CME

Guidelines for the Diagnosis and Management of Gastroesophageal Reflux Disease

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Gastroesophageal reflux disease (GERD) is arguably the most common disease encountered by the gastroenterologist. It is equally likely that the primary care providers will find that complaints related to reflux disease constitute a large proportion of their practice. The following guideline will provide an overview of GERD and its presentation, and recommendations for the approach to diagnosis and management of this common and important disease.

The document will review the presentations of any risk factors for GERD, the diagnostic modalities and their recommendation for use and recommendations for medical, surgical and endoscopic management including comparative effectiveness of different treatments. Extraesophageal symptoms and complications will be addressed as will the evaluation and management of "refractory" GERD. The document will conclude with the potential risks and side effects of the main treatments for GERD and their implications for patient management.

Each section of the document will present the key recommendations related to the section topic and a subsequent summary of the evidence supporting those recommendations. An overall summary of the key recommendations is presented in **Table 1**. A search of OVID Medline, Pubmed and ISI Web of Science was conducted for the years from 1960–2011 using the following major search terms and subheadings including "heartburn", "acid regurgitation", "GERD", "lifestyle interventions", "proton pump inhibitor (PPI)", "endoscopic surgery," "extraesophageal symptoms," "Nissen fundoplication," and "GERD complications." We used systematic reviews and meta-analyses for each topic when available followed by a review of clinical trials.

The GRADE system was used to evaluate the strength of the recommendations and the overall level of evidence (1,2). The level of evidence could range from "high" (implying that further research was unlikely to change the authors' confidence in the estimate of the effect) to "moderate" (further research would be likely to have an impact on the confidence in the estimate of effect) or "low" (further research would be expected to have an important impact on the confidence in the estimate of the effect and would be likely to change the estimate). The strength of a recommendation was graded as "strong" when the desirable effects of an intervention clearly outweigh the undesirable effects and as "conditional" when there is uncertainty about the trade-offs.

It is important to be aware that GERD is defined by consensus and as such is a disease comprising symptoms, end-organ effects and complications related to the reflux of gastric contents into the esophagus, oral cavity, and/or the lung. Taking into account the multiple consensus definitions previously published (3–5), the authors have used the following working definition to define the disease: GERD should be defined as symptoms or complications resulting from the reflux of gastric contents into the esophagus or beyond, into the oral cavity (including larynx) or lung. GERD can be further classified as the presence of symptoms without erosions on endoscopic examination (non-erosive disease or NERD) or GERD symptoms with erosions present (ERD).

SYMPTOMS AND EPIDEMIOLOGY

Epidemiologic estimates of the prevalence of GERD are based primarily on the typical symptoms of heartburn and regurgitation. A systematic review found the prevalence of GERD to be 10–20% of the Western world with a lower prevalence in Asia (6). Clinically troublesome heartburn is seen in about 6% of the population (7). Regurgitation was reported in 16% in the systematic review noted above. Chest pain may be a symptom of GERD, even the presenting symptom (2,3). Distinguishing cardiac from non-cardiac chest pain is required before considering GERD as a cause of chest pain. Although the symptom of dysphagia can be associated with uncomplicated GERD, its presence warrants investigation for a potential complication including an underlying motility disorder, stricture, ring, or malignancy (8). Chronic cough, asthma, chronic

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Table 1. Summary and strength of recommendations

Establishing the diagnosis of Gastroesophageal Reflux Disease (GERD)
1. A presumptive diagnosis of GERD can be established in the setting of typical symptoms of heartburn and regurgitation. Empiric medical therapy with a proton pump inhibitor (PPI) is recommended in this setting. (Strong recommendation, moderate level of evidence)
2. Patients with non-cardiac chest pain suspected due to GERD should have diagnostic evaluation before institution of therapy. (Conditional recommendation, moderate level of evidence). A cardiac cause should be excluded in patients with chest pain before the commencement of a gastrointestinal evaluation (Strong recommendation, low level of evidence)
3. Barium radiographs should not be performed to diagnose GERD (Strong recommendation, high level of evidence)
4. Upper endoscopy is not required in the presence of typical GERD symptoms. Endoscopy is recommended in the presence of alarm symptoms and for screening of patients at high risk for complications. Repeat endoscopy is not indicated in patients without Barrett's esophagus in the absence of new symptoms. (Strong recommendation, moderate level of evidence)
5. Routine biopsies from the distal esophagus are not recommended specifically to diagnose GERD. (Strong recommendation, moderate level of evidence)
6. Esophageal manometry is recommended for preoperative evaluation, but has no role in the diagnosis of GERD. (Strong recommendation, low level of evidence)
7. Ambulatory esophageal reflux monitoring is indicated before consideration of endoscopic or surgical therapy in patients with non-erosive disease, as part of the evaluation of patients refractory to PPI therapy, and in situations when the diagnosis of GERD is in question. (Strong recommendation, low level of evidence). Ambulatory reflux monitoring is the only test that can assess reflux symptom association (strong recommendation, low level of evidence).
8. Ambulatory reflux monitoring is not required in the presence of short or long-segment Barrett's esophagus to establish a diagnosis of GERD. (Strong recommendation, moderate level of evidence)
9. Screening for *Helicobacter pylori* infection is not recommended in GERD patients. Treatment of *H. pylori* infection is not routinely required as part of antireflux therapy. (Strong recommendation, low level of evidence)
Management of GERD
1. Weight loss is recommended for GERD patients who are overweight or have had recent weight gain. (Conditional recommendation, moderate level of evidence)
2. Head of bed elevation and avoidance of meals 2–3 h before bedtime should be recommended for patients with nocturnal GERD. (Conditional recommendation, low level of evidence)
3. Routine global elimination of food that can trigger reflux (including chocolate, caffeine, alcohol, acidic and/or spicy foods) is not recommended in the treatment of GERD. (Conditional recommendation, low level of evidence)
4. An 8-week course of PPIs is the therapy of choice for symptom relief and healing of erosive esophagitis. There are no major differences in efficacy between the different PPIs. (Strong recommendation, high level of evidence)
5. Traditional delayed release PPIs should be administered 30–60 min before meal for maximal pH control. (Strong recommendation, moderate level of evidence). Newer PPIs may offer dosing flexibility relative to meal timing. (Conditional recommendation, moderate level of evidence)
6. PPI therapy should be initiated at once a day dosing, before the first meal of the day. (Strong recommendation, moderate level of evidence). For patients with partial response to once daily therapy, tailored therapy with adjustment of dose timing and/or twice daily dosing should be considered in patients with night-time symptoms, variable schedules, and/or sleep disturbance. (Strong recommendation, low level of evidence).
7. Non-responders to PPI should be referred for evaluation. (Conditional recommendation, low level of evidence, see refractory GERD section).
8. In patients with partial response to PPI therapy, increasing the dose to twice daily therapy or switching to a different PPI may provide additional symptom relief. (Conditional recommendation, low level evidence).
9. Maintenance PPI therapy should be administered for GERD patients who continue to have symptoms after PPI is discontinued, and in patients with complications including erosive esophagitis and Barrett's esophagus. (Strong recommendation, moderate level of evidence). For patients who require long-term PPI therapy, it should be administered in the lowest effective dose, including on demand or intermittent therapy. (Conditional recommendation, low level of evidence)
10. H_2-receptor antagonist (H_2RA) therapy can be used as a maintenance option in patients without erosive disease if patients experience heartburn relief. (Conditional recommendation, moderate level of evidence). Bedtime H_2RA therapy can be added to daytime PPI therapy in selected patients with objective evidence of night-time reflux if needed, but may be associated with the development of tachyphlaxis after several weeks of use. (Conditional recommendation, low level of evidence)
11. Therapy for GERD other than acid suppression, including prokinetic therapy and/or baclofen, should not be used in GERD patients without diagnostic evaluation. (Conditional recommendation, moderate level of evidence)
12. There is no role for sucralfate in the non-pregnant GERD patient. (Conditional recommendation, moderate level of evidence)
13. PPIs are safe in pregnant patients if clinically indicated. (Conditional recommendation, moderate level of evidence)
Surgical options for GERD
1. Surgical therapy is a treatment option for long-term therapy in GERD patients. (Strong recommendation, high level of evidence)
2. Surgical therapy is generally not recommended in patients who do not respond to PPI therapy. (Strong recommendation, high level of evidence)
3. Preoperative ambulatory pH monitoring is mandatory in patients without evidence of erosive esophagitis. All patients should undergo preoperative manometry to rule out achalasia or scleroderma-like esophagus. (Strong recommendation, moderate level of evidence)
4. Surgical therapy is as effective as medical therapy for carefully selected patients with chronic GERD when performed by an experienced surgeon. (Strong recommendation, high level of evidence)
5. Obese patients contemplating surgical therapy for GERD should be considered for bariatric surgery. Gastric bypass would be the preferred operation in these patients. (Conditional recommendation, moderate level of evidence)
6. The usage of current endoscopic therapy or transoral incisionless fundoplication cannot be recommended as an alternative to medical or traditional surgical therapy. (Strong recommendation, moderate level of evidence)

