing the natural history of GERD exist. In the first, GERD is viewed as a progressive disease such that, in the absence of effective intervention, today's patient with nonerosive disease becomes tomorrow's patient with erosive disease, who then becomes a candidate for the development of Barrett's esophagus. This "spectrum of disease" approach has been contrasted with the view that GERD may be a disease with phenotypically discreet "categories," such as nonerosive disease, erosive esophagitis, and Barrett's esophagus. In this phenotypically preordained view, conversion from one disease manifestation to another is distinctly unusual, and subjects generally stay in their initial category. Available, albeit limited, data suggest that while subjects with GERD may sometimes progress from nonerosive disease to erosive esophagitis (making it not a strictly categorical disease), the reported rates of progression are relatively low over a 20-year period. In patients in whom stricture, Barrett's metaplasia, and adenocarcinoma were excluded in the setting of a healed mucosa at index endoscopy, the likelihood of these developing within a 7-year follow-up period is on the order of 1.9%, 0.0%, and 0.1%, respectively. On the other hand, the likelihood of developing Barrett's esophagus (or unmasking prevalent disease) with healing of Los Angeles C or D esophagitis is about 6%. Most importantly, endoscopically monitoring patients with chronic GERD symptoms has not been shown to diminish the risk of cancer, and this practice is discouraged.

8. What Maintenance Therapy Is Indicated for Patients With the Typical Esophageal Reflux Syndrome (With or Without Esophagitis)? When and How Should Antisecretory Therapy Be Decreased or Discontinued? What, If Any, Risks Are Associated With This?

Grade A: strongly recommended based on good evidence that it improves important health outcomes

I. Long-term use of PPIs for the treatment of patients with esophagitis once they have proven clinically effective. Long-term therapy should be titrated down to the lowest effective dose based on symptom control.

Grade D: recommend against, fair evidence that it is ineffective or harms outweigh benefits

I. Less than daily dosing of PPI therapy as maintenance therapy in patients with an esophageal syndrome who previously had erosive esophagitis.

The utility of maintenance therapy in patients with GERD depends on the manifestation of the disease being monitored, with the strongest data pertaining to erosive esophagitis. Subjects not maintained on continuous acid suppressive therapy have high rates of recurrence of erosive disease. Several randomized controlled trials have shown that the recurrence of erosive esophagitis in subjects with GERD is dramatically decreased by daily PPI treatment. Similarly strong are randomized controlled trials between H_2RAs and either healing-dose or maintenance-dose (usually half) PPIs, with subjects randomized to H_2RAs up to twice as likely to have recurrent esophagitis. The role of daily maintenance therapy in nonerosive disease is less clear. Patients with esophageal GERD syndrome without esophagitis who initially responded to PPI therapy are less likely to have recurrent symptoms when randomized to continuing PPI therapy than to H_2RAs or placebo. Whether PPI dosing needs to be continuous as opposed to "on demand" has also been studied, and patients with uninvestigated GERD or patients with an esophageal GERD syndrome without esophagitis did well with on-demand regimens. On balance, the data suggest that on-demand therapy is a reasonable strategy in patients with an esophageal GERD syndrome without esophagitis, where symptom control is the primary objective. In contrast, in those with a known history of erosive esophagitis who are healed with continuous PPI therapy and then randomized to either continuous or on-demand therapy, the recurrence rates of erosive disease

are high with on-demand compared with continuous therapy, and on-demand therapy cannot be recommended.

The previously described evidence makes it easy to say that continuous PPI therapy is recommended to maintain a healed mucosa and that discontinuing therapy will likely result in recurrent heartburn. However, there are no high-quality data to suggest that continuous antisecretory therapy alters the natural history of reflux disease other than to reduce the (already low) incidence of peptic stricture. There are also no data to the effect that intermittent esophageal erosions or some degree of residual symptomatology is harmful. Hence, the main identifiable risk associated with reducing or discontinuing PPI therapy is an increased symptom burden. It follows that the decision regarding the need for (and dosage of) maintenance therapy is driven by the impact of those residual symptoms on the patient's quality of life rather than as a disease control measure. Pragmatically, this means that many subjects beginning PPI therapy will receive this therapy chronically, but often intermittently.

