American Gastroenterological Association Institute Technical Review on the Management of Gastroesophageal Reflux Disease

Learning Objectives

At the end of this activity, the successful learner should:

1. Demonstrate an understanding of the natural history and manifestations of reflux disease
2. Evaluate the role of diagnostic testing such as endoscopy, esophageal manometry, ambulatory pH monitoring, and impedance-pH monitoring in the management of patients with gastroesophageal reflux disease
3. Evaluate the options for treatment of patients with complicated and uncomplicated reflux disease.

The objectives of this technical review were to evaluate diagnostic and management strategies for patients with gastroesophageal reflux disease (GERD). Specifically, 12 broad questions were developed by interaction among the authors, the American Gastroenterological Association (AGA) Institute, the Clinical Practice and Quality Management Committee, and representatives from the AGA Institute Council. The questions were designed to encapsulate the major management issues leading to consultations for GERD in clinical practice in 2008. The issue of management of Barrett's esophagus was intentionally excluded, because this will be the focus of a later treatise. However, the indications for performing endoscopy were within our purview. For each question, a comprehensive literature search was conducted, pertinent evidence reviewed, and the quality of relevant data evaluated. The resultant conclusions were based on the best available evidence or, in the absence of quality evidence, the expert opinion of the authors of the technical review and medical position statement. The strength of these conclusions was weighed using US Preventive Services Task Force (USPSTF) grades detailed in Table 1. The details of the development methodology used for this and subsequent AGA Institute technical reviews and medical position statements as well as the literature search methodology and yield associated with each of the questions in this technical review are available as a separate document on the AGA Institute Web site.

GERD has been the most common gastrointestinal diagnosis recorded on outpatient physician visits since 2006, even surpassing abdominal pain.[1] This is remarkable considering the vagaries of the diagnosis. Most patients with heartburn do not have esophagitis, even before treatment,[2] and this disconnect becomes more exaggerated after empirical antisecretory therapy or with atypical GERD symptoms. Furthermore, although the pathogenesis of reflux esophagitis and reflux symptoms share common elements, the two have several independent determinants as well. Finally, with respect to treatment, potent inhibition of gastric acid secretion reduces the lethality of gastric juice to esophageal epithelial cells such that esophagitis will heal, irrespective of whether or not gastroesophageal reflux is reduced or symptoms are resolved. Ironically, as refractory esophagitis has become a rare clinical problem, refractory "GERD" symptoms has become a substantial one. In the post–proton pump inhibitor (PPI) world, it is patients with symptoms, not esophagitis, who confront the practitioner in the overwhelming majority of clinical encounters for GERD.

Diagnosis and Initial Therapy

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

Regardless of how many citations are identified by literature review, 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, and presumably the best opinion upon which to base the answers is that of experts (USPSTF grade and quality not applicable). Fortuitously, a recent and unparalleled attempt at gaining consensus in defining GERD emanated from a panel of world experts utilizing a 4-iteration Delphi process that spanned a 2-year period.[3] The stated objective of that unique international consensus group was "to develop a global definition and classification of GERD, using rigorous methodology, that could be used clinically by primary care physicians and that embraces the needs of physicians, patients, researchers, and regulatory bodies from different parts of the world."[3] The output of the Montreal consensus group was a series of 50 statements pertaining to the diagnosis of GERD syndromes. For each statement, the level of consensus was determined by vote along a 6-point scale of agreement ranging from strong agreement to strong disagreement and, when applicable, the quality of supporting evidence was evaluated.

An overarching definition of GERD must encompass esophageal as well as extraesophageal syndromes: syn-

Abbreviations used in this paper: AGA, American Gastroenterological Association; GERD, gastroesophageal reflux disease; H_2RA, histamine$_2$ receptor antagonist; PPI, proton pump inhibitor; USPSTF, US Preventive Services Task Force.

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Table 1. USPSTF Recommendations and Grades

Strength of recommendations

A: The USPSTF strongly recommends that clinicians provide [the service] to eligible patients. *The USPSTF found good evidence that [the service] improves important health outcomes and concludes that benefits substantially outweigh harms.*

B: The USPSTF recommends that clinicians provide [this service] to eligible patients. *The USPSTF found at least fair evidence that [the service] improves important health outcomes and concludes that benefits outweigh harms.*

C: The USPSTF makes no recommendation for or against routine provision of [the service]. *The USPSTF found at least fair evidence that [the service] can improve health outcomes but concludes that the balance of benefits and harms is too close to justify a general recommendation.*

D: The USPSTF recommends against routinely providing [the service] to asymptomatic patients. *The USPSTF found at least fair evidence that [the service] is ineffective or that harms outweigh benefits.*

Insuff: The USPSTF concludes that the evidence is insufficient to recommend for or against routinely providing [the service]. *Evidence that the [service] is effective is lacking, of poor quality, or conflicting and the balance of benefits and harms cannot be determined.*

Quality of evidence

Good: Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes.

Fair: Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies, generalizability to routine practice, or indirect nature of the evidence on health outcomes.

Poor: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

NOTE. The USPSTF grades its recommendations according to one of 5 classifications (A, B, C, D, Insuff) reflecting the strength of evidence and magnitude of net benefit (benefits minus harms). The USPSTF grades the quality of the overall evidence for a service on a 3-point scale (good, fair, poor).

dromes with tissue injury as well as those without. Grappling with this dilemma, the Montreal consensus panel reached very strong agreement in defining GERD as "a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications."[3] Thereafter, the panel specified that symptoms were "troublesome" if they adversely affected an individual's well-being and delineated the broad array of GERD syndromes that have been demonstrated or proposed (Figure 1). Note that the extraesophageal syndromes are classified as of established or proposed association, acknowledging that while the evidence on hand is sufficient to link these syndromes to reflux, it is insufficient to establish causation.

A test of the word "troublesome" in the Montreal definition of GERD comes in attempting to draw a distinction between GERD and episodic heartburn. The Montreal group believed that for the typical esophageal GERD syndrome, defining a threshold at which heartburn becomes troublesome was useful in planning treatment trials or epidemiologic studies but not in clinical practice. In the individual case, symptom frequency, symptom intensity, and psychosocial factors must also be considered. Hence, in clinical practice, the determination of whether or not heartburn is troublesome should be made by the patient without the use of arbitrary cutoffs for frequency or duration and after the patient is assured of the benign nature of occasional symptomatic heartburn. Presumably, a patient will conclude that if heartburn regularly interferes with his or her normal daily activities, it is troublesome; the more substantial the limitations imposed on his or her life, the more troublesome it is.

In clinical trials of symptomatic GERD, a threshold measure of heartburn severity needs to be established for uniformity in the study population. However, there has been little consistency among symptomatic GERD trials in how this was done, with different studies utilizing symptom thresholds as low as 2 mild episodes of heartburn per week and as high as 5 daytime episodes and 1 nighttime episode per week as minimal entry criteria.[4,5] Dropping the threshold of heartburn severity required to define symptomatic GERD clearly enlarges the "disease" population, and variability in the definition makes comparisons of results among trials difficult, if not impossible. Moving forward with this, the Food and Drug Administration recently issued guidance on the criteria that will be required in the future to support labeling claims.[6] The catchphrase has become "patient-reported outcomes." Patient-reported outcomes measure a patient's health status in terms of symptoms and quality of life as relayed by the patient without the interpretation of the patient's responses by a physician. Disease-specific patient-reported outcomes must be developed and accepted by the Food and Drug Administration before their use in supporting a labeling claim. Acceptance of a patient-reported outcome is predicated on its demonstrated validity, reliability, and ability to identify meaningful differences in disease-specific measures of importance in the intended treatment population. For the example of a patient-reported outcome for symptomatic GERD, both the defining symptom burden and the minimal meaningful increment of improvement attributable to therapy would need to be developed through patient focus groups and vetted by the Food and Drug Administration. Hence, the development of a symptomatic GERD patient-reported outcome will result in defining the threshold symptom burden required for the diagnosis. Needless to say, few, if any, existing trials substantiating treatment efficacy in symptomatic GERD would meet the criteria now mandated by the Food and Drug Administration.