Table 1. Continued

Potential risks associated with PPIs
1. Switching PPIs can be considered in the setting of side-effects. (Conditional recommendation, low level of evidence)
2. Patients with known osteoporosis can remain on PPI therapy. Concern for hip fractures and osteoporosis should not affect the decision to use PPI long-term except in patients with other risk factors for hip fracture. (Conditional recommendation, moderate level of evidence)
3. PPI therapy can be a risk factor for *Clostridium difficile* infection, and should be used with care in patients at risk. (Moderate recommendation, moderate level of evidence)
4. Short-term PPI usage may increase the risk of community-acquired pneumonia. The risk does not appear elevated in long-term users. (Conditional recommendation, moderate level of evidence)
5. PPI therapy does not need to be altered in concomitant clopidogrel users as there does not appear to be an increased risk for adverse cardiovascular events. (Strong recommendation, high level of evidence)
Extraesophageal presentations of GERD: Asthma, chronic cough, and laryngitis
1. GERD can be considered as a potential co-factor in patients with asthma, chronic cough, or laryngitis. Careful evaluation for non-GERD causes should be undertaken in all of these patients. (Strong recommendation, moderate level of evidence).
2. A diagnosis of reflux laryngitis should not be made based solely upon laryngoscopy findings. (Strong recommendation, moderate level of evidence)
3. A PPI trial is recommended to treat extraesophageal symptoms in patients who also have typical symptoms of GERD. (Strong recommendation, low level of evidence)
4. Upper endoscopy is not recommended as a means to establish a diagnosis of GERD-related asthma, chronic cough, or laryngitis. (Strong recommendation, low level of evidence)
5. Reflux monitoring should be considered before a PPI trial in patients with extraesophageal symptoms who do not have typical symptoms of GERD. (Conditional recommendation, low level of evidence)
6. Non-responders to a PPI trial should be considered for further diagnostic testing and are addressed in the refractory GERD section below. (Conditional recommendation, low level of evidence)
7. Surgery should generally not be performed to treat extraesophageal symptoms of GERD in patients who do not respond to acid suppression with a PPI. (Strong recommendation, moderate level of evidence)
GERD refractory to treatment with PPIs
1. The first step in management of refractory GERD is optimization of PPI therapy. (Strong recommendation, low level of evidence)
2. Upper endoscopy should be performed in refractory patients with typical or dyspeptic symptoms principally to exclude non-GERD etiologies. (Conditional recommendation, low level of evidence)
3. In patients in whom extraesophageal symptoms of GERD persist despite PPI optimization, assessment for other etiologies should be pursued through concomitant evaluation by ENT, pulmonary, and allergy specialists. (Strong recommendation, low level of evidence)
4. Patients with refractory GERD and negative evaluation by endoscopy (typical symptoms) or evaluation by ENT, pulmonary, and allergy specialists (extraesophageal symptoms), should undergo ambulatory reflux monitoring. (Strong recommendation, low level of evidence)
5. Reflux monitoring *off* medication can be performed by any available modality (pH or impedance-pH). (Conditional recommendation, moderate level evidence). Testing *on* medication should be performed with impedance-pH monitoring in order to enable measurement of nonacid reflux. (Strong recommendation, moderate level of evidence).
6. Refractory patients with objective evidence of ongoing reflux as the cause of symptoms should be considered for additional antireflux therapies, which may include surgery or TLESR inhibitors. (Conditional recommendation, low level of evidence). Patients with negative testing are unlikely to have GERD and PPI therapy should be discontinued. (Strong recommendation, low level of evidence)
Complications Associated with GERD
1. The Los Angeles (LA) classification system should be used when describing the endoscopic appearance of erosive esophagitis. (Strong recommendations, moderate level of evidence). Patients with LA Grade A esophagitis should undergo further testing to confirm the presence of GERD. (Conditional recommendation, low level of evidence)
2. Repeat endoscopy should be performed in patients with severe erosive reflux disease after a course of antisecretory therapy to exclude underlying Barrett's esophagus. (Conditional recommendation, low level of evidence)
3. Continuous PPI therapy is recommended following peptic stricture dilation to improve dysphagia and reduce the need for repeated dilations. (Strong recommendation, moderate level of evidence)
4. Injection of intralesional corticosteroids can be used in refractory, complex strictures due to GERD. (Conditional recommendation, low level of evidence)
5. Treatment with a PPI is suggested following dilation in patients with lower esophageal (Schatzki) rings. (Conditional recommendation, low level of evidence)
6. Screening for Barrett's esophagus should be considered in patients with GERD who are at high risk based on epidemiologic profile. (Conditional recommendation, moderate level of evidence)
7. Symptoms in patients with Barrett's esophagus can be treated in a similar fashion to patients with GERD who do not have Barrett's esophagus. (Strong recommendation, moderate level of evidence)
8. Patients with Barrett's esophagus found at endoscopy should undergo periodic surveillance according to guidelines. (Strong recommendation, moderate level of evidence)

ENT, ear, nose, and throat; GERD, gastroesophageal reflux disease; LA, Los Angeles; PPI, proton pump inhibitor.

laryngitis, other airway symptoms and so-called extraesophageal symptoms are discussed in a subsequent section. Atypical symptoms including dyspepsia, epigastric pain, nausea, bloating, and belching may be indicative of GERD but overlap with other conditions. A systematic review found that ~38% of the general population complained of dyspepsia. Dyspepsia was more frequent in GERD patients than those without. These patients were at risk for a new diagnosis of GERD. Epigastric pain, early satiety, belching and bloating were more likely to respond to a PPI therapy compared with nausea. Overall, these symptoms can be considered to be associated with GERD if they respond to a PPI trial (9).

A recent systematic review on the burden of GERD on quality of life (QOL) included 19 studies. Patients with disruptive GERD (daily or >weekly symptoms) had an increase in time off work and decrease in work productivity. Low scores on sleep scales were seen compared with patients with less frequent symptoms. A decrease in physical functioning was also seen (10). Nocturnal GERD has a greater impact on QOL compared with daytime symptoms. Both nocturnal symptoms and sleep disturbances are critical to elucidate when evaluating the GERD patient (11).

The balance of evidence suggests that symptom frequency does not change as we age, however, the intensity of symptoms may decrease after the age of 50 (12). Aging increases the prevalence of erosive esophagitis, Los Angeles (LA) grades C and D (13). Barrett's esophagus increases in prevalence after age 50, especially in Caucasian males (14). There are little data addressing the features of GERD in women distinct from men. Patients with erosive esophagitis are more likely to be men, and women are more likely to have NERD. Barrett's esophagus is more frequent in men compared with women (15). The gender ratio for esophageal adenocarcinoma is estimated to be 8:1 male to female (14).

There is a definite relationship between GERD and obesity. Several meta-analysis suggest an association between body mass index (BMI), waist circumference, weight gain and the presence of symptoms and complications of GERD including ERD and Barrett's esophagus (16,17). The ProGERD study, likely the largest of its kind (>5,000 patients) used logistic regression analysis to identify several independent risk factors for ERD. The odds for higher degrees of ERD increased as BMI rose (18). It is of greatest concern that there has been a well-documented association between BMI and carcinoma of the esophagus and gastric cardia (19).

ESTABLISHING THE DIAGNOSIS OF GERD

Recommendations

1. A presumptive diagnosis of GERD can be established in the setting of typical symptoms of heartburn and regurgitation. Empiric medical therapy with a PPI is recommended in this setting. (Strong recommendation, moderate level of evidence).
2. Patients with non-cardiac chest pain suspected due to GERD should have diagnostic evaluation before institution of therapy. (Conditional recommendation, moderate level of evidence) A cardiac cause should be excluded in patients with chest pain before the commencement of a gastrointestinal evaluation (Strong recommendation, low level of evidence)
3. Barium radiographs should not be performed to diagnose GERD (Strong recommendation, high level of evidence)
4. Upper endoscopy is not required in the presence of typical GERD symptoms. Endoscopy is recommended in the presence of alarm symptoms and for screening of patients at high risk for complications. Repeat endoscopy is not indicated in patients without Barrett's esophagus in the absence of new symptoms. (Strong recommendation, moderate level of evidence)
5. Routine biopsies from the distal esophagus are not recommended specifically to diagnose GERD. (Strong recommendation, moderate level of evidence)
6. Esophageal manometry is recommended for preoperative evaluation, but has no role in the diagnosis of GERD. (Strong recommendation, low level of evidence)
7. Ambulatory esophageal reflux monitoring is indicated before consideration of endoscopic or surgical therapy in patients with NERD, as part of the evaluation of patients refractory to PPI therapy, and in situations when the diagnosis of GERD is in question. (Strong recommendation, low level evidence). Ambulatory reflux monitoring is the only test that can assess reflux symptom association (Strong recommendation, low level of evidence).
8. Ambulatory reflux monitoring is not required in the presence of short or long-segment Barrett's esophagus to establish a diagnosis of GERD. (Strong recommendation, moderate level of evidence).
9. Screening for *Helicobacter pylori* infection is not recommended in GERD. Eradication of *H. pylori* infection is not routinely required as part of antireflux therapy (Strong recommendation, low level of evidence)

The diagnosis of GERD is made using some combination of symptom presentation, objective testing with endoscopy, ambulatory reflux monitoring, and response to antisecretory therapy. (**Table 2**) The symptoms of heartburn and regurgitation are the most reliable for making a presumptive diagnosis based on history alone; however, these are not as sensitive as most believe. A systematic review of seven studies found the sensitivity of heartburn and regurgitation for the presence of erosive esophagitis to be 30–76% and the specificity from 62–96% (20). Empiric PPI therapy (a PPI trial) is a reasonable approach to confirm GERD when it is suspected in patients with typical symptoms. A response to therapy would ideally confirm the diagnosis; however, a well done meta-analysis suggested some limitations of this approach with a sensitivity of 78% and specificity of 54% (21). Therefore, empiric therapy (or a so called PPI trial) has some limitations.

Non-cardiac chest pain has often been associated with the presence of GERD, and can be the presenting symptom. A meta-analysis found a high probability that non-cardiac chest pain responds to aggressive acid suppression (22). This study supported earlier work suggesting the efficacy and cost effectiveness of a PPI trial (PPI twice daily in variable doses) in patients with chest pain in whom a cardiac cause had been excluded. However, a more recent systematic review suggested that the response of non-cardiac chest pain to a PPI trial was significantly higher than placebo in

Table 2. Diagnostic testing for GERD and utility of tests

Diagnostic test	Indication	Highest level of evidence	Recommendation
PPI trial	Classic symptoms, no warning signs,	Meta-analysis	Negative trial does not rule out GERD
Barium swallow	Not for GERD diagnosis. Use for evaluation of dysphagia	Case–control	Do not use unless evaluating for complication (stricture, ring)
Endoscopy	Alarm symptoms, screening of high-risk patients, chest pain	Randomized Controlled Trial	Consider early for elderly, those at risk for Barrett's, non-cardiac chest pain, patients unresponsive to PPI
Esophageal biopsy	Exclude non-GERD causes for symptoms	Case–Control	Not indicated for diagnosis of GERD
Esophageal manometry	Preoperative evaluation for surgery	Observational	Not recommended for GERD diagnosis. Rule out achalasia/scleroderma-like esophagus preop
Ambulatory reflux monitoring	Preoperatively for non-erosive disease. refractory GERD symptoms, GERD diagnosis in question	Observational	Correlate symptoms with reflux, document abnormal acid exposure or reflux frequency

GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor.

patients with objective evidence of GERD (ERD on endoscopy and/or abnormal pH monitoring) (23). The response to PPIs compared with placebo was almost non-existent in the absence of objective documentation of GERD. As such, a diagnostic evaluation with endoscopy and pH monitoring should be considered before a PPI trial (24). The presence of heartburn in conjunction with chest pain was not predictive of PPI response of the chest pain component.

Dysphagia has historically been an alarm symptom or warning sign and an indication for early endoscopy to rule out a GERD complication. Respiratory symptoms have been associated with GERD, based on retrospective case–control studies. In addition, dental erosions, erosion of dental enamel, sinusitis, chronic laryngitis and voice disturbance have similarly been associated with GERD. These are discussed later in the article. Overall, heartburn and regurgitation remain reliable symptoms of GERD as does non-cardiac chest pain. Other symptoms, while associated with GERD, are not as reliable. The causal relationship between GERD and the so-called atypical and extraesophageal manifestations remains difficult with only a history.