In summary, chronic PPI therapy will be required for adequate symptom control in the majority of subjects with GERD symptoms severe enough to warrant initial PPI therapy. While many subjects may tolerate dose reduction of their PPI and maintain adequate symptom control, the likelihood of long-term spontaneous remission of disease is low. Beyond recurrence of symptoms and/or erosive disease, the risks associated with cessation of therapy, including the possible development of Barrett's esophagus, appear minimal.

9. What Maintenance Therapy Is Indicated for Patients With Suspected Extraesophageal Reflux Syndromes (Asthma, Laryngitis, Cough)? When and How Should Antisecretory Therapy Be Decreased or Discontinued?

Grade B: recommended with fair evidence that it improves important outcomes

I. Acute or maintenance therapy with once- or twice-daily PPIs (or H_2RAs) for patients with a suspected extraesophageal GERD syndrome (laryngitis, asthma) with a concomitant esophageal GERD syndrome.

Grade Insuff: no recommendation, insufficient evidence to recommend for or against

I. Maintenance therapy with once- or twice-daily PPIs (or H_2RAs) for patients with potential extraesophageal GERD syndromes (laryngitis, asthma) in the absence of a concomitant esophageal GERD syndrome.
II. Once- or twice-daily PPIs for patients with suspected reflux cough syndrome.

Owing to the nonspecificity of the extraesophageal reflux syndromes for GERD, many patients will have persistent symptoms after 8 weeks of empirical PPI therapy. The need for continued PPI therapy in this group is predicated on the presence and severity of concomitant esophageal syndromes with or without mucosal injury. In the absence of concomitant esophageal GERD syndromes, PPI therapy should be discontinued and other diagnostic and/or therapeutic avenues pursued. There are no trials showing the effectiveness of maintenance therapy for patients in whom empirical therapy with twice-daily PPI therapy results in improvement of asthma, cough, or laryngitis. Thus, recommendations regarding maintenance therapy in this group of patients are based on expert opinion extrapolated from the typical esophageal reflux syndrome literature. Hence, the objective of continued maintenance therapy in patients with extraesophageal reflux syndrome is symptom control and, just as with the typical esophageal syndromes, step-down therapy should be attempted. The likelihood of symptom recurrence with step-down therapy in patients with an extraesophageal reflux syndrome is currently unknown.

10. What Are the Clinical Consequences of Chronic Potent Acid Inhibition? Do These Potential Side Effects Warrant Specific Testing (eg, Bone Density Studies, Calcium Supplementation, Helicobacter pylori Screening, and so on)?

Grade Insuff: no recommendation, insufficient evidence to recommend for or against

I. Advocating bone density studies, calcium supplementation, *H pylori* screening, or any other routine precaution because of PPI use.

Because PPIs work by profoundly reducing gastric acid secretion, which in turn results in a reactive increase in gastrin secretion, most consideration of long-term risk is focused on unwanted effects of secondary hypergastrinemia, hypochlorhydria, or even achlorhydria. Other, more generic considerations have to do with drug-drug interactions and potential teratogenicity. In general, these risks are slight if even demonstrable. Available data show no worrisome safety signals with PPIs. The most convincing data link PPI use with an increase in *Clostridium difficile* colitis and bacterial gastroenteritis, but in each case, the magnitude of risk is slight. With respect to the hip fracture issue, there are many potential confounders to the data, but the putative mechanism would be decreased calcium absorption, which has been demonstrated with PPI use. Regardless, it is good medical practice to screen and treat the elderly for osteoporosis irrespective of PPI use. To summarize all available risk/benefit data on PPIs, their use is strongly justified when clinically indicated and there is inadequate evi-

dence to mandate bone density studies, calcium supplementation, *H pylori* screening, or any other routine precautions because of PPI use.