In summary, the Montreal definition of GERD was adopted to use as a framework throughout this document. A distinguishing feature of the Montreal definition is that it does not use the term "nonerosive reflux

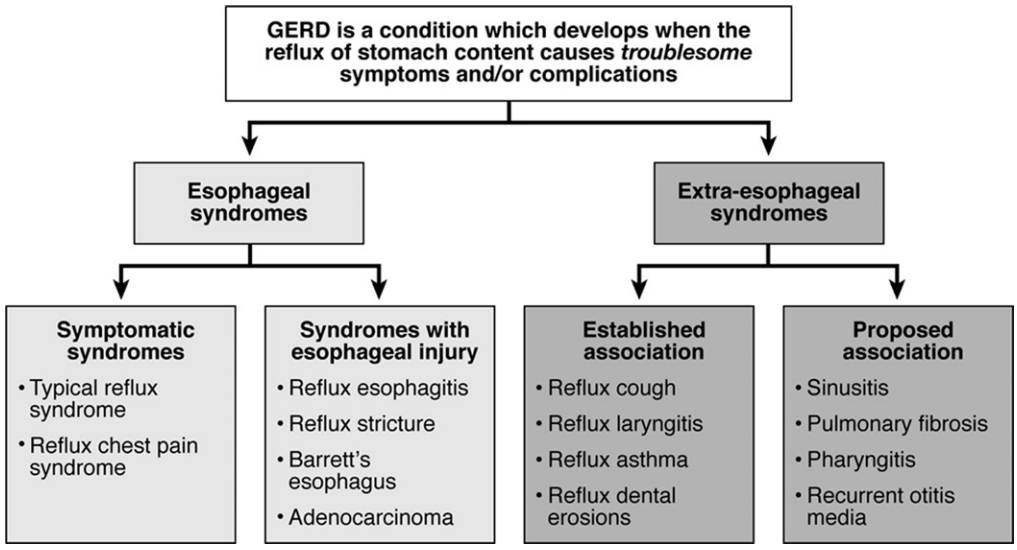

Figure 1. The Montreal definition of GERD. The overarching definition mandates that troublesome symptoms and/or complications are present regardless of syndrome(s) present and that those syndromes are caused by reflux.[3]

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 of insufficient intensity to be perceived as troublesome by the patient (after assurance of its benign nature) does 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?

There are a multitude of recommendations regarding lifestyle modifications as GERD therapy. Broadly speaking, these fall into 3 categories: (1) avoidance of foods that may precipitate reflux (coffee, alcohol, chocolate, fatty foods), (2) avoidance of acidic foods that may precipitate heartburn (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). Most evidence supporting such recommendations is weak, coming from observational and uncontrolled studies of small sample size, often with surrogate end points. In some cases, such as with dietary fat, the evidence is conflicting. Early studies suggested that a high-fat diet was harmful because it diminished lower esophageal sphincter (LES) pressure.[7] However, a subsequent controlled study comparing a low-fat diet with a high-fat diet did not find any change in LES pressure or objective reflux parameters by pH monitoring.[8] Similarly, the reported reduction in LES pressure with smoking has not extrapolated to improvement of GERD parameters with cessation of smoking.[9]

The recommendation to elevate the head of the bed by 6–8 inches in patients with reflux is intuitively based on reducing esophageal acid exposure by improving clearance. A corollary to this recommendation is to avoid eating for the 2- to 3-hour period before going to bed, because this is the period during which the most reflux events would be anticipated. There is some merit to this recommendation based on a randomized controlled trial of patients with moderately severe esophagitis (USPSTF grade B, quality fair).[10] The therapeutic gain from raising the head of the bed with a 20-cm block for the 6-week duration of the study was 20%–30%. However, the subgroup studied (moderate to severe esophagitis) is particularly prone to supine reflux and the applicability of the recommendation of elevation of the head of the bed to the majority of patients with GERD experiencing heartburn predominantly confined to the postprandial period is dubious.

Obesity merits special consideration because it has been the object of substantial study in recent years. There is good evidence that GERD is associated with obesity. Specifically, epidemiologic data from the Nurses' Health Study suggest a dose-dependent relationship between increasing body mass index and frequent reflux symptoms,[11] and a large meta-analysis similarly demonstrated a dose-response relationship between body mass index and the risk of reporting symptoms of GERD among both men and women.[12] Evidence also suggests that acid reflux measured by pH monitoring is increased in obese patients.[13] Proposed mechanisms for the obesity effect

include alteration in the pressure dynamics and anatomy of the esophagogastric junction[14] and an increase in transient LES relaxation and reflux frequency.[15] However, the contention that losing weight will improve GERD is less robustly supported by the literature (USPSTF grade B, quality fair). One observational study of 34 overweight and obese patients found that weight loss resulted in improvement in GERD symptoms,[16] and the Nurses' Health Study analysis found that reflux symptoms were exacerbated or improved over time concomitant with weight gain or loss, respectively.[11] On the other hand, a randomized controlled study did not find any objective or subjective improvement of GERD in 20 obese patients after a significant weight loss.[17]

In summary, the problem with advocating lifestyle modifications as GERD therapy is that there are simply too many and each is too narrowly applicable to enforce the whole set on every patient. The Genval Workshop Report on evidence-based reflux management concluded that "there is currently a significant overestimation of the possibility of patients deriving adequate relief from life style modification."[18] Thus, from the vantage point of high-quality evidence, there are insufficient data to suggest a consistent benefit of lifestyle changes for all patients with GERD (USPSTF grade Insuff). 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. A patient with symptoms of nighttime heartburn 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 despite acid suppressive therapy will benefit from avoidance of these factors. Finally, if the development of troublesome heartburn paralleled weight gain, it is perfectly reasonable to propose weight loss as an intervention that may prevent, or at least postpone, the need for continuous acid suppressive therapy.

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?

Initiating empirical treatment with a PPI amounts to a pragmatic therapeutic trial; if a patient reports symptoms consistent with GERD and responds to therapy for GERD, then he or she must have GERD. However, the notion that this constitutes a clinical test blurs the distinction between healing esophagitis and resolving putative reflux symptoms, the latter of which are neither perfectly sensitive nor specific for GERD. Such reasoning also ignores the existence of other diagnostic possibilities that may benefit from PPI therapy or a possible placebo response. The strategy of empirical therapy is also limited by the observation that PPI therapy is not as robust at resolving GERD symptoms as it is resolving esophagitis; a negative response to a PPI trial does not exclude GERD as a diagnostic possibility. Furthermore, it dampens the diagnostic utility of endoscopy because esophagitis, which would otherwise have been a robust marker of GERD, will likely be healed with treatment regardless of whether or not symptoms resolve. Nonetheless, these limitations withstanding, the current consensus is that empirical PPI therapy is appropriate for uncomplicated heartburn.[3,19,20]

As for the choice of therapeutic agent, there is an abundance of data demonstrating the effectiveness of PPIs in healing esophagitis and in relieving heartburn. A recent Cochrane review examined 134 treatment trials including 36,978 patients with esophagitis and concluded that PPIs exhibit a better healing effect and faster symptom relief than histamine$_2$ receptor antagonists (H_2RAs), which are in turn better than placebo.[21] That review also concluded that there is no major difference in efficacy among the currently available PPIs (esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole) and that the gain achieved by doubling the standard dose of PPI therapy is modest. Available 6- to 12-month data also suggest that PPIs are effective for maintaining symptom relief and preventing recurrence of esophagitis in patients who respond to an acute course of the same therapy. Table 2 summarizes the major observations from this voluminous pool of therapeutic data.[22–31] Thus, abundant data support treating patients with esophageal GERD syndromes with antisecretory drugs (USPSTF grade A, quality good) and there is ample evidence that, as a drug class, PPIs are more effective in these patients than are H_2RAs (USPSTF grade A, quality good). However, the data supporting the use of PPIs with doses higher than the standard are minimal. Similarly, there is no evidence of improved long-term efficacy by adding a nocturnal dose of an H_2RA to twice-daily PPI therapy (USPSTF grade Insuff). This combination was proposed to suppress "nocturnal acid breakthrough" on the assumption that this was clinically relevant.[32] However, subsequent data have failed to show any associated clinical benefit.[33–35] There are also no high-quality data supporting the use of metoclopramide as either monotherapy or adjunctive therapy in esophageal or suspected extraesophageal GERD syndromes, making the toxicity profile of the drug[36] ample grounds for recommending against its use (USPSTF grade D, quality fair). Finally, data supporting the use of PPIs for treatment of patients with extraesophageal GERD syndromes with an established association are weak (USPSTF grade B, quality fair).