Barium radiographs have been historically considered part of the potential diagnostic armamentarium in the patient with esophageal symptoms, including GERD. Although well-performed barium esophagrams with double contrast can detect signs of esophagitis, the overall sensitivity of this test is extremely low (25). The finding of barium reflux above the thoracic inlet with or without provocative maneuvers including the water siphon test does increase the sensitivity of the barium test; however, not sufficiently to be recommended as a diagnostic test without dysphagia (26).

The endoscope has long been the primary tool used to evaluate the esophageal mucosa in patients with symptoms suspected due to GERD. Findings of GERD include erosive esophagitis, strictures, and a columnar lined esophagus ultimately confirmed to be Barrett's esophagus. As such, endoscopy has excellent specificity for the diagnosis of GERD especially when erosive esophagitis is seen and the LA classification is used (27). However, the vast majority of patients with heartburn and regurgitation will not have erosions (or Barrett's) limiting upper endoscopy as an initial diagnostic test in patients with suspected GERD (28). Endoscopy allows for biopsy of rings and strictures and screening for Barrett's. Although epidemiologic risk factors for Barrett's esophagus have been well-defined (age over 50, symptoms for >5–10 years, obesity, male sex) the sensitivity and specificity of these symptoms for abnormal endoscopy makes the utility of screening for Barrett's a controversial topic. Recent data indicate that it may be reasonable to perform endoscopy for screening in certain high-risk groups in particular overweight white males over the age of 50 with chronic GERD symptoms (12). The finding of any Barrett's esophagus segment has been associated with pathologic GERD and generally obviates the need for pH testing (29). In a 2009 study, 90% of short-segment BE patients were found to have abnormal pH-impedance testing (30).

The addition of esophageal biopsies as an adjunct to an endoscopic examination has been re-emphasized because of the increased prevalence of eosinophilic esophagitis (EoE). Many clinicians routinely biopsy the esophagus in patients with reflux-type symptoms to look for EoE in the setting of an endoscopy that does not reveal erosive changes. Unfortunately, differentiating GERD from EoE using only biopsy is difficult and risks making a diagnosis and instituting treatment without supportive data. Low eosinophil counts in the distal esophagus while suggestive of GERD are not specific. In addition, a high eosinophil count may be seen with GERD and respond to PPIs (PPI responsive eosinophilia) (31). The sensitivity of the other histologic findings; basal cell hyperplasia, elongation of the rete pegs, papillary elongation, and even neutrophils, are of limited clinical usefulness (32,33). There are no studies examining the efficacy of PPIs based on microscopic findings alone. The use of routine biopsy of the esophagus to diagnose GERD cannot be recommended in a patient with heartburn and a normal endoscopy based on current literature. In addition, the practice of obtaining mucosal biopsies from a normal appearing esophagogastric junction has not been demonstrated to be useful in GERD patients (34).

Esophageal manometry is of limited value in the primary diagnosis of GERD. Neither a decreased lower esophageal sphincter pressure, nor the presence of a motility abnormality is specific enough to make a diagnosis of GERD. Manometry should be used to aid in placement of transnasal pH-impedance probes and is recommended before consideration of antireflux surgery primarily to rule out achalasia or severe hypomotility (scleroderma-like

esophagus), conditions that would be contraindications to Nissen fundoplication, but not to tailor the operation.

Ambulatory reflux monitoring (pH or impedance-pH) is the only test that allows for determining the presence of abnormal esophageal acid exposure, reflux frequency, and symptom association with reflux episodes. Performed with either a telemetry capsule (usually 48 h) or transnasal catheter (24 h), pH monitoring has excellent sensitivity (77–100%) and specificity (85–100%) in patients with erosive esophagitis; however, the sensitivity is lower in those with endoscopy-negative reflux symptoms (<71%) when a diagnostic test is more likely to be needed (24). A consensus statement (35) suggested that impedance added to pH monitoring increased the sensitivity of reflux monitoring to close to 90%. Telemetry capsule pH monitoring offers increased patient tolerability and the option to extend the monitoring period to 48 or perhaps to 96 h. The additional monitoring period allows for combining and on and off therapy study in selected situations and offers additional opportunity to correlate symptoms with acid reflux. Catheter-based monitoring allows for the addition of impedance and detection of weakly acidic or non-acid reflux. Optimal use of these two options is certainly debated as is whether to test on or off therapy. As a true diagnostic test (is abnormal acid exposure present) and for evaluation before considering surgery in a patient with NERD an off therapy test is recommended. The use of on and off therapy monitoring in refractory GERD is discussed subsequently.

When symptom correlation is required, the decision is more difficult. The two symptom association measures most often used are symptom index (SI) and symptom association probability (SAP). Both have methodological shortcomings that have been reviewed elsewhere (36) and prospective data to validate the ability of these symptom association measures to predict response to treatment is scarce. Both the SI and SAP have been validated when pH monitoring is performed off therapy in a patient with heartburn. A positive test on therapy, coupled with a symptom relationship, theoretically suggests GERD as a cause for symptoms but outcome studies are lacking for any symptom other than heartburn. For patient management, a strongly positive SI or SAP may suggest the need for a therapeutic intervention and a negative result supports the notion that the patient's symptoms are unlikely to be due to reflux. However, these indices should not be used in isolation and other reflux monitoring parameters as well the patient's presentation have to be taken into account.

The relationship between *H. pylori* infection and GERD is controversial. As such, a full discussion is beyond the scope of this article. One issue most often discussed is whether treatment of *H. pylori* should be altered because of an exacerbation of GERD and if patients on long-term PPIs require screening and subsequent eradication of the bug to prevent the possibility of increasing risk of gastric cancer. A meta-analysis of 12 studies found no increase in GERD (erosive esophagitis) in patients with dyspeptic symptoms who were eradicated compared with those not. This same study found, in subgroup analysis, patients with peptic ulcer disease might experience the new onset of GERD symptoms after *H. pylori* eradication (37). Concern for the use of long-term PPI therapy in patients with *H. pylori* infection has been raised because of the potential for development of atrophic gastritis in infected patients on long-term PPI (38). This study prompted a Food and Drug Administration (FDA) review panel that concluded that the evidence was not sufficient to recommend testing of all patients on long-term PPI. The flaws in this study and lack of observational data on negative outcomes lead us to recommend against screening of GERD patients for *H. pylori* despite the European recommendation in favor of screening (39).

GERD is frequent during pregnancy, manifests as heartburn, and may begin in any trimester. One study found onset of 52% in the first trimester, 40% in the second trimester, and 8% in the third trimester (40). Among 607 pregnant women attending an antenatal clinic, 22% experienced heartburn in the first trimester, 39% in the second, and 72% in the third, whereas only 14% of these women reported mild heartburn before their pregnancy (41). Severity also increased throughout pregnancy. Significant predictors of heartburn are increasing gestational age, heartburn before pregnancy, and parity. Maternal age is inversely correlated with heartburn. Race, pre-pregnancy BMI, and weight gain in pregnancy do not correlate with the onset of heartburn. Despite its frequent occurrence during pregnancy, heartburn usually resolves after delivery (42). Pregnancy and amount of weight gain during pregnancy were risk factors for frequent GERD symptoms 1 year post delivery (43). No other GERD symptom has been studied in pregnancy. The diagnosis of GERD during pregnancy should be based on symptoms and treatment symptom-based. Additional diagnostic testing is generally not required for the majority of patients with suspected GERD. In the occasional pregnant patient who does require testing, upper endoscopy is the test of choice, but should be reserved for patients whose symptoms are refractory to medical therapy or who have suspected complications. If possible however, endoscopy should be delayed until after the first trimester. It is uncommon to require ambulatory pH monitoring during pregnancy.

MANAGEMENT OF GERD

Recommendations

1. Weight loss is recommended for GERD patients who are overweight or have had recent weight gain. (Conditional recommendation, moderate level of evidence)
2. Head of bed elevation and avoidance of meals 2–3 h before bedtime should be recommended for patients with nocturnal GERD. (Conditional recommendation, low level of evidence)
3. Routine global elimination of food that can trigger reflux (including chocolate, caffeine, alcohol, acidic and/or spicy foods) is not recommended in the treatment of GERD. (Conditional recommendation, low level of evidence)
4. An 8-week course of PPIs is the therapy of choice for symptom relief and healing of erosive esophagitis. There are

no major differences in efficacy between the different PPIs. (Strong recommendation, high level of evidence)

5. Traditional delayed release PPIs should be administered 30–60 min before meal for maximal pH control. (Strong recommendation, moderate level of evidence). Newer PPIs may offer dosing flexibility relative to meal timing (Conditional recommendation, moderate level of evidence)
6. PPI therapy should be initiated at once a day dosing, before the first meal of the day. (Strong recommendation, moderate level of evidence). For patients with partial response to once daily therapy, tailored therapy with adjustment of dose timing and/or twice daily dosing should be considered in patients with night-time symptoms, variable schedules, and/or sleep disturbance. (Strong recommendation, low level of evidence)
7. Non-responders to PPI should be referred for evaluation. (Conditional recommendation, low level of evidence, see refractory GERD section)
8. In patients with partial response to PPI therapy, increasing the dose to twice daily therapy or switching to a different PPI may provide additional symptom relief. (Conditional recommendation, low level of evidence)
9. Maintenance PPI therapy should be administered for GERD patients who continue to have symptoms after PPI is discontinued and in patients with complications including erosive esophagitis and Barrett's esophagus. (Strong recommendation, moderate level of evidence). For patients who require long-term PPI therapy, it should be administered in the lowest effective dose, including on demand or intermittent therapy. (Conditional recommendation, low level of evidence)
10. H_2-receptor antagonist therapy can be used as a maintenance option in patients without erosive disease if patients experience heartburn relief. (Conditional recommendation, moderate level of evidence). Bedtime H_2RA therapy can be added to daytime PPI therapy in selected patients with objective evidence of night-time reflux if needed but may be associated with the development of tachyphlaxis after several weeks of usage. (Conditional recommendation, low level of evidence)
11. Therapy for GERD other than acid suppression, including prokinetic therapy and/or baclofen, should not be used in GERD patients without diagnostic evaluation. (Conditional recommendation, moderate level of evidence)
12. There is no role for sucralfate in the non-pregnant GERD patient. (Conditional recommendation, moderate level of evidence)
13. PPIs are safe in pregnant patients if clinically indicated. (Conditional recommendation, moderate level of evidence)

SUMMARY OF THE EVIDENCE

Lifestyle interventions are part of therapy for GERD. (**Table 3**) Counseling is often provided regarding weight loss, head of bed elevation, tobacco and alcohol cessation, avoidance of late-night meals, and cessation of foods that can potentially aggravate reflux symptoms including caffeine, coffee, chocolate, spicy foods, highly acidic foods such as oranges and tomatoes, and foods with high fat content.