11. What Is the Role of Endoscopy in Long-term Management of Patients With GERD, and Under What Circumstances Should Mucosal Biopsy Specimens Be Obtained When Endoscopy Is Performed?

Grade B: recommended with fair evidence that it improves important outcomes

I. Endoscopy with biopsy for patients with an esophageal GERD syndrome with troublesome dysphagia. Biopsies should target any areas of suspected metaplasia, dysplasia, or in the absence of any visual abnormalities, normal mucosa (at least 5 samples to evaluate for eosinophilic esophagitis).

Grade Insuff: no recommendation, insufficient evidence to recommend for or against

I. Routine upper endoscopy in the setting of chronic GERD symptoms to diminish the risk of death from esophageal cancer.
II. Endoscopic screening for Barrett's esophagus and dysplasia in adults 50 years or older with >5–10 years of heartburn to reduce mortality from esophageal adenocarcinoma.

Because PPI treatment is usually initiated before the test, the sensitivity of endoscopy as a diagnostic test for GERD is poor. Hence, the principal use of endoscopy in suspected GERD is the evaluation of treatment failures and risk management. Most of the morbidity and mortality from reflux disease stems from its link with esophageal adenocarcinoma. Putting the risk of cancer in perspective, data from the Surveillance Epidemiology and End Results (SEER) database suggest that there were about 8000 incident cases of esophageal adenocarcinoma in the United States in 2004 and this disease burden has increased an estimated 2- to 6-fold relative to 20 years prior.

The 5-year survival of patients with esophageal adenocarcinoma is very poor, but it is greatly improved by early detection. The other potential benefit of endoscopy in the setting of chronic GERD is detection of Barrett's esophagus, an acknowledged premalignant condition. The risk of developing esophageal adenocarcinoma in Barrett's esophagus is estimated at 0.5% per year. Thus, the proposed strategy for controlling the risk of cancer is to screen the GERD population for Barrett's esophagus, to survey identified individuals for the development of dysplasia and adenocarcinoma, and to resect or ablate these lesions when found. However, no direct data exist to substantiate the utility of screening or surveillance endoscopy to detect Barrett's esophagus or to monitor the condition for progression to cancer. The available data were previously reviewed by an AGA Institute consensus workshop in 2004. This group, composed of 18 experts in the field of Barrett's esophagus, strongly rejected the statement "Endoscopic screening for Barrett's esophagus and dysplasia has been shown to improve mortality from esophageal adenocarcinoma" and concluded that the grade of evidence in support of this intervention was insufficient to form an opinion. Regarding the corollary statement that "Endoscopic screening for BE and dysplasia should be performed in all adults ≥50 years of age with >5–10 years of heartburn," the supporting evidence was again graded only at the level of expert opinion, and again the majority of the group rejected it.

In summary, despite the ubiquity of the practice, no direct evidence supports the use of endoscopy as a screening test for Barrett's esophagus or esophageal adenocarcinoma in the setting of chronic GERD. Regarding the criteria for obtaining mucosal biopsy specimens in the course of performing an endoscopy, there is no basis to advocate doing this routinely but, clearly, biopsy specimens of any areas suspected of being metaplastic obtained and carefully evaluated for dysplasia.

12. What Are Indications for Antireflux Surgery, and What Is the Efficacy of This Therapy?

Grade A: strongly recommended based on good evidence that it improves important health outcomes

I. When antireflux surgery and PPI therapy are judged to offer similar efficacy in a patient with an esophageal GERD syndrome, PPI therapy should be recommended as initial therapy because of superior safety.
II. When a patient with an esophageal GERD syndrome is responsive to, but intolerant of, acid suppressive therapy, antireflux surgery should be recommended as an alternative.