The data in Table 2 are very robust with respect to the short-term healing of esophagitis but much more limited with respect to defining the parameters for maintenance therapy or the management of patients with an inade-

Table 2. Summary of GERD Treatment Data With Inhibitors of Gastric Acid Secretion

Esophagitis healing (all severities)	PPIs are superior to placebo: 83% vs 18% at 8 wk, NNT = 1.7[21]
	PPIs dose-response curve exhibits a plateau: low vs standard dose, NNT = 10 at 4 wk; standard vs high or split dose, NNT = 25 at 4 wk[21]
	PPIs are superior to H_2RAs: 84% vs 52%,[20] RR = 0.51[21]
	H_2RA are superior to placebo: 41% vs 20% at 6 wk, NNT = 5[21]
	H_2RAs show no dose-response curve (standard vs high or split dose)[21]
Heartburn resolution (patients with esophagitis)	PPIs are superior to placebo: 56% vs 8% at 4 wk, NNT = 2–3[22]
	PPIs show no dose-response curve: low vs standard dose, 75% vs 79% at 4 wk; standard vs high or split dose, 73% vs 76% at 4 wk[21]
	PPIs are superior to H_2RAs: 77% vs 48% at 4–12 wk[23]
	H_2RAs are superior to placebo: 56% vs 45% at 12 wk[24]
Heartburn resolution (endoscopy negative or uninvestigated patients)	PPIs are superior to placebo: 36.7% vs 9.5%, NNT = 3–4[22]
	PPIs show no dose-response curve (low vs standard dose)
	PPIs are superior to H_2RAs: 61% vs 40%, NNT = 5,[25] RR = 0.66, 95% confidence interval = 0.60–0.73[26]
	H_2RAs are superior to placebo: RR = 0.77, 95% confidence interval = 0.60–0.99[26]
	H_2RAs show no dose-response curve (standard vs high dose): 45.8% vs 44.8% at 8 wk[27]
Maintenance of esophagitis healing or symptom control (6-12 months)	PPIs are superior to placebo for maintaining healing: 93% vs 29%[28]
	Low-dose PPI therapy is sufficient to maintain endoscopic remission in 35%–95% of patients with esophagitis[20]
	Low-dose on-demand PPI therapy yields acceptable symptom control in 83%–92% of endoscopy-negative patients[20]
Extraesophageal syndromes (with established association)	High-dose PPIs are no better than placebo for reflux laryngitis syndrome without frequent heartburn[29]
	High-dose PPIs show modest benefit in morning peak expiratory flow vs placebo for subgroup of asthmatic patients with nocturnal GERD symptoms[30]
	Standard- or high-dose PPIs show some improvement in some patients with reflux cough syndrome with objectively demonstrated GERD: NNT = 5[31]

NOTE. Low and standard doses of PPIs are as follows: esomeprazole 20 mg, 40 mg; lansoprazole 15 mg, 30 mg; pantoprazole 20 mg, 40 mg. All omeprazole and rabeprazole data were 20 mg. Standard doses of H_2RAs (all twice daily): cimetidine 400 mg, famotidine 20 mg, nizatidine 150 mg, ranitidine 150 mg.
NNT, estimated number of patients needed to treat to demonstrate this benefit; RR, risk ratio, compares the probability of treatment failure in each group.

quate symptom response to once-daily PPI therapy, basically the 2 most common issues faced by the clinician. The other notable disconnect between clinical trial data and clinical practice is in the use of PPIs twice daily; although the pharmacodynamics of the drugs logically supports twice-daily dosing, the pharmaceutical industry has been reluctant to advocate it, primarily due to marketing considerations. Hence, guidance on these issues comes primarily from expert opinion based on clinical experience. Expert opinion 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 (USPSTF grade B, quality fair). The general principle of maintenance therapy is to titrate the strength of antisecretory therapy up or down to find the lowest dose that provides satisfactory control of heartburn. As a rule of thumb, 80% symptom relief is a reasonable, albeit somewhat arbitrary, target; at that point, persistent symptoms are often triggered only by indulgence. Furthermore, the significance of these unresolved symptoms is only in the lifestyle compromises they impose: limited diet, restricting physical activity, poor sleep, and so on. They should not be framed as a threat to one's well-being.

Although PPIs are more effective overall, H_2RAs have a more rapid onset of action and will suffice for some patients. If patients need to take a PPI twice daily because they are experiencing breakthrough symptoms toward the end of the day or during the night, the optimal timing is 30–60 minutes before breakfast and dinner. Patients may find on-demand or intermittent short courses of therapy sufficient. However, antacids are most effective once heartburn is already present; PPIs and H_2RAs are more effective in preventing heartburn. Patients whose heartburn has not adequately responded to twice-daily PPI therapy should be considered treatment failures; in other words, that is 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, none of which occur more frequently than with placebo, but all of which can occur with any drug in the class and can be confirmed in some patients with a test-retest strategy. Potential side effects should also be considered in wholesale transitioning of patients from one PPI to another, as shown by the

28% of patients who failed the switch from omeprazole to lansoprazole because of either therapeutic failure (15%) or side effects (13%) in a VA hospital experience of 78 patients.[37] Switching among alternative PPI drugs or to a lower dose can usually circumvent side effects; it is rare for a patient to exhibit intolerance to any dose of the entire drug class. 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. However, the clinical benefits of such combination therapies have yet to be demonstrated in clinical trials.

Some data suggest differences among the various PPIs with respect to healing of erosive esophagitis.[38,39] However, absolute differences in efficacy in these studies are modest,[21] and subgroup analyses have suggested that differences in healing rates may be more pronounced in grade C and D disease. Given that these medications are often given empirically and that grade C and D esophagitis will be present in only a small fraction of those with GERD symptoms, medication selection predicated on prescription plan coverage, side effects, and onset of action will likely govern the selection of the initial therapy for most patients.

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

As evident in Figure 1, widely accepted diagnostic criteria for esophageal GERD syndromes are (1) a symptom complex attributable to gastroesophageal reflux and of sufficient severity to compromise quality of life or (2) endoscopic findings of erosive esophagitis, stricture, or Barrett's metaplasia. In the simplest case, when symptoms are typical and the patient responds to therapy intended to address those symptoms, no diagnostic tests are requisite. Rather, diagnostic testing 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. With respect to performing endoscopy to screen for Barrett's metaplasia, although clearly a mainstream issue, this is specifically addressed in the section on chronic management (see question 11 in the following text).

The discussion of misdiagnosis and identifying complications of reflux disease usually revolves around the concept of "alarm features" found on clinical evaluation. Alarm features dictate circumstances in which diagnostic testing is indicated as part of the initial evaluation, either because they suggest that complications of GERD are present or because they suggest 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. Proposed alarm features include vomiting, evidence of gastrointestinal blood loss, involuntary weight loss, dysphagia, anemia, chest pain, or epigastric mass.[20,40] It is not always endoscopy that is invoked, but some specific evaluation as mandated by the suspected disease entity. High-quality evidence supporting the broad utility of alarm features as a diagnostic tool is quite limited (USPSTF grade Insuff). However, a recent meta-analysis addressed the specific issue of the utility of alarm signs and symptoms in diagnosing upper gastrointestinal malignancy based on 15 published prospective evaluations encompassing 46,161 patients, 8669 with one or more alarm feature, and 150 subsequently found to have gastric or esophageal cancer on endoscopy.[40] Although those investigators concluded that alarm features performed poorly as a diagnostic test, they reported the overall pooled sensitivity and specificity to be 67% (95% confidence interval, 54%–83%) and 66% (95% confidence interval, 55%–79%), respectively. Individual alarm features with the best performance were weight loss, dysphagia, and epigastric mass on examination. Given those numbers, and viewing this as a screening test rather than a diagnostic test, it seems reasonable that patients being evaluated for GERD should be queried regarding dysphagia and weight loss and examined for an epigastric mass. If judged significant, any of these should be evaluated with endoscopy (USPSTF grade B, quality fair).