A systematic review (44) evaluated the effect of dietary and other lifestyle modifications on lower esophageal sphincter pressure, esophageal pH, and GERD symptoms. Consumption of tobacco (12 trials), chocolate (2 trials), and carbonated beverages (2 trials) and right lateral decubitus position (3 trials) were shown to lower pressure of the lower esophageal sphincter (LES), whereas consumption of alcohol (16 trials), coffee and caffeine (14 trials), spicy foods (2 trials), citrus (3 trials), and fatty foods (9 trials) had no effect. There was an increase in esophageal acid exposure times with tobacco and alcohol consumption in addition to ingestion of chocolate and fatty foods. However, tobacco and alcohol cessation (4 trials) were not shown to raise LESP, improve esophageal pH, or improve GERD symptoms. In addition, there have been no studies conducted to date that have shown clinical improvement in GERD symptoms or complications associated with cessation of coffee, caffeine, chocolate, spicy foods, citrus, carbonated beverages, fatty foods, or mint. A recent systematic review concluded that there was lack of evidence that consumption of carbonated beverages causes or provokes GERD (45).

Weight gain even in subjects with a normal BMI has been associated with new onset of GERD symptoms (46). Multiple cohort studies have demonstrated reduction in GERD symptoms with weight loss (47,48). Roux-en-Y gastric bypass, but not vertical banded gastroplasty, has been demonstrated to be effective in reduction of GERD symptoms (49). A large case–control study based on the Nurses Health Cohort demonstrated a 40% reduction in frequent GERD symptoms for women who reduced their BMI by 3.5 or more compared with controls (46).

Assumption of the recumbent position has been associated with worsening of esophageal pH values and GERD symptoms. Three randomized controlled trials have demonstrated improvement in GERD symptoms and esophageal pH values with head of bed elevation using blocks or foam wedges (50–52).

Medical options for patients failing lifestyle interventions include antacids, histamine-receptor antagonists (H_2RA), or PPI therapy. A meta-analysis published in 2010 demonstrated that the placebo response in GERD clinical trials approximated 20% and was lower in patients with erosive esophagitis (11%) and PPI trials (14%) compared with trials with H_2RAs (25%) (53). PPI therapy has been associated with superior healing rates and decreased relapse rates compared with H_2RAs and placebo for patients with erosive esophagitis (54). A 1997 meta-analysis demonstrated superior healing rates for all grades of erosive esophagitis using PPI therapy compared with H_2RAs, sucralfate, or placebo (55). The mean (±s.d.) overall healing proportion irrespective of drug dose or treatment duration was highest with PPIs (84%±11%) vs H_2RAs (52%±17%), sucralfate (39%±22%), or placebo (28%±16%). PPIs showed a significantly faster healing rate (12%/week) vs. H_2RAs (6%/week) and placebo (3%/week). PPIs provided faster, more complete heartburn relief (11.5%/week) vs. H_2RAs (6.4%/week) (35). PPIs are associated with a greater rate of symptom relief in patients with ERD (~70–80%) compared to patients with NERD (where the symptom relief approximates 50–60%) (56,57).

Table 3. Efficacy of lifestyle interventions for GERD

Lifestyle intervention	Effect of intervention on GERD parameters	Sources of data	Recommendation
Weight loss (46,47,48)	Improvement of GERD symptoms and esophageal pH	Case–Control	Strong recommendation for patients with BMI>25 or patients with recent weight gain
Head of bed elevation (50–52)	Improved esophageal pH and symptoms	Randomized Controlled Trial	Head of bed elevation with foam wedge or blocks in patients with nocturnal GERD
Avoidance of late evening meals (180, 181)	Improved nocturnal gastric acidity but not symptoms	Case–Control	Avoid eating meals with high fat content within 2–3 h of reclining
Tobacco and alcohol cessation (182–184)	No change in symptoms or esophageal pH	Case–Control	Not recommended to improve GERD symptoms
Cessation of chocolate, caffeine, spicy foods, citrus, carbonated beverages	No studies performed	No evidence	Not routinely recommended for GERD patients. Selective elimination could be considered if patients note correlation with GERD symptoms and improvement with elimination

BMI, body mass index; GERD, gastroesophageal reflux disease.

For patients with non-erosive reflux disease, a Cochrane systematic review demonstrated superiority for PPI therapy compared with H_2RAs and prokinetics for heartburn relief (58). On the basis of 32 trials with over 9,700 participants, the relative risk (RR) for heartburn remission (the primary efficacy variable) in placebo-controlled trials for PPI was 0.37 (two trials, 95% confidence interval (CI) 0.32–0.44), for H_2RAs 0.77 (two trials, 95% CI 0.60–0.99) and for prokinetics 0.86 (one trial, 95% CI 0.73–1.01). In a direct comparison, PPIs were more effective than H_2RAs (seven trials, RR 0.66, 95% CI 0.60–0.73) and prokinetics (two trials, RR 0.53, 95% CI 0.32–0.87).

There are currently seven available PPIs including three that can be obtained over-the-counter (omeprazole, lansoprazole, and omeprazole-sodium bicarbonate). Four are available only by prescription (rabeprazole, pantoprazole, esomeprazole, and dexlansoprazole). Meta-analyses fail to show significant difference in efficacy for symptom relief between PPIs (59). A meta-analysis published in 2006 examining efficacy of PPI therapy for healing of erosive esophagitis included 10 studies (15,316 patients) (except for omeprazole-sodium bicarbonate and dexlansoprazole) (59). At 8 weeks, there was a 5% (RR, 1.05; 95% CI 1.02–1.08) relative increase in the probability of healing of erosive esophagitis with esomeprazole, yielding an absolute risk reduction of 4% and number needed to treat (NNT) of 25. The calculated NNTs by LA grade of erosive esophagitis (grades A–D) were 50, 33, 14, and 8, respectively. Esomeprazole conferred an 8% (RR, 1.08; 95% CI 1.05–1.11) relative increase in the probability of GERD symptom relief at 4 weeks. The clinical importance of this small difference is unclear. All of the PPIs with the exception of omeprazole-sodium bicarbonate and dexlansoprazole, should be administered 30–60 min before meals to assure maximal efficacy. Omeprazole-sodium bicarbonate, an immediate-release PPI, has been demonstrated to more effectively control nocturnal gastric pH in the first 4 h of sleep compared with other PPIs when each is administered at bedtime (60). Whether this effect leads to any superior clinical outcomes including symptom control, requires further study. Dexlansoprazole is a dual delayed release PPI released in 2009. Comparative trials of dexlansoprazole compared only with lansoprazole 30 mg demonstrated superior control in esophageal pH values in one trial, and the convenience of being able to dose the drug any time of the day regardless of food intake (61). Superiority to lansoprazole in healing of erosive esophagitis was demonstrated in one trial, with non-inferiority in another study (62).

As stated above, it would be expected that ~70–80% of patients with ERD would demonstrate complete relief on PPI therapy and 60% of patients with NERD. Partial relief of GERD symptoms after a standard 8-week course of PPI therapy has been found in 30–40% of patients and does not differ in patients taking PPI once or twice daily. The evaluation and management of patients with incomplete response are discussed in the refractory GERD section. Risk factors for lack of symptom control have included patients with longer duration of disease, presence of hiatal hernia, extraesophageal symptoms, and lack of compliance (63). Delayed release PPIs are most effective in controlling intragastric pH when taken before a meal (64) and are generally less effective when taken at bedtime. The exceptions to this rule appear to be for the administration of dexlansoprazole (65), which appears to have similar efficacy in pH control regardless of meal timing, and omeprazole-sodium bicarbonate, which can control nighttime pH when given at bedtime. Suboptimal dosing is common in practice (66). Although PPI switching is common in clinical practice, there is limited data to support this practice. Data from one randomized controlled trial demonstrated that in GERD patients refractory to once-daily lansoprazole, switching patients to esomeprazole therapy once daily was as effective as increasing to twice daily lansoprazole (67). There is no data to support switching PPIs more than once in partial or non-responders.

Maintenance PPI therapy should be administered for GERD patients who continue to have symptoms after PPI is discontinued and in patients with complications including erosive esophagitis and Barrett's esophagus. In patients found to have NERD, two-third of the patients will demonstrate symptomatic relapse off of PPIs over time (68). For patients found to have LA grade B–C esophagitis, nearly 100% will relapse by 6 months (69). In patients found to have any length of BE, retrospective studies have suggested a decreased risk for dysplasia in patients continuing PPI usage (70). On the other hand, studies have demonstrated that patients with NERD and otherwise non-complicated GERD

can be managed successfully with on-demand or intermittent PPI therapy. In a randomized controlled trial (71) published in 1999, 83% of NERD patients randomized to 20 mg of omeprazole on demand were in remission at 6 months compared with 56% of patients on placebo. In a systematic review of randomized controlled trials comparing on-demand PPI vs. placebo, 17 studies were included (5 in NERD patients, 4 with NERD and mild esophagitis, and 2 studies with ERD) (72). The symptom-free days for patients in the on-demand arms were equivalent to rates for patients on continuous PPI therapy and superior to placebo in patients with NERD, but not for patients with ERD. Step-down therapy to H_2RAs is another acceptable option for NERD patients (73).

Medical options for GERD patients with incomplete response to PPI therapy are limited. The addition of bedtime H_2RA has been recommended for patients with symptoms refractory to PPI. This approach gained popularity after multiple intragastric pH studies demonstrated overnight pH control. One well-done study suggested potential tachyphylaxis of pH control occurring after a month of therapy (74). In light of this study and a lack of prospective clinical trial use of a bedtime H_2RA might be most beneficial if dosed on as needed basis in patients with provocable night-time symptoms and patients with objective evidence on pH monitoring of overnight esophageal acid reflux despite optimal PPI use.

Prokinetic therapy with metoclopramide in addition to PPI therapy is another option often considered for these patients. Metoclopramide has been shown to increase LESP, enhance esophageal peristalsis and augment gastric emptying (75). Clinical data showing additional benefit of metoclopramide to PPI therapy has not been adequately studied. Combination therapy of metoclopramide with H_2RA has not been shown to be more effective compared with H_2RA or prokinetic therapy alone (76). The usage of metoclopramide has been limited by central nervous system side effects including drowsiness, agitation, irritability, depression, dystonic reactions, and tardive dyskinesia in $<1\%$ of patients (77). Practically speaking, in the absence of gastroparesis, there is no clear role for metoclopramide in GERD. For the small number of patients who may benefit from a prokinetic, another option is domperidone, a peripherally acting dopamine agonist, which can be obtained through application for an investigational drug usage permit from the FDA as it does not have approval for usage in GERD. The efficacy of domperidone has been demonstrated to be equivalent to that of metoclopramide for gastric emptying but little to no data are available in GERD (78). Monitoring for QT prolongation is performed due to a small risk for ventricular arrhythmia and sudden cardiac death (79).