Grade B: recommended with fair evidence that it improves important outcomes

I. Antireflux surgery for patients with an esophageal GERD syndrome with persistent troublesome symptoms, especially troublesome regurgitation, despite PPI therapy. The potential benefits of antireflux surgery should be weighed against the deleterious effect of new symptoms consequent from surgery, particularly dysphagia, flatulence, an inability to belch, and postsurgery bowel symptoms.

Grade C: balance of benefits and harms is too close to justify a general recommendation

I. Patients with an extraesophageal GERD syndrome with persistent troublesome symptoms despite PPI therapy should be considered for antireflux surgery. The potential benefits of antireflux surgery should be weighed against the deleterious effect of new symptoms consequent from surgery, particularly dysphagia, flatulence, an inability to belch, and postsurgery bowel symptoms.

Grade D: recommend against, fair evidence that it is ineffective or harms outweigh benefits

I. Antireflux surgery for patients with an esophageal syndrome with or without tissue damage who are symptomatically well controlled on medical therapy.
II. Antireflux surgery as an antineoplastic measure in patients with Barrett's metaplasia.

Grade Insuff: no recommendation, insufficient evidence to recommend for or against

I. The use of currently commercially available endoluminal antireflux procedures in the management of patients with an esophageal syndrome.

Just as with PPI therapy, evidence on the utility of antireflux surgery depends on the manifestation of the disease being monitored, with the strongest data pertaining to erosive esophagitis. Illustrative of this are 7-year results of a randomized controlled trial comparing PPI therapy with laparoscopic antireflux surgery in patients with esophagitis. At 7 years, the 2 treatment arms were very similar with respect to the incidence of recurrent esophagitis. Hence, if the outcome of importance is maintaining a healed esophageal mucosa, the 2 therapies are both effective and appear to be equivalent. However, from the vantage point of risk, PPI therapy should be strongly recommended as initial therapy in view of its superior safety profile. As for other manifestations of the esophageal GERD syndromes with esophageal injury, there are no data comparing the efficacy of PPIs with antireflux surgery in stricture prevention, and controlled data have shown no change in the prevalence of Barrett's esophagus or in the incidence of adenocarcinoma when patients treated surgically were compared with those treated medically. Furthermore, even though the safety profile of antireflux surgery is excellent for a surgical procedure, antireflux surgery mortality estimates exceed the low risk of mortality from esophageal adenocarcinoma (less than 1 in 10,000 per patient-year). Even among subjects with Barrett's esophagus, who have a higher risk of cancer than the general GERD population, randomized controlled trial data and a recent meta-analysis fail to substantiate any protective effect of surgery against cancer.

The relative efficacy of antireflux surgery to PPIs in controlling symptomatic esophageal syndromes and extraesophageal syndromes with an established association with GERD is less clear. If the analysis is restricted to the control of heartburn and acid regurgitation, studies suggest modest superiority of antireflux surgery to PPI therapy, on the order of a 10% therapeutic gain. However, the data are widely divergent. As many as 30% of patients have resumed medical therapy by 5 years after antireflux surgery, and surgical revision is common. Although community-based outcome data are sparse, the data suggest that patients from community-based antireflux surgery series may have poorer outcomes and lower satisfaction than those from specialized centers. With respect to the extraesophageal syndromes, there are no controlled data comparing PPIs with antireflux surgery, but observational studies suggest some benefit of antireflux surgery for selected patients with reflux cough syndrome and reflux asthma syndrome. Hence, if the outcome of importance is controlling either symptomatic esophageal syndromes or extraesophageal symptoms in carefully selected patients, antireflux surgery has greater efficacy than PPI therapy. However, these benefits must be weighed against the deleterious effect of new symptoms consequent from antireflux surgery. Dysphagia of sufficient severity to require esophageal dilation occurs in about 6% of patients undergoing antireflux surgery, and both controlled and uncontrolled trials have shown a significant increase in flatulence, an inability to belch, and increased bowel symptoms after antireflux surgery. Given this balance, the recommendation for antireflux surgery is stronger in the case of the symptomatic esophageal syndromes, especially with troublesome regurgitation, than for extraesophageal symptoms.