Dysphagia merits special consideration as an alarm symptom because it can be indicative of a stricture or malignancy. However, dysphagia was also reported by 37% of 11,945 patients with esophagitis without stricture or Barrett's esophagus participating in esophagitis clinical trials, and it resolved in 83% with PPI therapy.[41] This discrepancy led the Montreal consensus group to suggest that not all dysphagia, but only "troublesome" dysphagia, warrants investigation[3] (USPSTF grade B, quality fair). Troublesome dysphagia is present when patients need to alter their eating patterns, when patients have symptoms of solid food getting impacted, when it exhibits a worsening pattern, or when it does not resolve with PPI therapy. Although not specifically mentioned by the Montreal consensus group, the latter circumstance is significantly associated with failed esophagitis healing.[41] A final caveat in the endoscopic evaluation of dysphagia is that the endoscopist should have a low threshold for obtaining multiple (preferably 5) esophageal mucosal biopsy specimens or even biopsy specimens from multiple levels to evaluate for eosinophilic esophagitis.[42] The increasing recognition of eosinophilic esophagitis as a confounding clinical entity has increased the potential value of biopsies when performing upper endoscopy for GERD. The traditional teaching that histologic assessment of mucosa in the setting of GERD is of limited utility due to the poor specificity of histologic findings for GERD has been tempered by the need to differentiate eosinophilic

esophagitis from GERD. A recent systematic review and consensus conference on eosinophilic esophagitis suggested that

> mucosal pinch biopsy specimens should be obtained from all patients in whom EE (eosinophilic esophagitis) is in the differential diagnosis. Biopsy specimens should be obtained regardless of the gross appearance of the mucosa, and multiple biopsy specimens should be obtained from different esophageal locations along the length of the esophagus.[43]

Given the high rate of eosinophilic disease in the setting of dysphagia without an obvious obstructing lesion, such subjects may benefit from mucosal biopsies[44] (USPSTF grade B, quality fair). No evidence demonstrates the utility of routine esophageal biopsies in the setting of reflux symptoms without dysphagia.

The other broad scenario under which diagnostic testing is performed is in the evaluation of troublesome symptoms that have not 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? In current practice, this dilemma is usually faced when the patient has already been treated with twice-daily PPI therapy for a significant period and it is unlikely that endoscopy will reveal esophagitis. Endoscopy may, however, still demonstrate Barrett's metaplasia, stricture, or an alternative upper gastrointestinal diagnosis, so it is still the most useful initial diagnostic test (USPSTF grade B, quality fair).

In the setting of persistent troublesome symptoms and normal findings on 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. Logically then, further evaluation should be targeted to the detection of conditions that are likely to respond to antireflux surgery. High-quality evidence on the efficacy of antireflux surgery exists only for esophagitis and/or excessive distal esophageal acid exposure determined by ambulatory esophageal pH monitoring in a study obtained when PPI therapy was withheld (see discussion of question 12 in the following text). Another requirement for antireflux surgery is that some peristaltic function be preserved. Although the precise cutoff is uncertain, severe peristaltic dysfunction is a relative contraindication for antireflux surgery.[45] Certainly, complete absence of peristalsis is an absolute contraindication. Finally, it is important to identify alternative diagnoses that may masquerade as GERD: functional heartburn, eosinophilic esophagitis, subtle cases of achalasia, or distal esophageal spasm. Given these priorities, the second diagnostic evaluation should be an esophageal manometry study, which will serve to localize the LES for subsequent pH monitoring, to evaluate peristaltic function preoperatively, and to diagnose the major motor disorders. Recent studies suggest that high-resolution manometry has superior sensitivity in recognizing atypical cases of achalasia and distal esophageal spasm compared with conventional manometry[46,47] (USPSTF grade B, quality fair). The third evaluation should then be to ascertain whether or not there is excessive esophageal acid exposure, data that can be obtained with a conventional catheter-type pH monitoring study, a combined impedance-pH study, or a wireless pH monitoring study (USPSTF grade B, quality fair). Whether this examination should be performed with the patient on or off 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 unequivocally demonstrate PPI nonresponse. That, however, rarely occurs. However, a study performed with PPIs withheld that demonstrates only marginally abnormal esophageal acid exposure and poor symptom correlation in a patient being evaluated for persistent symptoms despite twice-daily PPI therapy raises concern about causality. Given that the next therapeutic consideration in this clinical setting is often antireflux surgery, further work is urgently needed to answer this question.

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 no high-quality evidence supporting one management approach or another (USPSTF grade Insuff). Because of its added ability to detect weakly and nonacidic reflux, the best tool available to test reflux-symptom association is impedance-pH monitoring,[48,49] but the optimal algorithm to use in data analysis has yet to be validated.[50] Conversely, the value of a negative impedance-pH monitoring study on or off therapy is more clear. In the absence of endoscopic findings, with normal esophageal acid exposure, without significant manometric findings, and with an impedance-pH monitoring study that failed to show significant symptom association probability between reflux events and troublesome symptoms, one has gone as far as currently possible to rule out GERD.

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

Reflux chest pain syndrome was accepted as one of the esophageal syndromes without mucosal injury by the Montreal consensus group (Figure 1), and there was strong agreement that chest pain indistinguishable from ischemic cardiac pain can be caused by GERD.[3] Often referred to as noncardiac chest pain, the

epidemiology of this disorder is poorly understood, but population-based studies report community prevalence rates ranging from 23% to 33%.[51–53] In a study using the General Practice Research Database that compared 13,740 patients with new-onset chest pain with 20,000 age- and sex-matched patients without chest pain, the odds of patients with chest pain having ischemic heart disease was 14.9, having GERD was 3.0, having peptic ulcer disease was 3.0, and having dyspepsia was 2.7.[54] Another community sample of patients with chest pain concluded that low socioeconomic status increased the likelihood of cardiac etiology, while affluent social strata favored noncardiac etiologies.[55]

Because the morbidity and mortality associated with ischemic heart disease are 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. This important priority substantially increases the economic impact of the reflux chest pain syndrome.[53,54,56] However, 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.[57–59] Illustrative of the rarity of significant motility disorders in this patient group, a manometric study of 140 patients with noncardiac chest pain found diffuse esophageal spasm in 2%, nutcracker esophagus in 10%, hypertensive LES in 10%, and normal motility in 70% of patients.[58] Thus, although esophageal motility disorders are potential etiologies of noncardiac chest pain, significant motility disorders are rare.[59]

With finding support for a diagnosis of GERD the next priority, a common clinical strategy in chest pain is an empirical trial of PPI therapy. Meta-analyses of treatment trials in patients with suspected reflux chest pain (based on objective findings from endoscopy or pH monitoring) suggest clinical benefit with twice-daily PPI therapy over placebo.[57,60] The reported pooled sensitivity, specificity, and diagnostic odds ratio for a short course of PPI therapy are 80%, 74%, and 13.83 (95% confidence interval, 5.48–34.91), respectively. Extending the duration of PPI therapy beyond 4 weeks was not beneficial in these patients.[60] A cost-effectiveness analysis has also found empirical treatment with PPIs to be superior to other clinical strategies for this patient group.[61]

In summary, the first priority in patients with suspected reflux chest pain syndrome is to exclude ischemic heart disease as a potential etiology. Once a cardiac etiology is excluded, there is sufficient evidence (USPSTF grade A, quality good) to recommend empirical therapy with twice-daily PPIs for 4 weeks. 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 (see also question 4 in the previous text).

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?