The usage of baclofen is another alternative for refractory GERD patients. Baclofen, a GABA(b) agonist, has been demonstrated to be effective in GERD by its ability to reduce transient LES relaxations (80), and reflux episodes (81). Baclofen has also been demonstrated to decrease the number of postprandial acid and non-acid reflux events (82), nocturnal reflux activity (83), and belching episodes (84). Given the limited treatment options for GERD symptoms refractory to PPIs, a trial of baclofen at a dosage of 5–20 mg three times a day can be considered in patients with objective documentation of continued symptomatic reflux despite optimal PPI therapy, based on two short-term randomized controlled trials that demonstrated symptomatic improvement with this agent (82,83). The clinician should be aware that there has not been long-term data published regarding efficacy of baclofen in GERD. Usage is limited by side effects of dizziness, somnolence, and constipation. Baclofen is not approved by the FDA for the treatment of GERD.

SURGICAL OPTIONS FOR GERD

Recommendations

1. Surgical therapy is a treatment option for long-term therapy in GERD patients. (Strong recommendation, high level of evidence)
2. Surgical therapy is generally not recommended in patients who do not respond to PPI therapy. (Strong recommendation, high level of evidence)
3. Preoperative ambulatory pH monitoring is mandatory in patients without evidence of erosive esophagitis. All patients should undergo preoperative manometry to rule out achalasia or scleroderma-like esophagus. (Strong recommendation, moderate level of evidence)
4. Surgical therapy is as effective as medical therapy for carefully selected patients with chronic GERD when performed by an experienced surgeon. (Strong recommendation, high level of evidence)
5. Obese patients contemplating surgical therapy for GERD should be considered for bariatric surgery. Gastric bypass would be the preferred operation in these patients. (Conditional recommendation, moderate level of evidence)
6. The usage of current endoscopic therapy or transoral incisionless fundoplication cannot be recommended as an alternative to medical or traditional surgical therapy. (Conditional recommendation, moderate level of evidence)

SUMMARY OF THE EVIDENCE

Potential surgical options for GERD include laparoscopic fundoplication or bariatric surgery in the obese. Reasons to refer GERD patients for surgery may include desire to discontinue medical therapy, non-compliance, side-effects associated with medical therapy, the presence of a large hiatal hernia, esophagitis refractory to medical therapy, or persistent symptoms documented to be caused by refractory GERD. With the introduction of esophageal pH-impedance monitoring, patients found to have abnormal amounts of non-acid reflux on PPI therapy with good symptom correlation may be considered for surgery (85). Refractory dyspeptic symptoms including nausea, vomiting, and epigastric pain are less likely to demonstrate symptomatic response. The highest surgical responses are seen in patients with typical symptoms of heartburn and/or regurgitation that demonstrate good response to PPI therapy or have abnormal

ambulatory pH studies with good symptom correlation (86). In this patient cohort, long-term remission rates can be expected to be comparable and in some cases statistically superior to medical therapy. In a long-term follow-up of a Veterans Affairs Cooperative cooperative randomized controlled trial comparing medical to surgical therapy for GERD, 92% of the patients in the medical arm were using medical therapy compared with 62% of the surgical cohort at 10 years (87). In a 12-year long-term follow-up of patients randomized to fundoplication compared with omeprazole, 53% of the surgery cohort were in remission compared with 45% of the medically treated patients ($P=0.02$), although symptoms of gas-bloat syndrome remained more common in the surgical cohort (88).

Patients choosing to undergo surgical therapy for GERD may face some additional risks including increased short-term risk of mortality. The most common adverse events associated with fundoplication include the gas-bloat syndrome in 15–20% of patients. A recent meta-analysis concluded that the prevalence of postoperative dysphagia and inability to belch were significantly lower in patients undergoing partial fundoplication compared with patients undergoing total fundoplication (89). In a Cochrane review, four randomized trials with over 1,200 subjects randomized to medical or surgical therapy were included (90). All four studies reported significant improvements in GERD-specific QOL after surgery compared with medical therapy although data were not combined. There was evidence to suggest that symptoms of heartburn, reflux, and bloating were improved more after surgery compared with medical therapy, but a small proportion of participants reported persistent postoperative dysphagia. Overall rates of postoperative complications were low, but fundoplication was associated with a potential for adverse postoperative events.

Outcomes in patients with extraesophageal symptoms undergoing Nissen fundoplication have been less encouraging. In patients enrolled in a VA Cooperative study, no significant change in pulmonary function tests were demonstrated after 1 year of surgery, even in patients with abnormal baseline pulmonary function tests (91). A randomized controlled trial of cimetidine vs. fundoplication and placebo for asthma symptoms demonstrated equivalent efficacy for medical and surgical therapy compared with placebo but no significant change in FEV1 at 6 months (92). In a 2003 Cochrane review, medical or surgical antireflux therapy was not associated with improvement in pulmonary function, asthma symptoms, or use of medication (93). Although surgery can be effective in carefully selected patients with extraesophageal or atypical symptoms, response rates are lower than in patients with heartburn (86). It is particularly important to carefully evaluate patients with so-called laryngopharyngeal reflux before considering fundoplication. A response to PPI is critical. In the absence of a PPI response, surgery is unlikely to be effective even with an abnormal pH study (94).

Given the increasing prevalence of obesity in the US, gastric bypass has become a more common procedure compared with Nissen fundoplication. A 2009 review assessed the efficacy for surgical therapies for obesity on gastroesophageal reflux (95). In studies assessing Roux-en-Y gastric bypass surgery, GERD symptoms improved when assessed postoperatively via questionnaire. Roux-en-Y was more effective compared with gastric banding in one study. Of the eight studies assessing vertical banded gastroplasty, one study showed improvement in GERD symptoms, but the other studies demonstrated no change or an increase in reflux symptoms. The effects of gastric banding on GERD symptoms in eight studies were conflicting.

Endoscopic therapies for GERD have been developed but have not demonstrated long-term efficacy. These therapies included radiofrequency augmentation to the lower esophageal sphincter, silicone injection into the lower esophageal sphincter, and endoscopic suturing of the LES. None of these therapies demonstrated long-term improvement in esophageal pH levels or the ability for patients to stop antireflux therapy and were subsequently removed from the US marketplace (96). Recent alternative approaches have included transoral incisionless fundoplication, a suturing device designed to create a full thickness gastroesophageal valve from inside the stomach. Unfortunately long-term data regarding efficacy of this device are limited to a small number of subjects and short duration of follow-up (97). A recent study suggested that at 36 months of follow-up, the majority of patients had required additional medical therapy or a revisional fundoplication (98).

Sphincter augmentation using the LINX Reflux system constructed of titanium beads has shown efficacy up to 4 years in the reduction of the amount of pathologic esophageal acid exposure in a small number of subjects (99). This device has been approved by the FDA based on a clinical study in 100 GERD patients. This study found that performance of LINX resulted in consistent symptom relief and pH control with markedly fewer side effects than traditional laparoscopic fundoplication in well-selected patients. More data are required before widespread usage can be recommended.

POTENTIAL RISKS ASSOCIATED WITH PPIs

Recommendations

1. Switching PPIs can be considered in the setting of side effects. (Conditional recommendation, low level of evidence)
2. Patients with known osteoporosis can remain on PPI therapy. Concern for hip fractures and osteoporosis should not affect the decision to use PPI long-term except in patients with other risk factors for hip fracture. (Strong recommendation, moderate level of evidence)
3. PPI therapy can be a risk factor for Clostridium difficile infection and should be used with care in patients at risk. (Strong recommendation, moderate level of evidence)
4. Short-term PPI usage may increase the risk of community-acquired pneumonia. The risk does not appear elevated in long-term users. (Conditional recommendation, moderate level of evidence)
5. PPI therapy does not need to be altered in concomitant clopidogrel users as clinical data does not support an increased risk for adverse cardiovascular events. (Strong recommendation, high level of evidence)

SUMMARY OF THE EVIDENCE

Potential adverse events associated with PPI therapy have included headache, diarrhea, and dyspepsia in <2% of users. Switching to another PPI can be attempted in these patients or in patients who fail to respond to an initial PPI, although data supporting this practice are limited. Other potential adverse associations have included vitamin and mineral deficiencies, association with community-acquired infections including pneumonia and diarrhea, hip fractures and osteoporosis, and increased cardiovascular events in patients using concomitant clopidogrel therapy. The FDA issued warnings regarding the potential for wrist, hip, and spine fractures among PPI users in 2010 and warnings regarding potential for adverse cardiovascular events among clopidogrel users taking PPI therapy in 2009. Because of these concerns, multiple meta-analyses and systematic reviews have been published.

The reason for concern regarding potential vitamin B12 deficiency in PPI users derives from the fact that the first step in cobalamin absorption requires gastric acid and pepsin in order to release cobalamin from dietary proteins. In two recent reviews, there was no supporting clinical evidence to document the development of B12 deficiency in chronic PPI users (100,101). However, recent studies have suggested that in elderly institutionalized long-term PPI users, B12 deficiency is more likely to develop and should be considered in this cohort.

Gastric acid is necessary to allow absorption of non-heme iron and also enhances iron salt dissociation from ingested food. Iron deficiency anemia has been reported in patients with atrophic gastritis, gastric resection, or vagotomy. There currently is no data demonstrating the development of iron deficiency anemia in normal subjects on PPI therapy (100).

By their effects in increasing gastric pH levels, the usage of PPIs may encourage growth of gut microflora and increase susceptibility to organisms including *Salmonella*, *Campylobacter jejuni*, *Escherichia coli*, *Clostridium difficile*, *Vibrio cholerae,* and *Listeria*. A systematic review published in 2011 found an increased susceptibility in PPI users for Salmonella infections (adjusted RR ranging from 4.2–8.3 in two studies), Campylobacter (RR 3.5–11.7 in four studies) and *C. difficile* infections (RR 1.2–5.0 in 17 out of 27 studies demonstrating a positive association) (102). The studies failing to demonstrate an association were predominantly in older patients >65 years of age where because of the presence of co-morbid conditions and associated hypochlorhydria, the addition of PPI therapy did not raise the risk of infection. On the basis of the available evidence, PPI usage can be a risk factor for Clostridium difficile and other enteric infections and should be used with care in patients at risk.