In summary, the current indications for antireflux surgery are well circumscribed. Patients with esophagitis who are well maintained on medical therapy have nothing to gain from antireflux surgery and incur added risk; they should be advised against surgery. Patients with esophagitis who are intolerant of PPIs will likely benefit from antireflux surgery and should be so advised. Patients with esophageal GERD syndrome poorly controlled by PPIs may benefit from surgery, especially in the setting of persistent troublesome regurgitation. However, the recommendation for antireflux surgery must be balanced with a thorough discussion of potential post–antireflux surgery symptoms. Finally, patients with extraesophageal GERD syndromes in whom a reflux causality has been established to the greatest degree possible may benefit from antireflux surgery, and it should be recommended with appropriate restraint.

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Supplementary Data

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American Gastroenterological Association Institute Guideline Development Methodology for Management of Gastroesophageal Reflux Disease

In July 2007, the American Gastroenterological Association (AGA) Institute began the implementation of a new process for developing clinical practice guidelines summarized in a policy statement entitled "AGA Institute Practice Recommendations Development Manual." The guideline on management of patients with gastroesophageal reflux disease (GERD) was the first to be developed using this new process, which we briefly describe in the following text. Because this was the first trial of the new process, practical modifications were made as necessary to facilitate the process; these modifications are also noted.

AGA Institute clinical practice guidelines are composed of 2 main elements: a technical review (TR) and a medical position statement (MPS). The TR is written by experts in the field and provides a thorough review of the literature concerning the topic. The MPS is a concise document derived from the TR summarizing the final management recommendations. The MPS is intended to serve as a brief document to which a clinician can refer to determine, for a given condition, "what is the best evidence based care for my patient?" The TR is intended as a reference for the clinician desiring to dig deeper into the literature (specific citations, quality and level of evidence, and so on) behind the recommendations. Both documents combined are referred to as the "clinical practice guideline" or "guideline" for short.

One difference between the old and new process in AGA Institute guideline development is the involvement of the AGA Institute Council in the selection of TR authors and external reviewers. The AGA Institute Council is composed of elected representatives from the 12 AGA Institute sections. Including the Council in the guideline development process fulfills one element of their mission, which is to develop guidelines/standards of practice and other educational resources to help members of the AGA Institute provide high-quality clinical care. For the GERD guideline, a list of potential authors and external reviewers was initially generated by the Council; the list was subsequently refined to improve the balance among the coauthors in terms of their specific areas of interest. A lead author and 2 coauthors were selected.

The 12 broad GERD management questions addressed by the TR were developed by interaction among the authors, the AGA Institute Clinical Practice and Quality Management Committee, and representatives from the AGA Institute Council. Thereafter, primary responsibility for drafting answers to each question was assigned to the authors by the lead author. With the assistance of AGA staff, literature searches pertinent to each question were performed. To conserve space in GASTROENTEROLOGY and to allow a more detailed and comprehensive description of the evidence reviewed, the authors decided that the details of the literature search methodology and the yield of the process would appear as a separate online appendix for readers rather than within the TR itself. This action was also mandated in response to strict TR word count and citation limits specified in the AGA Institute Practice Recommendations Development Manual.

Another difference from the old guideline development process is in the formation of a Medical Position Panel (MPP), consisting of the authors of the TR, a community-based gastroenterologist, a payer, a general surgeon, a patient (or patient advocate), a primary care physician, and a gastroenterologist with expertise in health services research. The intended purpose of having this wide stakeholder representation on the MPP was to add strength and credibility to the guideline development process. The composition of the MPP may vary depending on the guideline topic and the required expertise. For the GERD guideline, all of the aforementioned participants were included. Members of the MPP were selected by members of the Clinical Practice and Quality Management Committee with input from AGA Institute Council and TR authors.