The Montreal consensus group divided manifestations of GERD into esophageal and extraesophageal syndromes, with the latter divided into those with established or proposed association (Figure 1).[3] Chronic cough, laryngitis, and asthma were accepted to have an established association with GERD on the basis of population-based studies confirming an increased risk of these symptoms among patients with either esophagitis or esophageal reflux symptoms,[51,62,63] with odds ratios ranging from 1.2 to 3.0. However, because cough, laryngitis, and asthma have a multitude of potential etiologies other than GERD, they are clearly 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 demonstrating a significant treatment effect for a GERD therapy in these syndromes were in patients who had esophageal GERD syndromes in addition to either chronic laryngitis[64] or asthma.[30,65,66] Considering these data, the Montreal consensus group concluded that existing evidence supports

> 1) the existence of an association between these syndromes and GERD, 2) the rarity of extraesophageal syndromes occurring in isolation without concomitant manifestations of the typical esophageal syndrome, 3) that these syndromes are usually multifactorial with GERD as one of the several potential aggravating cofactors, and 4) that data substantiating a beneficial effect of reflux treatments on the extraesophageal syndromes are weak.[3]

Recognizing the difficulty in establishing a causal relationship between extraesophageal syndromes and reflux, substantial investigational effort has been expended in validating diagnostic tests. However, 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. The health care impact of this overdiagnosis is substantial, usually resulting in multiple (often repeated) diagnostic tests and expensive unsuccessful therapies. Alternative factors (or cofactors) that are often insufficiently explored in these nonspecific extraesophageal syndromes include postnasal drip, allergic rhinitis, infections, habitual throat clearing, tobacco, alcohol, excessive voice use, allergens, exercise, temperature or climate changes, emo-

Table 3. Recommendation for or Against PPI Therapy (Daily or Twice Daily) and the Strength of Evidence Supporting That Recommendation for Treatment of Patients With Suspected Extraesophageal GERD Syndromes

	With concomitant esophageal syndrome	Without concomitant esophageal syndrome
Chronic cough	Yes (USPSTF grade Insuff)	No (USPSTF grade D, quality fair)[31]
Laryngitis	Yes (USPSTF grade B, quality fair)[64]	No (USPSTF grade D, quality fair)[29]
Asthma	Yes (USPSTF grade B, quality fair)[30]	No (USPSTF grade D, quality fair)[30]

NOTE. The evidence evaluated pertains to the treatment response of the nonspecific extraesophageal symptoms.

tional conflicts, and environmental irritants.[67,68] Evidence supporting the multifactorial nature of the extraesophageal syndromes comes from therapeutic trials targeting GERD in which these nonspecific syndromes improved but were not resolved.[64,69–71]

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,[68] empirical therapy with PPIs has become common practice. The majority of therapeutic trials of these syndromes have used twice-daily dosing of PPIs for treatment periods of 3–4 months.[68,69] The rationale for this unapproved dosing for unapproved indications comes from pH monitoring data demonstrating that the likelihood of normalizing esophageal acid exposure with twice-daily PPI therapy in patients with GERD is 93% and in those with chronic cough, asthma, or laryngeal symptoms is 99%,[72] 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 patients with suspected reflux laryngitis[71] or asthma.[73] Furthermore, despite widespread treatment with PPIs twice daily, high-quality evidence supporting treatment efficacy in these syndromes is still scant.[3,68,69] Most enthusiastically supportive studies were uncontrolled with small sample size. Subsequent attempts to confirm these findings with controlled trials have shown no therapeutic benefit of PPIs over placebo for chronic cough[31] or laryngitis.[74] A recent controlled trial in patients with asthma suggested slight therapeutic benefit with PPIs only in the subgroup of asthmatic patients with both nocturnal respiratory and GERD symptoms but no benefit in those without nocturnal GERD symptoms.[30] Table 3 summarizes the evidence-based treatment recommendations that can currently be made for these extraesophageal syndromes.

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 have 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 (USPSTF grade B, quality fair; Table 3). However, once- or twice-daily PPIs (or H_2RAs) for acute treatment of potential extraesophageal GERD syndromes, including laryngitis and asthma, in the absence of a concomitant esophageal GERD syndrome cannot be supported and appears ineffective based on presently available data (USPSTF grade D, quality fair).

The role of pH or impedance-pH monitoring in establishing these diagnoses is controversial and unproven. Conversely, similar to the case with symptomatic esophageal syndromes, the value of a negative pH or impedance-pH monitoring study is clearer. In the absence of troublesome esophageal symptoms or endoscopic findings, with a failed 8-week therapeutic trial of twice-daily PPI therapy, and with normal esophageal acid exposure (PPI therapy withheld) on 24-hour monitoring, one has gone as far as currently possible to rule out GERD as a significant contributor to these nonspecific syndromes. Such patients should have etiologies other than GERD 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?

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.[75] This "spectrum of disease" approach has been contrasted with the view that GERD may be a disease with phenotypically discrete "categories," such as nonerosive disease, erosive esophagitis, and Barrett's esophagus.[76] In this phenotypically preordained view, conversion from one disease manifestation to another is

Table 4. Cohort Studies of the Natural History of Reflux Disease

Authors	Cohort size and composition	Mean or range of years followed up	Progression data	Regression data (treatment variable)
Schindlbeck et al, 1992[77]	24 (NERD, 16; EE, 8)	3.4	NERD to EE: 25% Grade 2 to grade 3: 12.5%	Grade 3 to grade 1: 25%
Isolauri et al, 1997[78]	60 Severe GERD symptoms	17–22	NERD to esophagitis: 17% Worsened esophagitis: 40% Esophagitis to BE: 0%	NR
McDougall et al, 1997 and 1998[79,80]	77 (NERD, 23; EE, 33)	3–4.5	NERD to esophagitis: 24% Esophagitis to BE: 11% Symptoms only to positive pH study and/or esophagitis: 31%	NR
Wetscher et al, 2001[81]	83 Mild EE	2	14.5% mild esophagitis to BE	NR
Manabe et al, 2002[82]	105 First diagnosis EE	5.5	10.5% (to more severe EE)	29.5% (EE to nonerosive)
Pace et al, 2004[83]	18 NERD	10	NERD to esophagitis: 89%	NR
Bajbouj et al, 2005[84]	34 NERD	2.9	5.9% NERD to BE	—
Kawanishi, 2006[85]	497 (NERD, 47; normal, 450)	5.0 NERD 5.3 Normal	Normal to LA A/B: 11.3% NERD to LA A/B: 36.2%	NERD to normal: 10.6%
Labenz et al, 2006[86]	3894 (NERD, 1717; LA A/B, 1512; LA C/D, 278; BE, 387)	2	NERD to LA A/B: 24.9% LA A/B to LA C/D: 1.6% NERD to LA C/D: 0.6% NERD to BE: 0.5% LA A/B to BE: 1.4% LA C/D to BE: 5.8%	LA A/B to NERD: 61.3%, LA C/D to LA A/B: 41.8% LA C/D to NERD: 50.4%
Stoltey et al, 2007[87]	684 (GERD, 515 [103 erosive]; BE, 169)	3.4	EE to BE: 1% Nonerosive to BE: 0% Nonerosive to EE: NR	NR
Sontag et al, 2006[2]	2306 (NERD, 1313; EE, 957; BE excluded)	7.6 (1–20)	NERD to erosive: 15.6% NERD to stricture: 0.1% Erosive to stricture: 1.9% GERD to adenocarcinoma: 0.1%	EE to NERD: 43.7%

NERD, nonerosive reflux disease; EE, erosive esophagitis; BE, Barrett's esophagus; NR, not reported; LA, Los Angeles classification of esophagitis.

distinctly unusual, and subjects generally stay in their initial category.