An increased risk for community-acquired pneumonia cannot be clearly documented in association with PPI therapy. A systematic review identified 31 studies (five case–control studies, three cohort studies, and 23 randomized controlled trials) (103). A meta-analysis of the eight observational studies showed that the overall risk of pneumonia was higher among patients using PPIs (adjusted odds ratio (OR) 1.27, 95% CI 1.11–1.46) and H_2RAs (adjusted OR 1.22, 95% CI 1.09–1.36). However, when the randomized controlled trial data were analyzed, only use of H_2RAs was associated with an elevated risk of hospital-acquired pneumonia (RR 1.22, 95% CI 1.01–1.48) A more recent meta-analysis (six nested case–control studies) found an increased risk of community acquired pneumonia (CAP) associated with PPI usage (OR 1.36, 95% CI 1.12–1.65), but the results were confounded by significant heterogeneity (104). In exploratory subgroup analysis, short duration of use was associated with an increased odds of CAP (OR 1.92 (95% CI 1.40–2.63), $P=0.003$), whereas chronic use was not (OR 1.11 (95% CI 0.90–1.38), $P<0.001$). Other studies have also demonstrated an increased risk of CAP associated only with short-term PPI usage (105,106). In summary, PPI therapy should not be withheld in patients requiring therapy due to a potential risk of CAP; however, the diagnosis of pneumonia and timing of initiation of PPI therapy deserves further study.

Reduction in gastric acid has been associated with decreased release of ionized calcium from calcium salts and protein-bound calcium. Although some physiologic data have suggested that PPIs might inhibit osteoclast-mediated bone resorption, clinical studies have rendered mixed results. In the Manitoba Bone Mineral Density Database, the study with the longest follow-up to date (107), cases with osteoporosis at the hip or lumbar vertebrae were matched to three controls with normal bone mineral density. PPI use over the previous 5 years was not associated with having osteoporosis at either the hip (OR 0.84; 95% CI, 0.55–1.34) or the lumbar spine (OR 0.79; 95% CI, 0.59–1.06), and it was concluded that the association between PPI use and hip fracture was probably related to factors independent of osteoporosis. A 2010 case–control study demonstrated that the excess hip fracture risk among PPI users was only present in persons with at least one other risk factor (108). Two meta-analyses published in 2011 demonstrated small increases in risk of hip fracture (OR 1.2) but were limited by substantial heterogeneity among studies included (109,110).

In 2009, the FDA issued a warning regarding the potential for increased adverse cardiovascular events in concomitant users of PPI and clopidogrel therapy, particularly among users of omeprazole, lansoprazole, and esomeprazole. The concern arises from the fact that the antiplatelet activity of clopidogrel requires activation by CYP 2C19, the same pathway required for metabolism of some PPIs. Initial studies raised concern for a potential interaction based on *in vitro* tests demonstrating that clopidogrel's ability to inhibit platelet aggregation was decreased in the presence of PPIs (111,112). Subsequent retrospective studies yielded conflicting results with some publications suggesting an increased risk for cardiovascular events (113–115) and others showing lack of effect (116,117). In two randomized controlled trials, PPIs did not increase the risk of adverse events in patients receiving clopidogrel (118,119). Meta-analyses have demonstrated that the strength of potential interactions is dependent upon the assessment of clinical outcomes, adjustment for confounders, and data quality. For example, in a meta-analysis including 26 studies (16 published articles, 10 abstracts), the authors divided the analyses between

primary outcomes (myocardial infarction, stroke, stent occlusion, or death) and secondary outcomes (re-hospitalization for cardiac symptoms or revascularization procedures) (120). Clinical data from the two randomized controlled trials which included usage of all PPIs except for dexlansoprazole did not show an increased risk for adverse cardiovascular events (risk difference, RD 0.0, 95% CI −0.01, 0.01). The meta-analysis of primary outcomes showed a RD of 0.02 (95% CI 0.01, 0.03) for all studies. The meta-analysis for secondary outcomes yielded a RD of 0.02 (95% CI 0.01–0.04) based on 19 published papers and abstracts. When primary and secondary outcomes were combined, the meta-analysis for published papers yielded an overall RD of 0.05 (95% CI 0.03–0.06). The authors concluded that in patients using concomitant clopidogrel and PPI therapy, the risk of adverse cardiac outcomes was 0% based on data from well-controlled randomized trials. Data from retrospective studies and the addition of probable vascular events significantly increased the RD estimates, likely due to lack of adjustment for potential confounders (76). Subsequent meta-analyses have concluded that the data from two randomized trials did not support an adverse effect, and that analysis of cardiovascular events from the remainder of the studies was limited by moderate-substantial heterogeneity (121,122).

EXTRAESOPHAGEAL PRESENTATIONS OF GERD: ASTHMA, CHRONIC COUGH, AND LARYNGITIS

Recommendations

1. GERD can be considered as a potential co-factor in patients with asthma, chronic cough, or laryngitis. Careful evaluation for non-GERD causes should be undertaken in all of these patients. (Strong recommendation, moderate level of evidence).
2. A diagnosis of reflux laryngitis should not be made based solely upon laryngoscopy findings (Strong recommendation, moderate level of evidence).
3. A PPI trial is recommended to treat extraesophageal symptoms in patients who also have typical symptoms of GERD. (Strong recommendation, low level of evidence)
4. Upper endoscopy is not recommended as a means to establish a diagnosis of GERD-related asthma, chronic cough, or laryngitis. (Strong recommendation, low level of evidence)
5. Reflux monitoring should be considered before a PPI trial in patients with extraesophageal symptoms who do not have typical symptoms of GERD. (Conditional recommendation, low level of evidence).
6. Non-responders to a PPI trial should be considered for further diagnostic testing, and are addressed in the refractory GERD section below. (Conditional recommendation, low level of evidence)
7. Surgery should generally not be performed to treat extraesophageal symptoms of GERD in patients who do not respond to acid suppression with a PPI. (Strong recommendation, moderate level of evidence)

SUMMARY OF THE EVIDENCE

The spectrum of clinical presentations attributed to GERD has expanded from typical esophageal symptoms of heartburn and regurgitation, to an assortment of extraesophageal manifestations including respiratory and laryngeal symptoms. Several epidemiological studies have identified an association between GERD and these extraesophageal symptoms, but causality cannot be inferred from these studies. A systematic review of 28 studies found that symptoms of GERD and abnormal 24-h pH monitoring were present in 59% and 51% of asthma patients, but concluded that there was little data to clarify the direction of causality in this association (123). Cohort studies suggest that GERD may be the cause in 21–41% of chronic nonspecific cough (124). A large VA population case–control study found increased odds ratios for pharyngitis (OR 1.60), aphonia (OR 1.81), and chronic laryngitis (OR 2.01) in cases with esophagitis or esophageal stricture compared with controls (125). The Montreal Consensus recognized established associations between GERD and asthma, chronic cough, and laryngitis, while acknowledging that these disorders frequently have a multi-factorial etiology and that gastro-esophageal reflux may be a co-factor rather than a cause. The Montreal consensus also recognized the rarity of extraesophageal syndromes occurring in isolation without concomitant typical symptoms of GERD (3). Currently available diagnostic tools to establish GERD as the cause of extraesophageal symptoms have serious limitations, and recent placebo-controlled trials have failed to show a clear therapeutic benefit of PPIs in treating all-comers with extraesophageal symptoms. Therefore, patients with asthma, chronic cough, or laryngitis should have careful evaluation for non-GERD causes. GERD should be viewed as a possible contributing factor in some but not all patients presenting with these clinical entities.

Diagnosing GERD as the cause of extraesophageal symptoms has proven to be very challenging. Upper endoscopy can document the presence of GERD when erosive esophagitis is present, but it is found in only one third of patients with GERD symptoms (126) and is even rarer after treatment with PPIs (59). Even when present, finding erosive esophagitis does not establish a diagnosis of GERD-related asthma, chronic cough, or laryngitis.

Ambulatory reflux monitoring can confirm the presence of GERD by documenting a pathological amount of gastroesophageal reflux. Current consensus is that the total percentage of time the pH is <4 is the most useful single discriminator between physiologic and pathologic reflux (127). There is great variability in the reported prevalence of abnormal pH monitoring in patients with asthma (123), chronic cough (128), and laryngitis (129). Similar to the finding of erosive esophagitis on endoscopy, documentation of pathological reflux on ambulatory monitoring does not establish GERD as the cause of the extraesophageal symptoms. On the other hand, a negative reflux monitoring test should direct the diagnostic effort toward non-GERD etiologies. Beyond establishing the presence of pathological reflux, ambulatory reflux monitoring may be used to determine whether the patient's symptoms are due to reflux. The two most commonly used methods to evaluate the temporal association between reflux episodes and symptoms are the symptom index (SI) (130) and the symptom-association

probability (SAP) (131). Both methods rely on precise and timely symptom recording by the patient, along with accurate reflux detection by the testing device. Symptom association analysis performed during reflux monitoring may document a temporal association between reflux episodes and asthma attacks or cough events. The sensitivity and specificity of symptom association analysis tools is limited and there are no outcome studies to support treatment of extraesophageal GERD based on this parameter alone (127). A recent study of 237 patients with extraesophageal reflux symptoms that were refractory to PPI, found that the presence of heartburn or abnormal acid exposure on pH monitoring predicted response to escalation of therapy, but the SI, SAP, or impedance variables did not (132). The recent development of ambulatory reflux-cough monitoring by combining impedance-pH to measure reflux (acid or nonacid) along with acoustic detection of cough, which eliminates the subjectivity of patient-reported cough, has enabled a more accurate assessment of the relationship between reflux and cough; a recent study using this approach was able to document reflux-induced cough as well as cough-induced reflux (133). Whether these technical improvements increase the yield of symptom association analysis in patients with cough attributed to reflux requires further studies.

Laryngoscopic findings, especially edema and erythema, are often used to diagnose reflux-induced laryngitis (134). It should be pointed out that laryngoscopy revealed one or more signs of laryngeal irritation in over 80% of healthy controls in a well-done prospective study (135). Moreover, in a study of five ENT (ear, nose, and throat) physicians who blindly evaluated 120 video recordings of laryngoscopy exams, concordance among physicians was low for edema, erythema, as well as likelihood and severity of laryngopharyngeal reflux; similarly, intra-rater reliability was extremely variable for these findings (136). It is important to keep in mind that signs of laryngeal irritation may also be the result of non-GERD etiologies such as allergy, smoking, or voice abuse. Therefore, it is recommended that a diagnosis of reflux-induced laryngitis not be made based on laryngoscopy findings alone.

A course of action that is often pursued in clinical practice is to empirically prescribe acid suppression with PPIs, especially in patients with concomitant typical symptoms of GERD. Two randomized controlled trials have shown that PPIs result in improvement of various asthma outcomes (137,138). However, a meta-analysis of 11 randomized controlled trials concluded that PPI therapy in adults with asthma results in a statistically significant but overall only a small improvement in peak expiratory flow rate, that is unlikely to be of meaningful clinical significance. Thus, there is insufficient evidence to recommend PPIs for routine asthma treatment when other GERD symptoms are absent (139). Improvement in peak expiratory flow was greater, though still modest, in the eight studies that required evidence of GERD (by symptoms, endoscopy, or reflux monitoring) compared with the three studies that did not require evidence of GERD. A meta-analysis of nine randomized controlled trials found no advantage for PPI compared with placebo for total resolution of cough (OR 0.46, 95% CI 0.19 to 1.15), although sensitivity analysis found significant improvement in cough scores in those receiving PPI (standardized mean difference −0.41, 95% CI −0.75 to −0.07) (140). The experience with treating laryngeal symptoms attributed to reflux disease is comparable. A meta-analysis of eight randomized controlled trials found that PPI therapy had no significant advantage over placebo in achieving improvement of symptoms of suspected GERD-related chronic laryngitis (RR 1.28, 95% CI 0.94 to 1.74) (141).