The TR was subject to external peer review before the face-to-face meeting of the MPP. Hence, before the MPP meeting, members of the panel had both the draft TR and the critiques of 4 external peer reviewers to consider. Then, during the MPP meeting, held in Bethesda, Maryland, on April 2, 2008, the TR authors led an open discussion regarding both the specific practice recommendations pertinent to each management question in the TR and the reviewer commentary relevant to each. The MPP then charged the TR authors to make specific modifications to the TR in view of their own and peer reviewer feedback and tasked them to draft the MPS. These revised documents were again reviewed by the MPP and the AGA Institute Clinical Practice and Quality Management Committee. Final feedback was obtained, and continuing medical education (CME) questions were drafted. Thereafter, the documents were sent to members of the AGA Institute Governing Board for review and approval. The final TR, MPS, and CME questions were then sent to the AGA Institute Clinical Practice and Quality Management Committee for review and approval after Digestive Disease Week 2008.

For each question, a comprehensive literature search was conducted on MEDLINE and the Cochrane Library. Pertinent evidence was reviewed, and the quality of relevant data was evaluated. Studies involving adults and English-only papers published after 1990 were considered; letters, commentaries, narrative reviews, and case reports were excluded from the search. Meta-analyses, practice guidelines, randomized controlled trials, and systematic reviews were included. The connector word "and"

was used to combine terms; the connector word "not" was used to exclude nonrelevant papers, and the connector word "or" was used to eliminate duplicate papers. Bibliographies of retrieved articles were reviewed for additional relevant publications. The final reference list was further modified and augmented in the peer review process. The specifics of the search strategy used are provided below each question.

1. What Is an Operational Definition of GERD? What Is the Distinction Between GERD and Episodic Heartburn?

To identify relevant papers on an operational definition of GERD and those describing the distinction between GERD and episodic heartburn, the text words "definition" and "episodic heartburn" were combined with the MeSH search term "GERD." Relevant papers were selected by the authors from a yield of 114.

Commentary

Although many citations were found by this search, the relevance of most of them was minimal. The exception was reference 1, describing the Montreal definition of reflux disease, which was the result of an international workshop convened with the specific intention of developing an evidence-based definition of GERD.[1] The output of that report was a series of statements that were distilled by an international panel of experts using a Delphi process of 4 iterations over 2 years. The Montreal definition was adopted for the purposes of this report because it was found to be very operational.

2. What Is the Efficacy of Lifestyle Modifications for GERD? Which Elements Should Be Recommended and in Which Circumstances?

To identify papers describing the efficacy of nonpharmacologic therapy for GERD, the following text words were searched: "GERD" or "reflux" or "LES" and either "weight loss," "obesity," "diet," "exercise," or "nonpharmacologic therapy." Reports describing recommended elements for nonpharmacologic therapy and under which circumstances they are to be used were identified excluding the text words "bariatric surgery," "pediatric," and "functional gastrointestinal disorder." A total of 407 publications were retrieved.

Commentary

Relevant articles from the many citations were reviewed and highlighted in the text. References 2 and 3 were based on references within the retrieved citations and by themselves were not identified in the primary search.[2,3] Overall, most rigorous studies were those recently published regarding the role of obesity and GERD. Most identified citations were case series and of poor study design otherwise.

3. How Do Antisecretory Therapies Compare in Efficacy and Under What Circumstances Might One Be Preferable to Another? What Is an Acceptable Upper Limit of Empirical Therapy in Patients With Suspected Typical Esophageal GERD Syndromes Before Performing an Esophagogastroduodenoscopy?