Given the high prevalence of GERD in Western populations, there is a decided paucity of data with which to address the question of long-term manifestations of GERD and the risk of progression in an evidence-based manner. Add to this the fact that essentially all reported cohorts are treatment cohorts, and our ability to describe the natural history of the disease becomes even more limited. Several long-term cohort studies have been reported and are described in Table 4, along with reported conversion rates to more severe forms of disease.[2,77–87] As shown, length of follow-up and disease progression vary substantially among the studies. Furthermore, whether these data represent true progression or the relapsing and remitting nature of a chronic disease is unclear. However, the data do permit some generalizations. First, in subjects with GERD treated in an uncontrolled fashion, there is some risk of progression from nonerosive disease to erosive esophagitis. However, the risk of developing a stricture, conversion to Barrett's metaplasia, or developing adenocarcinoma appears to be low within the 2- to 20-year time frame of these studies. Substantial numbers of subjects, especially if treated with antisecretory medications,[2] appear to regress to lesser grades of erosive esophagitis and even to nonerosive disease. Progression and regression are not predictable based on symptom duration or demographics.[88]

Patients with GERD often inquire how often they should undergo endoscopy to monitor the condition of their mucosa. The role of endoscopy in the management of GERD will be discussed more completely in the following text, but there are no data demonstrating that routine endoscopy to assess for disease progression in subjects with erosive or nonerosive reflux disease results in improved patient outcomes, and this practice should be discouraged (USPSTF grade D, quality fair). However, it is likely that slow disease progression will occur over a period of decades in a small subset of patients, because severe esophagitis, Barrett's esophagus, and esophageal

adenocarcinoma are all more prevalent among older individuals.[89]

In summary, data suggest that while subjects with GERD may sometimes progress from nonerosive disease to erosive esophagitis, demonstrating that it is not a strictly categorical disease, the reported rates of progression are relatively low over a 20-year period, the longest time frame for which published data exist. In patients in whom stricture, Barrett's metaplasia, and adenocarcinoma were carefully 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.[2] On the other hand, the likelihood of developing Barrett's esophagus after the healing of high-grade esophagitis (or unmasking prevalent disease) is about 6%,[86] making endoscopy in the setting of Los Angeles grade C or D esophagitis an inadequate examination to exclude the presence of Barrett's esophagus. Most importantly, upper endoscopy has not been shown to diminish the risk of cancer in the setting of chronic GERD symptoms (USPSTF grade Insuff).

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 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, with some studies documenting a >80% recurrence rate within 12 months of discontinuing treatment.[90,91] Multiple rigorous randomized controlled trials,[92,93] summarized in a recent high-quality meta-analysis,[94] show that the recurrence of erosive esophagitis in subjects with GERD is dramatically decreased by PPI treatment. The meta-analysis found that in 10 studies assessing maintenance therapy with maintenance doses of PPI (generally half the healing dose) for 26–52 weeks, 36% of subjects taking PPIs experienced relapse of erosive disease, compared with 75% taking placebo. The relative risk of relapse in PPI users was 0.46, and the number needed to treat was 2.4. Reflux symptoms were also better controlled with maintenance-dose PPI therapy than with placebo (44.4% vs 73.4% had significant symptoms). The therapeutic gain was even more substantial when healing-dose PPI therapy was compared with placebo. Although several of the comparisons showed heterogeneity among individual trial results, on balance, the data strongly suggest that, when compared with placebo, chronic acid suppression with PPIs prevents relapse of erosive esophagitis for at least 6–12 months in subjects healed of the condition (USPSTF grade A, quality good). Similarly strong are randomized controlled trials between H_2RAs and either healing- or maintenance-dose PPIs, with subjects randomized to H_2RAs up to twice as likely to have recurrent esophagitis.[95,96]

The role of daily maintenance therapy in patients with nonerosive disease is less clear. Patients with an esophageal GERD syndrome without esophagitis who initially responded to a PPI randomized to maintenance-dose PPI therapy are less likely to have recurrent symptoms than when randomized to an H_2RA[97] or placebo.[98] Whether PPI dosing needs to be continuous as opposed to "on-demand" (daily until resolution of symptoms) has also been studied, using the willingness of the patient to continue on-demand therapy and the proportion of days that the patient self-medicates as outcomes. A systematic review of 17 such studies (15 of which were randomized controlled trials) showed that subjects with either nonerosive or uninvestigated GERD did well with on-demand regimens.[99] For example, Tsai et al randomized 622 subjects with nonerosive disease to either on-demand esomeprazole 20 mg or daily lansoprazole 15 mg.[100] Subjects assigned to on-demand therapy were actually slightly more likely to be willing to continue therapy than subjects in the continuous therapy arm (93% vs 88%) and used much less medication (0.3 vs 0.8 doses per day). 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 (USPSTF grade B, quality good). In contrast, in those with known 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 in subjects treated with on-demand compared with continuous therapy (42% vs 19% at 6 months; $P < .00001$).[101] Therefore, on-demand therapy cannot be recommended for maintaining healing of erosive esophagitis (USPSTF grade D, quality good).

The evidence presented in the previous text 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.[102,103] 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.[2] 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 of 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. Certainly, the data in Table 4 do not support the contention that residual GERD symptoms predispose

patients to the development of Barrett's esophagus or esophageal adenocarcinoma. Pragmatically, this means that many subjects beginning PPI therapy will receive this therapy chronically, but often intermittently. Interestingly, an accumulating body of literature now shows that even when subjects are instructed to take daily PPI therapy for GERD, compliance plummets within 3 months of instituting therapy, such that the majority of subjects become noncompliant with daily dosing.[104]

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 and conservative measures are unlikely to suffice on their own. Beyond recurrence of symptoms and/or erosive disease, the risks associated with cessation of therapy, including the possible development of Barrett's esophagus, are minimal. Data suggest that on-demand dosing or intermittent courses of PPIs is the regimen preferred by most patients regardless of physician instructions.

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?

Owing to the nonspecificity of the extraesophageal reflux syndromes for GERD, at least 40%–50% of patients will have persistent symptoms after 8 weeks of empirical PPI therapy. In this group of patients, the need for continued PPI therapy is predicated on the presence and severity of concomitant esophageal syndromes with or without mucosal injury. Although the true prevalence of esophageal mucosal abnormalities in this group of patients is unknown, uncontrolled observational studies of small sample sizes suggest the presence of esophagitis and Barrett's mucosa in 12% and 7%, respectively.[105,106] In the absence of concomitant esophageal GERD syndromes, PPI therapy should be discontinued and other diagnostic and/or therapeutic avenues explored.

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 (see discussion of question 8 in the previous text) (USPSTF grade Insuff). Although early observations suggested some association between reflux-induced laryngeal inflammation and laryngeal cancer,[107] critical appraisal of these data suggests that such associations are inconclusive and mostly biased.[108] Hence, the objective of continued maintenance therapy in patients with an 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. However, a double-blind placebo-controlled trial addressing the issue of discontinuing PPI therapy in an unselected group of patients on chronic PPI therapy reported a disappointing 21% likelihood of remaining PPI free at 1 year in patients with typical GERD symptoms and 48% in patients without typical GERD symptoms, highlighting the tendency toward long-term use in many patients.[109]

In summary, step-down therapy should be attempted in all patients with extraesophageal reflux syndromes after empirical twice-daily PPI therapy. Continuing maintenance PPI therapy should be predicated on either the requirements of therapy for concomitant esophageal GERD syndromes or extraesophageal syndrome symptom response. In both cases, maintenance therapy should be with the lowest PPI dose necessary for adequate symptom relief.

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)?

Most of the mortality from reflux disease stems from its link with esophageal adenocarcinoma, and there is no high-level evidence that the risk is reduced by any currently available GERD therapy.[110] Epidemiologic evidence does, however, suggest a substantial risk reduction with aspirin or nonsteroidal anti-inflammatory drug use.[111] Apart from esophageal adenocarcinoma, the mortality associated with reflux disease is very low, estimated at 0.46/100,000 in the year 2000.[112] Given the profoundly low mortality rate of this disease, therapies for GERD must be extremely safe to satisfy an acceptable risk-benefit ratio.

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, but the widespread use of PPIs coupled with the frequent need for chronic, often open-ended therapy mandate that they be scrutinized. Table 5 summarizes the available data on the risks of long-term PPI use.[113–128]

The data in Table 5 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.