There are no high-quality randomized controlled trials evaluating the effectiveness of laparoscopic fundoplication for the treatment of extraesophageal symptoms of GERD. A recent Agency for Healthcare Research and Quality review on the comparative effectiveness of GERD treatments summarized the available data on fundoplication for asthma, cough, and laryngitis (142). As explained in detail in this review, all the data on surgery for extraesophageal GERD come from surgical cohort studies with wide variation in population treated, severity of symptoms, outcome measures, surgical intervention, and duration of follow-up. Although some of these studies may show benefit, the conclusion of the review was that the strength of the evidence was insufficient, and no consistent benefit could be attributed to surgery.

On the basis of the information summarized above, PPI therapy seems reasonable in patients with asthma, chronic cough, and laryngitis who also have typical symptoms of GERD or objective evidence of GERD by endoscopy or reflux monitoring. In these patients, acid suppression with PPIs has proven to be beneficial to heal esophagitis and treat typical symptoms; whether the extraesophageal symptoms will improve is less predictable. We have few well-defined markers to predict which patients will respond to therapy. Empirical treatment for patients without typical symptoms or objective evidence of GERD thus cannot be routinely recommended. The historic recommendation is to treat patients with higher dose PPI (twice daily) than patients with typical GERD symptoms; however, this is based on uncontrolled and observational data only (143,144). Patients who are treated with PPI and who do not respond to a 2–3 month course of acid suppression can be evaluated and managed as proposed in the "refractory GERD" section. The importance of pursuing non-GERD etiologies in this group of patients is critical.

GERD REFRACTORY TO TREATMENT WITH PPIs

Recommendations

1. The first step in management of refractory GERD is optimization of PPI therapy. (Strong recommendation, low level of evidence)
2. Upper endoscopy should be performed in refractory patients with typical or dyspeptic symptoms principally to exclude non-GERD etiologies. (Conditional recommendation, low level of evidence)
3. In patients in whom extraesophageal symptoms of GERD persist despite PPI optimization, assessment for other etiologies should be pursued through concomitant evaluation by ENT, pulmonary, and allergy specialists (Strong recommendation, low level of evidence)

4. Patients with refractory GERD and negative evaluation by endoscopy (typical symptoms) or evaluation by ENT, pulmonary, and allergy specialists (extraesophageal symptoms), should undergo ambulatory reflux monitoring (Strong recommendation, low level of evidence)
5. Reflux monitoring *off* medication can be performed by any available modality (pH or impedance-pH) (Conditional recommendation, moderate level of evidence). Testing *on* medication should be performed with impedance-pH monitoring in order to enable measurement of nonacid reflux. (Strong recommendation, moderate level of evidence)
6. Refractory patients with objective evidence of ongoing reflux as the cause of symptoms should be considered for additional antireflux therapies that may include surgery or TLESR inhibitors. (Conditional recommendation, low level of evidence). Patients with negative testing are unlikely to have GERD and PPI therapy should be discontinued. (Strong recommendation, low level of evidence)

SUMMARY OF THE EVIDENCE

We are seeing increasing numbers of patients treated empirically with PPIs for symptoms that are suspected to be due to GERD who do not respond to these medications. The term refractory GERD encompasses a heterogeneous group of patients that may differ in symptom frequency and severity, PPI dosing regimen (once or twice daily), and response to therapy (from partial to absent). Although there is no established consensus regarding the definition of refractory GERD in terms of symptom burden, degree of therapeutic response, and PPI dose at which failure occurs, we should accept that refractory GERD is a patient-driven phenomenon (145). Not surprisingly, refractory GERD has a significant impact on QOL. A recent systematic review of nine studies found that persistent reflux symptoms on PPI therapy are associated with reduced physical and mental health-related QOL (10). Therefore, any patient who seeks consultation for bothersome symptoms that are attributable to GERD and that persist despite treatment with a PPI merits evaluation and management. As not all patients who fail to respond to PPIs will have GERD, the most important goal of the diagnostic evaluation in these patients is to differentiate those with persistent reflux as the cause of the ongoing symptoms, from those with non-GERD etiologies.

The reported proportion of patients with heartburn who do not respond to PPIs varies among studies, likely due to differing definitions of failure, dissimilar patient groups, and different medication dosing. It has been estimated that failure to control symptoms occurs in up to 40% of patients treated with a PPI (146). A recent systematic review found persistent, troublesome typical symptoms of GERD (heartburn and regurgitation) in 32% of patients in randomized primary care trials and 45% of patients in observational studies (147). The proportion of patients with extraesophageal presentations of GERD that do not respond to medication is less well documented, but the success rate of treating extraesophageal reflux symptoms is lower than that for typical symptoms (139–141). A recent comparison of PPI responders and non-responders found that PPI failure appears to be significantly more common in those with atypical symptoms. Additional factors associated with PPI failure were longer duration of disease, poor compliance, and obesity (63).

The first step in the management of refractory GERD is to optimize PPI therapy by confirming compliance and ensuring appropriate dosing. Poor compliance is associated with lack of response to PPI (63). Furthermore, adherence to PPI therapy was found in only 60% of patients with GERD in a large population-based VA study (148). The efficacy of PPIs (as discussed above) is generally maximized when PPIs are taken before a meal (149). Optimal PPI dosing (before meals) was seen in only 46% of 100 patients who were referred for persistent GERD symptoms despite treatment (66). A survey of 491 physicians found that nearly 70% of primary care physicians and 20% of gastroenterologists in the US advised patients to take the PPI dose at bedtime or did not believe that the relationship to meals was important (150). Therefore, any patient with refractory symptoms should be instructed regarding optimal dosing of the PPI being used. Once compliance and appropriate dosing are ensured, a single trial of a different PPI can be considered. Recent evidence from a multicenter randomized trial showed this strategy to be helpful in some patients (67). A randomized controlled trial in patients with persistent GERD symptoms despite a single daily dose of PPI, showed that increasing PPI to twice daily or switching to another PPI both resulted in symptomatic improvement in roughly 20% of patients, without a clear advantage for either strategy (151).

Patients with persistent symptoms despite optimization of PPI therapy require further work-up (**Figure 1**). Those with typical, esophageal symptoms should undergo endoscopy principally to exclude non-reflux esophageal disorders such as EoE, which can present with esophageal symptoms refractory to PPI and to look for the rare patient with erosive esophagitis, a finding that provides evidence of ongoing acid reflux. Although the prevalence of EoE in patients with refractory GERD in the US has not been studied, a recent Markov model found that obtaining esophageal biopsies to diagnose EoE in refractory GERD patients is cost-effective only when the prevalence of EoE is 8% or greater (152). If endoscopy is negative, as is frequently the case, the next step is to perform reflux monitoring to quantify reflux and assess the relationship between reflux episodes and the patient's symptoms. Reflux monitoring should also be considered in patients with extraesophageal symptoms that persist despite PPI optimization and in whom non-GERD etiologies have been ruled out through pulmonary, ENT, and allergy evaluation.

Reflux monitoring enables further characterization of the refractory patient, as the study may reveal: (a) PPI failure with ongoing acid reflux, which will require escalation of therapy to control acid reflux (b) adequate acid control but ongoing symptomatic non-acid reflux, which may respond to specific therapy or (c) no reflux. Among refractory GERD patients with a negative reflux monitoring study, those with heartburn may be classified as having "functional heartburn" while those with extraesophageal symptoms (asthma, cough, laryngitis) will need additional

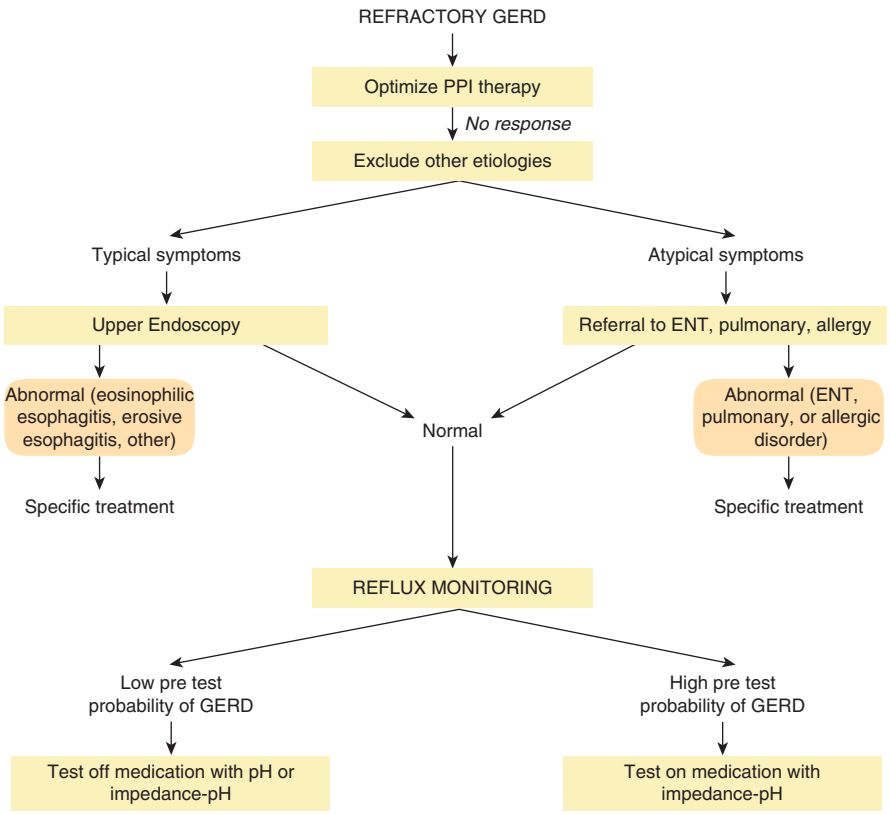

Figure 1. Algorithm for the evaluation of refractory gastroesophageal reflux disease (GERD). ENT, ear, nose, and throat; PPI, proton pump inhibitor.

or repeat work-up for non-GERD (pulmonary, allergic, ENT) etiologies.

Two key issues to consider are whether reflux monitoring should be performed after stopping PPI therapy or while *on* medication, and what technique to use (catheter-based pH, wireless pH, or impedance-pH). At the present time there are limited data and no clear consensus regarding the optimal testing methodology for refractory GERD. The approach to testing may be chosen based on the patient's clinical presentation and pretest likelihood of GERD, as well as on the available technology and expertise. Reflux monitoring both off as well as on PPI offers important and clinically useful information as outlined below.