To identify relevant papers comparing the efficacy of antisecretory therapies, the text words "proton pump inhibitors" and "histamine (H2) receptor antagonists" were combined with the MeSH term "GERD." The text words "empiric therapy" and "EGD" were then combined with the text word "esophageal GERD syndrome," which resulted in a yield of 400. Relevant papers describing studies involving the comparison of 2 or more treatments were selected by authors.

Commentary

Additionally, data regarding the efficacy of various forms of acid suppressive therapies have recently undergone rigorous meta-analysis by the Cochrane Library, which encompassed a much larger data set with extensive analysis.[4] Data from illustrative individual trials as well as this meta-analysis are reported.

4. What Is the Role and Priority of Diagnostic Tests (Endoscopy, Esophageal Manometry, Ambulatory pH Monitoring, Combined Multichannel Intraluminal Impedance-pH Testing) in the Evaluation of Patients With Suspected Esophageal GERD Syndromes?

To identify papers on the role and priority of diagnostic tests, the text words "diagnostic interventions," "endoscopy," "esophageal manometry," "ambulatory pH monitoring," "pH testing," and "diagnostic evaluation" were combined with the text words "esophageal GERD syndrome." The MeSH term "GERD" and text words "multichannel intraluminal impedance" were then combined with the preceding terms to yield 125 relevant papers.

Commentary

This was a particularly difficult question to address in an evidence-based fashion because of the nature of the literature on the topic. Very little of the literature focused on testing management strategy trials but rather tended to demonstrate the capabilities of new technologies without rigorously testing the clinical validity of the

result. This was especially true of impedance monitoring where, despite the large number of citations, there were no high-quality outcome trials. Hence, there was only one B-level recommendation regarding the reflux testing methodologies and it failed to distinguish among them; with respect to the unique capabilities of impedance monitoring, only an "I" level recommendation could be made.

5. What Are the Unique Management Considerations in Patients With Suspected Reflux Chest Pain Syndrome?

To identify papers describing unique management considerations in suspected reflux chest pain syndrome, the text words "non cardiac chest pain or non-cardiac chest pain" were searched alone and in combination with "GERD"; the text words "GERD chest pain" and "esophageal chest pain" was combined with the text word "management." The following text words were excluded: "pediatrics," "children," "infants," "pediatrics," "bariatric surgery," "constipation," "dyspepsia," "functional gastrointestinal disorder," and "duodenal ulcer." This resulted in 388 relevant articles.

Commentary

Additional relevant references[5–8] were derived from reviews of the articles above and from references within the review of a recent global evidence-based consensus.[1] Most citations in this field were case series and/or highlighted the prevalence of reflux symptoms in patients with GERD and were not mechanistically designed to address causal or physiologic association between patients' symptoms of GERD and chest pain.

6. What Is the Best Initial Management for Patients With Suspected Extraesophageal Reflux Syndromes (Asthma, Laryngitis, Cough)? What Are the Unique Management Considerations With Each? What Is the Appropriate Dose and Course of Antisecretory Therapy in Each?

Relevant papers were identified using the search terms "GERD" and "asthma," "cough," "laryngitis," and "dental erosion." The text words "proton pump inhibitors" and "histamine (H2) receptor antagonists" were combined with the results, and duplicate papers were eliminated. The text words "children," "infants," and "pediatrics" were excluded to yield 477 relevant papers.

Commentary

The relevant citations were reviewed and used as the basis for the text. Important articles needing special emphasis include the meta-analysis of reflux therapy in laryngitis[9] and the critical analysis of the role of medical therapy in asthma.[10]

7. Does GERD Progress in Severity, Such That Symptomatic Patients Without Esophagitis Develop Esophagitis and Barrett's Metaplasia, or Are These Distinct Disease Manifestations That Do Not Exist Along a Continuum? If Patients Do Progress, at What Rate Does This Occur, and Does It Warrant Endoscopic Monitoring?