Table 5. Potential Risks of Long-term PPI Therapy

Potential risks of hypochlorhydria (trophic, absorptive)	Risk magnitude/possible consequence
Hypergastrinemia-induced carcinoid tumors	Not demonstrated in humans[113]
Accelerated progression of atrophic gastritis/gastric cancer with concomitant *H pylori* gastritis[115]	No documentation of an increase in atrophic gastritis and no basis to recommend testing or treatment for *H pylori* before long-term PPI use[116]
Formation of gastric fundic gland polyps[168]	Odds ratio of 2.2 for developing fundic gland polyps within 1–5 years,[168] negligible, if any, risk of dysplasia
Vitamin B_{12} malabsorption	Some patients show decreased vitamin B_{12} levels after years of acid inhibition,[113] case reports (2) of clear deficiency[114]
Calcium malabsorption	Nested case-control study of UK patients older than 50 years; adjusted odds ratio of 1.44 (95% confidence interval, 1.30–1.59) of hip fracture with PPI use longer than 1 year[122]
Iron malabsorption	Poor response to oral iron supplement absorption in 2 iron-deficient individuals improved after cessation of omeprazole; no clear clinical relevance[169]
Potential risks of hypochlorhydria (infectious)	
Increased risk of *C difficile* colitis	PPI use is independent risk of *C difficile* diarrhea in antibiotic users, odds ratio of 2.1 (95% confidence interval, 1.2–3.5)[120]
Increased risk of community-acquired pneumonia (presumably aspiration)	Nested case-control analysis, adjusted odds ratio for pneumonia with PPI use of 1.73 (95% confidence interval, 1.33–2.25)[121]
Gastric colonization with bacteria that convert nitrates to carcinogenic *N*-nitroso compounds that then reflux[117]	Data on PPI use and increased gastric *N*-nitrosamine remain uncertain and the risk of cancer is speculative[113]
Generic pharmacologic risks	
Safety in pregnancy (omeprazole crosses placenta and is pregnancy safety category C; other PPIs are category B)	Based on 345 accidental exposures compared with 787 controls, no observed increased teratogenecity[123]
Drug-drug interactions; PPIs metabolized by cytochrome P450 and may induce or inhibit drug metabolism (phenytoin, warfarin, and so on)	Clinically significant PPI drug-drug interactions are rare (<1/million prescriptions)[124]
Anaphylaxis	One case report with lansoprazole[125]
Acute interstitial nephritis	64 cases worldwide, partially reversible (one case requires dialysis, no deaths), estimated risk 1/12,500 patient-years of therapy[126,127]
Pancreatitis	Population-based case-control study adjusted odds ratio of 3.2 (95% confidence interval, 1.4–7.4[128]

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 shown with PPI use.[129] 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 (USPSTF grade A, quality good). Conversely, there is inadequate evidence to mandate bone density studies, calcium supplementation, *H pylori* screening, or any other routine precautions because of PPI use (USPSTF grade Insuff). Having said that, many of the potential rare side effects of PPIs are dose related, and PPIs should be used for conditions in which they have proven efficacy and at the minimal effective dosage. After all, in the absence of benefit, a risk-benefit ratio is always unacceptable.

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?

Because PPI treatment is usually rendered empirically before testing, the sensitivity of endoscopy as a diagnostic test for GERD is poor. Hence, the principal use of endoscopy in patients with 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, and that risk has not been shown to be decreased by any current GERD therapy.[110] Otherwise, the mortality associated with reflux disease is very low, estimated at 0.46/100,000 in the year 2000, and mainly attributable to hemorrhagic esophagitis (38%), ulcer perforation or esophageal rupture (19%), aspiration pneumonia (19%), and complications of antireflux surgery (11%).[112] Putting the risk of adenocarcinoma in perspective, data from the Surveillance Epidemiology and End Results database suggest that there were about 8000 incident cases of esophageal adenocarcinoma in the United States in 2004[130] and, depending on interpretation of the data, this disease burden has increased anywhere from 2- to 6-fold relative to 20 years prior.[131,132]

The 5-year survival of patients with esophageal adenocarcinoma is very poor, but it is greatly improved by early detection: 58% for patients with tumors detected in situ versus 10% for patients with tumors detected after regional spread.[133] The other potential benefit of endoscopy in the

setting of chronic GERD is detection of Barrett's esophagus, a metaplastic change of the distal esophageal mucosa acknowledged to be a premalignant condition. The risk of developing esophageal adenocarcinoma in Barrett's esophagus is estimated at 0.5% per year.[134] 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. In the hope of controlling the risk of adenocarcinoma, past societal guidelines, including those of the American Society of Gastrointestinal Endoscopy[135] and the American College of Gastroenterology,[136,137] have supported consideration of the use of at least once-in-a-lifetime endoscopy to screen subjects with chronic GERD symptoms for the presence of Barrett's esophagus or early cancer. However, these guidelines are based solely on expert opinion because 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.

Evidence supporting the strategy of reducing esophageal adenocarcinoma mortality by screening for Barrett's esophagus is scarce. For such a strategy to work well, patients with Barrett's esophagus would need to constitute the majority of patients at risk for cancer, the severity of reflux symptoms would have to be predictive of finding Barrett's esophagus, and endoscopy would effectively identify patients with Barrett's esophagus, leading to altered clinical management that improved the clinical outcome. To date, none of these conditions have been borne out in clinical trials. (1) In a Swedish population-based endoscopy study, the prevalence of Barrett's esophagus (1.6%) was not correlated with reflux symptoms.[138] (2) In a nationwide case-control study, more than 40% of Swedes destined to develop esophageal adenocarcinoma reported no antecedent reflux symptoms.[139] (3) In a Kaiser Permanente cohort study, 454 of 589 patients with esophageal or gastric cardia adenocarcinoma had no identifiable Barrett's metaplasia evident in any pathology specimen.[140] (4) In the same cohort, among 64 patients who had undergone endoscopy before detection of cancer, only 38% had Barrett's esophagus identified.[140] (5) Analyses of 2 large Barrett's esophagus surveillance programs concluded that, although a small number of incident esophageal adenocarcinomas were detected, there was no improvement in survival attributable to the surveillance program.[141,142] These data were reviewed by an AGA consensus workshop composed of 18 experts in the field of Barrett's esophagus in 2004.[143] After conducting an evidence-based review of the utility of endoscopic screening of subjects with chronic GERD symptoms for the detection of Barrett's esophagus or cancer, this group strongly rejected the statement that "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" (USPSTF grade Insuff). 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 either rejected the statement or rejected it with reservation (USPSTF grade Insuff).

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 should be obtained and carefully evaluated for dysplasia.

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

Few topics in the management of patients with GERD are as controversial as the indications for and efficacy of antireflux surgery. With the introduction of laparoscopic Nissen fundoplication in 1991, the number of adult antireflux surgeries performed in the United States rapidly increased from 11,000 per year in 1985 to 31,695 in 1999.[144] This increase was largely driven by the enthusiastic endorsement of the procedure by endoscopic surgeons and surgery departments in a number of disease scenarios, typified by guidelines from the Society for Gastrointestinal and Endoscopic Surgeons claiming that the procedure was curative in 85%–93% of cases.[145] However, since 1999, the number of adult antireflux surgeries performed in the United States has steadily fallen; by 2003, it had declined by 30% to 23,998 cases.[144] The decline has been greatest among young patients, 18–39 years of age (38%), and at teaching versus nonteaching hospitals (36% vs 23%). There is also substantial regional variation in the utilization of antireflux surgery, suggesting a lack of consensus among practitioners with respect to the appropriate indications.[144]

Just as with PPI therapy, evidence of the utility of antireflux surgery depends on the manifestation of the disease being monitored, with the strongest data pertaining to erosive esophagitis. However, the utility of older data randomizing subjects to either medical care with H_2RAs or Nissen fundoplication by the open approach[146] are limited because of advances in care in both domains. More recent data comparing laparoscopic fundoplication with PPI therapy are more germane to current practice and will be considered here. Illustrative of this, Lundell et al have reported 5- and 7- year results of a randomized controlled trial of patients with esophagitis treated with

omeprazole 20–60 mg/day or antireflux surgery. At 7 years, the 2 treatment arms were similar with respect to the incidence of recurrent esophagitis (10.3% omeprazole vs 11.8% antireflux surgery).[147] Hence, if the outcome of importance is maintaining a healed esophageal mucosa, the 2 therapies appear to be equivalent.

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.[110,148] It is important for providers and patients to understand that the risk of this cancer to the average subject with reflux symptoms is extremely low (<1 in 10,000 per patient-year).[149] Even though the safety profile of antireflux surgery is excellent for a surgical procedure, the low risks of morbidity and mortality still dwarf any potential benefit in reduction of cancer risk. Even among subjects with Barrett's esophagus, who have a higher risk of cancer than the general GERD population, randomized controlled trial data[150] and a recent meta-analysis[151] 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 as determined by investigator interview or questionnaire, studies suggest modest superiority of antireflux surgery to PPI therapy, on the order of a 10% therapeutic gain.[147,152] However, the data are widely divergent. As many as 30% of subjects who undergo this procedure continue to use medical therapy by 5 years after the procedure and surgical revision is common. Also, although community-based outcome data are sparse compared with that generated from specialized referral centers, the data suggest that subjects from community-based series may have poorer outcomes and lower patient satisfaction than those in specialized, presumably higher-volume centers.[153,154] 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 highly selected patients with reflux cough syndrome[66,155] and reflux asthma syndrome.[65,156] 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 treated with antireflux surgery,[157,158] and both controlled[147] and uncontrolled trials[159] 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 (USPSTF grade B, quality fair), than for extraesophageal symptoms (USPSTF grade C, quality fair).