Reflux monitoring off PPI (7 days after cessation of PPI) can be performed with any of the available techniques (catheter or wireless pH, or impedance-pH). If reflux monitoring *off* medication is negative (normal distal esophageal acid exposure and a negative symptom-reflux association), GERD is very unlikely. In a patient with a negative test *off* therapy, PPIs can be stopped and the diagnostic effort should be steered toward non-GERD etiologies. On the other hand, a positive test after PPI cessation offers objective evidence of GERD but it does not provide insight regarding the reason for the failure to respond to treatment.

Reflux monitoring on PPI should be performed with impedance-pH monitoring to enable measurement of nonacid reflux. The yield of pH monitoring without impedance in a patient taking a PPI is very low because in acid-suppressed patients reflux becomes predominantly nonacid (153). In fact, pH monitoring revealed normal acid exposure in 96% of patients with refractory GERD that were tested on twice daily PPI (154). Although rare, an abnormal pH test in a patient taking a PPI (i.e. ongoing acid reflux despite treatment) is evidence of therapeutic failure or noncompliance. A negative pH test in treated patients makes ongoing acid reflux as the cause of their symptoms very unlikely, but it cannot account for the possibility of nonacid reflux, which can be measured using impedance-pH monitoring. A study that used the SI to evaluate 144 patients refractory to twice daily PPI therapy found that ongoing symptoms were related to non-acid reflux in 37% and acid reflux in 11% (155). In the remaining 52% of patients, there was no association between reflux (either acid or non-acid) and symptoms. A positive SI was more common in patients with typical symptoms (heartburn, regurgitation, and chest pain) compared with those with an atypical presentation (55% vs. 25%). A different study using the SAP in patients who were symptomatic despite PPI therapy found an association between reflux and symptoms in 37% of 60 patients; the SAP was positive due to nonacid reflux in 17%, acid reflux in 5%, and acid plus nonacid reflux in 15% (156). As demonstrated by these studies, impedance-pH testing covers all possible scenarios for persistent symptoms in a treated patient: ongoing acid reflux, ongoing non-acid reflux, or no reflux. Furthermore, a systematic review that quantified acid and nonacid (both weakly acidic and weakly alkaline) reflux in studies of GERD patients taking a PPI, found that weakly acidic reflux underlies the majority of reflux episodes in these patients and is the main cause of persistent symptoms despite PPI therapy (157). Finally, a negative imped-

ance-pH test on medication strongly supports that the patient's complaints are not due to reflux of any type. Needless to say, the full context of the patient (including clinical presentation, presence of hiatus hernia, endoscopy findings, and/or degree of response to therapy) always needs to be considered.

Studies comparing the yield of "*off* vs. *on*" therapy reflux monitoring in refractory GERD patients are limited. Hemmink *et al.* (158) concluded that testing should be performed off PPI. In contrast, Pritchett *et al.* (159) found that reflux monitoring on PPI may be the preferred strategy. At present no single approach can be recommended due to the heterogeneous group of patients. A recent technical review on this topic suggested that, in the absence of high-quality studies to guide this decision, the method of testing may be chosen based upon the patient's clinical presentation (127). In patients with a low likelihood of GERD (for instance, atypical presentations without concomitant typical GERD symptoms) pH monitoring *off* medication may be preferred as it will enable ruling out GERD. Patients with a higher likelihood of GERD (typical symptoms, at least partial response to PPI) can be tested with impedance-pH testing on medication in search of ongoing reflux (either acid or non-acid) despite PPI. Clearly, more studies are needed to bring clarity to this issue.

Finally, it is important to stress the importance of stopping PPI therapy in patients with refractory symptoms in whom all testing is negative. In a recent study, after a negative evaluation for refractory GERD that included normal endoscopy and impedance-pH monitoring, 42% of 90 patients reported continued use of PPI despite negative results (160). This study underscores the importance of educating the patient about the need to stop PPIs once GERD has been ruled out.

There are few studies in which refractory GERD patients with documented ongoing reflux have been treated with either medication or surgery. Patients with abnormal frequency of non-acid reflux can be considered for treatment with the GABA B agonist, baclofen as this drug has been shown to decrease reflux episodes and symptoms due to all types of reflux (81,82). Unfortunately, high-quality controlled trials evaluating the role of baclofen in refractory symptoms are not available. Small uncontrolled studies have demonstrated a benefit for baclofen when used for refractory duodeno-gastro-esophageal reflux in patients with persistent symptoms on PPI therapy (81). A small observational study with limited follow-up suggested a positive symptom response to surgery in this group, but improvement in reflux control was not objectively documented (161). A more recent prospective, uncontrolled study found that 3 months after fundoplication, both the number of reflux episodes and typical symptoms of GERD (heartburn and regurgitation) improved in patients who were PPI-nonresponders (162). However, it must be pointed out that these patients are carefully selected and were not in a controlled trial. High-quality, controlled trials evaluating surgery in patients unresponsive to PPIs are lacking, so this approach is not recommended except in highly individual circumstances. In this context, performing a reflux monitoring test *off* PPI can confirm the presence of pathological reflux before surgery. Finally, there is no data to support the use of transoral incisionless fundoplication, or other endoscopic therapy in refractory GERD.

WHAT ARE THE COMPLICATIONS ASSOCIATED WITH GERD?

Recommendations

1. The Los Angeles (LA) classification system should be used when describing the endoscopic appearance of erosive esophagitis (Strong recommendation, moderate level of evidence). Patients with LA Grade A esophagitis should undergo further testing to confirm the presence of GERD. (Conditional recommendation, low level of evidence)
2. Repeat endoscopy should be performed in patients with severe ERD after a course of antisecretory therapy to exclude underlying Barrett's esophagus. (Conditional recommendation, low level of evidence)
3. Continuous PPI therapy is recommended following peptic stricture dilation to improve dysphagia and reduce the need for repeated dilations. (Strong recommendation, moderate level of evidence)
4. Injection of intralesional corticosteroids can be used in refractory, complex strictures due to GERD. (Conditional recommendation, low level of evidence)
5. Treatment with a PPI is suggested following dilation in patients with lower esophageal ring (Schatzki) rings. (Conditional recommendation, low level of evidence).
6. Screening for Barrett's esophagus should be considered in patients with GERD who are at high risk based on epidemiologic profile. (Conditional recommendation, moderate level of evidence)
7. Symptoms in patients with Barrett's esophagus can be treated in a similar fashion to patients with GERD who do not have Barrett's esophagus. (Strong recommendation, moderate level of evidence)
8. Patients with Barrett's esophagus found at endoscopy should undergo periodic surveillance according to guidelines. (Strong recommendation, moderate level of evidence)

SUMMARY OF THE EVIDENCE

Numerous "complications" have been associated with GERD including erosive esophagitis, stricture, and Barrett's esophagus. Obesity has been demonstrated to be a risk factor for symptoms, ERD, BE, and adenocarcinoma (17). It may be that the presence of an abnormal waist-to-hip ratio is the greatest risk factor for the presence of BE (163). Although many classification systems for erosive esophagitis have been used in the literature, a classification system, introduced in 1994, appears to be most logical to use in practice. Using an A,B,C,D system to describe esophageal erosions, this system has been used in the largest and most modern trials. In contrast to other systems (164), the LA classification system has been tested and shown to have good inter and intraobserver variability (27). This system offers a commonality of language among endoscopists for grading this complication of GERD and is recommended as the system of choice for reporting. Erosive esophagitis

is seen in a minority of patients with symptomatic GERD, with the majority of the patients having LA grade A or B esophagitis present. LA grades C and D have been described as "severe" and have the lowest healing rate with PPIs (54,165). Severe erosive esophagitis (grades C and D) is more common in the elderly and in general would relapse if maintenance therapy is not instituted. There are limited data to suggest that a columnar lined esophagus (Barrett's esophagus) can be obscured by any grade of erosive esophagitis, most commonly it is obscured by grades C and D (166,167). On the basis of these data, a repeat endoscopy after a minimum 8-week course of PPI therapy is recommended in patients with grades C and D esophagitis and can be considered in lower grades. In patients not found to have BE on repeat endoscopy and in patients with a normal initial endoscopic examination, the utility of repeated examinations to screen for the development of BE has not been demonstrated (168). Other than the above clinical scenarios, repeating an endoscopy in GERD patients who do not demonstrate new symptoms is not recommended.

Peptic strictures are infrequent in practice, likely related to the widespread use of antisecretory therapy. Strictures tend to occur most often in Caucasians, older patients with a longer duration of untreated symptoms, and in the setting of abnormal esophageal motility (169,170). With rare exceptions (e.g. the presence of an inlet patch), true peptic strictures occur at the squamocolumnar junction. A stricture elsewhere should raise suspicion for another etiology. PPIs are clearly superior to H_2-receptor antagonists and when used in a maintenance fashion improve dysphagia, decrease the need for repetitive dilations and/or prolong the interval between dilations (171,172).

Intralesional corticosteroids (40 mg of triamcinolone injected in four 1 ml aliquots) in a four quadrant pattern can be considered in peptic strictures refractory to dilation. The limited randomized controlled trials support the efficacy of steroid injection in conjunction with antisecretory therapy and dilation in tough strictures (173,174). The availability of so-called removable stents has generated enthusiasm in patients with benign esophageal strictures. These should be rarely necessary and are associated with stent migration and complications that preclude routine use in a benign peptic stricture. There appears to be no role for endoscopic incision in a typical benign peptic stricture.

Lower esophageal rings (Schatzki) are felt by many to be linked with GERD, raising the question of whether antisecretory therapy should be part of the treatment approach. Dilation remains the mainstay of treatment; however, one trial found that no patient with documented GERD (endoscopy or pH) had a recurrent Schatzki ring on PPI therapy post dilation. The same group randomized 30 patients without proven GERD to PPI or placebo and found a statistical decrease in recurrence of rings (mean follow up 43 months) in PPI-treated patients (175). This prompts many to recommend PPIs in patients with Schatzki ring, particularly if they recur.

Barrett's esophagus is the only complication of GERD with malignant potential. Barrett's can be found in 5 to 15% of patients who have endoscopy for symptoms of GERD (176) and tends to be seen at the higher end of this range in patients with long duration of symptoms, who are over the age of 50, male, and Caucasian. The difficulty in risk stratification is highlighted by the fact that 25% of patients with Barrett's are women or under the age of 50 (177,178). Despite the well-identified epidemiologic risk factors there is no clear profile that mandates screening. As such, these guidelines can only recommend consideration of screening perhaps concentrating on those of higher epidemiologic risk but more importantly with an informed discussion with the patient. Although there is debate about the value of surveillance, current guidelines recommend that patients with endoscopically confirmed Barrett's esophagus be enrolled in a surveillance program (179).

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