To identify papers describing GERD disease progression, the text word "GERD progression" was searched; the text word "Barrett*" was then combined with the MeSH term "GERD." The truncation symbol * was used to allow for a search that includes all forms of the word "Barretts" (eg, "Barrett's," "Barrets," "Barretts," and so on). Relevant papers were selected by authors out of a yield of 620.

Commentary

The number of studies with careful follow-up of subjects with GERD for periods longer than 3 years was very limited and patient groups were somewhat heterogeneous, making conclusions with respect to certain transition rates tenuous. Additionally, most data were from tertiary centers, raising the issue of generalizability to the general population.

8. What Maintenance Therapy Is Indicated for Patients With the Typical Esophageal Reflux Syndrome (With or Without Esophagitis)? When and How Should Antisecretory Therapy Be Decreased or Discontinued? What, If Any, Risks Are Associated With This?

The text words "erosive esophagitis" and "nonerosive symptomatic GERD" were searched to identify papers on maintenance therapy for patients with typical esophageal reflux syndrome. The text terms "nonerosive esophagitis" were then combined with the text words "maintenance," "erosive maintenance," and "proton pump inhibitors" to result in a yield of 157 papers. Relevant papers were selected by authors.

Commentary

Additionally, data regarding the efficacy of various forms of acid suppressive therapies have recently undergone rigorous meta-analysis by the Cochrane Library.[11] Data from illustrative individual trials as well as this meta-analysis are reported.

9. What Maintenance Therapy Is Indicated for Patients With Suspected Extraesophageal Reflux Syndromes (Asthma, Laryngitis, Cough)? When and How Should Antisecretory Therapy Be Decreased or Discontinued?

To identify papers on maintenance therapy indicated for patients with extraesophageal reflux syndromes, the search terms "asthma," "cough," and "laryngitis" were combined with "maintenance therapy" and "GERD."

Commentary

The search for maintenance therapy in patients with possible reflux-related asthma, laryngitis, or cough resulted in only 7 citations, none of which were relevant to the question. There were no studies addressing this important clinical issue, and most suggestions were based on expert opinion and data from typical GERD.

10. What Are the Clinical Consequences of Chronic Potent Acid Inhibition? Do These Potential Side Effects Warrant Specific Testing (eg, Bone Density Studies, Calcium Supplementation, *Helicobacter pylori* Screening, and so on)?

The text word "proton pump inhibitors" were first combined with "side effects" and the MeSH term "GERD" was combined with the text words "histamine (H2) receptor antagonists" and "H pylori screening" to yield 67 articles.

Commentary

This was a rather straightforward search because the MeSH terms effectively retrieved the relevant data. Additional references were found by cross-referencing.

11. What Is the Role of Endoscopy in Long-term Management of Patients With GERD, and Under What Circumstances Should Mucosal Biopsy Specimens Be Obtained When Endoscopy Is Performed?

The MeSH term "GERD" was combined with the text words "endoscopy," "biopsies," and "role of endoscopy"; the text word "dysphagia" was then combined with the text word "eosinophilic esophagitis." These searches resulted in a yield of 2766 papers. These were then limited to clinical trials. Relevant papers were selected by authors.

Commentary

Evidence-based TRs and guidelines for the use of endoscopy from various professional organizations were also reviewed. Randomized data comparing subjects managed with routine endoscopy with those managed with endoscopy only in response to preset indications were not available. Therefore, conclusions in this section are based on expected yield of endoscopy, derived largely from data from cohort studies.

12. What Are Indications for Antireflux Surgery, and What Is the Efficacy of This Therapy?

To identify relevant papers on indications for and efficacy of surgical antireflux procedures, the text words "Nissen," "efficacy," and "laparoscopy" were combined with the MeSH term "GERD. This resulted in a yield of 572 articles; relevant papers were selected by authors.

Commentary

Several randomized controlled trials of medical versus surgical therapy of complicated and uncomplicated reflux disease have been reported. These studies, as well as outcomes studies of cohorts of medically and surgically treated patients with GERD, form the evidence base for this section.

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