As alluded to in the discussion of the risks associated with chronic PPI therapy (question 10), the otherwise low morbidity and mortality associated with GERD mandate that GERD therapies must be extremely safe to satisfy an acceptable risk-benefit ratio. Table 6 summarizes the available morbidity and mortality data on antireflux surgery.[153,157,160–165] Note that unlike the treatment efficacy data, in which case it is reasonable to restrict the analysis to controlled studies from highly specialized centers, it is more relevant to assess morbidity and mortality data from the perspective of larger data sets reflective of the overall impact of the intervention on public health. Similarly, it is reasonable to compare the data in Table 6 with that in Table 5, detailing what is known of the risks of long-term PPI therapy. Given that comparison, from the vantage point of risk, if antireflux surgery and PPI therapy were estimated to be equally effective for a patient, PPI therapy should be strongly recommended (USPSTF grade A, quality good).

In contrast to the data regarding antireflux surgery, high-quality data on endoluminal antireflux procedures remain sparse. Most available studies were designed to show proof of principle in this rapidly evolving area. To date, no studies compare the efficacy of these devices with either optimal medical therapy or antireflux surgery. Although the latest of these devices show promise,[166,167] the dearth of comparative data, as well as the small number and relatively short follow-up of subjects treated, make it premature to frame recommendations for their use in GERD (USPSTF grade Insuff).

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 significant risk; they should be advised against surgery (USPSTF grade A, quality good). Patients with esophagitis who are intolerant of PPIs will likely benefit from antireflux surgery and should be so advised (USPSTF grade A, quality good). Patients with symptoms of the esophageal GERD syndrome poorly controlled by PPIs may benefit from surgery, especially in the setting of persistent troublesome regurgitation (USPSTF grade B, quality fair). However, the recommendation for antireflux surgery must be balanced with a thorough discussion of potential post–antireflux surgery symptoms. Finally, carefully selected patients with extraesophageal GERD syndromes in whom a reflux causality has been established to the greatest degree possible (see question 4) may benefit from antireflux surgery, and it should be recommended with appropriate restraint (USPSTF grade C, quality fair). The paucity of comparative data on endoluminal antireflux

Table 6. Complications From Antireflux Surgery

Death	
Population-based, Finland; January 1, 1987, to January 1, 1996; n = 1162 LNF; n = 3993 OF[163]	LNF = 0.1% OF = 0.2%
Danish, population-based; 1997–2005; n = 2465 primary fundoplication and 124 RF[162]	Primary = 0.45% RF = 0.81%
US VA database; October 1, 1990, to January 29, 2001; n = 3145[157]	LNF and OF = 0.8%
US population-based cohorts, Washington state and US Health Care Utilization Project, 1992–1997[164]	Washington = 0.4% US Health Care Utilization Project = 0.8%
Meta-analysis of reports published from 1991 to 1995; specialty centers, n = 2453; follow-up, 0–36 mo[160]	LNF = 0.2%
Life-threatening complications	
Population-based, Finland; January 1, 1987, to January 1, 1996; n = 1162 LNF; n = 3993 OF[163]	LNF = 1.2% OF = 0.6%
Danish, population-based; 1997–2005; n = 2465 primary FP and 124 RF[162]	Primary FP = 1.3% RF = 1.6%
US population-based cohorts, Washington state and US Health Care Utilization Project, 1992–1997[164]	Washington = 2.0% US Health Care Utilization Project = 3.4%
Meta-analysis of reports published from 1991 to 1995; specialty centers, n = 2453[160]	LNF = 1.5%
Wisconsin managed care network; community practices, n = 87[153]	LNF = 3.4%
Reoperations (redo)	
Danish, population-based; 1997–2005; n = 2465 primary fundoplications[162]	1.5%/yr in first 2 yr 1.0%/yr next 2 yr 0.3%/yr in following years
US VA database; October 1, 1990, to January 29, 2001; n = 3145 with a median follow-up of 4.5 yr[157]	LNF and OF = 2.3%
Wisconsin managed care network; community practices, n = 87[153]	LNF = 7.0%
Dysphagia severe enough to require dilation	
US VA database; October 1, 1990, to January 29, 2001; n = 3145 with a median follow-up of 4.5 yr[157]	LNF and OF = 6.4%
Meta-analysis of reports published from 1991 to 1995; specialty centers, n = 2453; follow-up, 0–36 mo[160]	LNF = 3.5%
Wisconsin managed care network; community practices, n = 87[153]	LNF = 11%
Specialty center, retrospective review of June 1996 to October 1998; n = 233[165]	LNF = 12%

LNF, laparoscopic fundoplication; OF, open fundoplication; RF, redo fundoplication.

procedures with either optimal medical therapy or antireflux surgery makes it impossible to define the role of such techniques in our current treatment algorithm (USPSTF grade Insuff).

Conclusions

In formulating guidelines for the management of patients with GERD, we found the Montreal definition of GERD[3] (Figure 1) to be very useful and structured our recommendations around it. Contemplating the broad domain of the Montreal definition, an immediate conclusion was that much of the management of patients with GERD in terms of diagnostic tests and disease management is based on uncontrolled trials, clinical experience, or expert opinion rather than randomized controlled clinical trials; high-quality trials in these areas simply do not exist. Randomized controlled clinical trials are, however, ubiquitous in the domain of therapy for the esophageal GERD syndromes, especially pharmacologic therapies for esophagitis. Hence, it is not surprising that most of the highest-level evidence-based recommendations that can be made pertain to that scenario. However, the acute management of patients with esophagitis is rarely a clinical dilemma in current practice. Hence, we focused instead on the clinical quandaries that do confront the clinician with great regularity and examined the evidence that could be brought to bear on those issues. We used the USPSTF grades detailed in Table 1 to ascertain whether or not particular practices or therapies could be recommended based on published evidence. Conceptually, USPSTF grades evaluate a risk-benefit assessment for diagnostic or therapeutic interventions. Although relatively few of our conclusions achieved the highest USPSTF grade, a substantial number achieved an adequate grade upon which to base pro or con recommendations. Our major conclusions follow.

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, symptomatic relief, and maintaining healing

of esophagitis). In these uses, PPIs are more effective than H_2RAs, which are more effective than placebo.

II. 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.

III. 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.

IV. 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.

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

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.

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.

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

IV. 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.

V. 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).

VI. 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.

VII. 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 LES 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.

VIII. 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.

IX. Antireflux surgery for patients with an esophageal GERD syndrome with persistent troublesome symptoms, especially troublesome regurgitation, despite PPI therapy. The potential benefits or 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.

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

II. 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.

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

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

V. Antireflux surgery for patients with an esophageal syndrome with or without tissue damage who are symptomatically well controlled on medical therapy.

VI. Antireflux surgery as an antineoplastic measure in patients with Barrett's metaplasia.

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.
II. Using alarm symptoms (other than troublesome dysphagia) as a screening tool to identify patients with GERD at risk for esophageal adenocarcinoma.
III. Adding a nocturnal dose of an H_2RA for patients with an esophageal syndrome with an inadequate symptom response to twice-daily PPI therapy.
IV. Routine upper endoscopy in the setting of chronic GERD symptoms to diminish the risk of death from esophageal cancer.
V. 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.
VI. 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.
VII. Combined impedance-pH, catheter pH, or wireless pH esophageal monitoring studies performed while taking PPIs.
VIII. 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.
IX. Once- or twice-daily PPIs for patients with suspected reflux cough syndrome.
X. Advocating bone density studies, calcium supplementation, *H pylori* screening, or any other routine precaution because of PPI use.
XI. The use of currently commercially available endoluminal antireflux procedures in the management of patients with an esophageal syndrome.

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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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