

PRACTICE GUIDELINES

Updated Guidelines for the Diagnosis and Treatment of Gastroesophageal Reflux Disease

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Guidelines for the diagnosis and treatment of gastroesophageal reflux disease (GERD) were published in 1995 and updated in 1999. These and other guidelines undergo periodic review. Advances continue to be made in the area of GERD, leading us to review and revise previous guideline statements. GERD is defined as *symptoms or mucosal damage produced by the abnormal reflux of gastric contents into the esophagus*. These guidelines were developed under the auspices of the American College of Gastroenterology and its Practice Parameters Committee, and approved by the Board of Trustees. Diagnostic guidelines address empiric therapy and the use of endoscopy, ambulatory reflux monitoring, and esophageal manometry in GERD. Treatment guidelines address the role of lifestyle changes, patient directed (OTC) therapy, acid suppression, promotility therapy, maintenance therapy, antireflux surgery, and endoscopic therapy in GERD. Finally, there is a discussion of the rare patient with refractory GERD and a list of areas in need of additional study.

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INTRODUCTION AND PREAMBLE

Guidelines for the diagnosis and treatment of gastroesophageal reflux disease (GERD) were published by the American College of Gastroenterology in 1995 and updated in 1999 (1, 2). These and other guidelines undergo periodic review. Advances continue to be made in the area of GERD, leading us to review and revise our previous guidelines statements. These and the original guidelines are intended to apply to all health-care providers who address GERD and are intended to indicate the preferred, but not only, acceptable approach. Treatment should be based on the course best suited to the individual patients and the variables that exist at the moment of the decision. These guidelines are applicable to adult patients with the symptoms, tissue damage, or both that result from the reflux of gastric content into the esophagus. For the purpose of these guidelines, GERD is defined as *symptoms or mucosal damage produced by the abnormal reflux of gastric contents into the esophagus*.

These and the previous guidelines were developed under the auspices of the American College of Gastroenterology and its Practice Parameters Committee, and approved by the Board of Trustees. The world literature was reviewed extensively for the original guidelines and again reviewed for each revision using the National Library of Medicine database. Appropriate studies were reviewed and any additional studies found in the reference list of these papers were obtained and reviewed. Evidence was evaluated along a hierarchy, with randomized, controlled trials given the greatest weight. Abstracts presented at national and international meetings were only used when unique data from ongoing trials were pre-

sented. When scientific data were lacking, recommendations were based on expert consensus obtained from both the literature and the experience of the authors and the Practice Parameters Committee. The committee evaluated each italicized guideline and a strength of evidence score was given (Table 1).

DIAGNOSTIC GUIDELINE I: EMPIRICAL THERAPY

If the patient's history is typical for uncomplicated GERD, an initial trial of empiric therapy (including lifestyle modification) is appropriate. Endoscopy at presentation should be considered in patients who have symptoms suggesting complicated disease, those at risk for Barrett's esophagus, or when the patient and physician feel early endoscopy to be appropriate.

Level of Evidence: IV

Symptoms which are highly specific for GERD include heartburn (pyrosis), regurgitation, or both, which often occur after meals (especially large or fatty meals) (3). These symptoms are often aggravated by recumbency or bending over and are relieved by antacids. The combination of symptoms and endoscopic changes are highly specific (97%) for GERD (confirmed with pH testing) (4). Expert opinion holds that it is appropriate to offer empiric therapy for GERD to patients with symptoms consistent with GERD. It is also reasonable to assume a diagnosis of GERD in patients who respond to appropriate therapy. Further diagnostic testing should be considered if the patient does not respond to therapy, when there

Table 1. Rating of Levels of Evidence Used for this Guideline

I	Strong evidence from at least one published systematic review of multiple well-designed randomized controlled trials
II	Strong evidence from at least one published properly designed randomized controlled trial of appropriate size and in an appropriate clinical setting
III	Evidence from published well-designed trials without randomization, single group prepost, cohort, time series or matched case-controlled studies
IV	Evidence from well-designed nonexperimental studies from more than one center or research group or opinion of respected authorities, based on clinical evidence, descriptive studies, or reports of expert consensus committees

are alarm symptoms suggesting complicated disease (dysphagia, odynophagia, bleeding, weight loss, or anemia) and when patients have a sufficient duration of symptoms to put them at risk for Barrett's esophagus. Patients who do not respond to therapy often have another cause for their symptoms, but this lack of response does not always exclude reflux as a possibility. Even when the most effective therapy for GERD is prescribed, some patients will continue to reflux acid (5). A short trial of a high dose proton pump inhibitor has 75% sensitivity, but only 55% specificity for reflux in heartburn patients using ambulatory pH testing as the "gold standard" (6). These problems with the sensitivity and specificity of using a therapeutic trial as a test for GERD must be weighed against the ease of use and decreased cost (primarily related to decreased use of diagnostic testing of this approach) (7). Finally, symptoms do not seem to predict the degree of esophagitis and are far from perfect in predicting complications of GERD including Barrett's esophagus (8).

The purpose of evaluating patients with long-term symptoms and patients who have complicated symptoms is to exclude complications of GERD. Compared with patients with symptoms consistent with GERD for less than 1 yr, the odds ratio for Barrett's esophagus in patients with symptoms for 1–5 yr is 3.0 and for greater than 10 yr is 6.4. These concepts have been challenged by reports suggesting that both the frequency and severity of reflux symptoms are poorly predictive of the presence of Barrett's esophagus (9, 10). Patients with alarm symptoms are more likely to have peptic strictures and esophagitis than those without alarm symptoms.

DIAGNOSTIC GUIDELINE II: USE OF ENDOSCOPY IN GERD

Endoscopy is the technique of choice used to identify suspected Barrett's esophagus and to diagnose complications of GERD. Biopsy must be added to confirm the presence of Barrett's epithelium and to evaluate for dysplasia.

Level of Evidence: III

Endoscopy allows direct visualization of the esophageal mucosa. This is the only reliable method for the diagnosis of Bar-

rett's esophagus. A reticular pattern on barium esophagram is neither sensitive (26%) nor specific (50%) when compared to endoscopy with biopsy (11). Barium radiography is reasonably accurate in cases of severe esophagitis (80% or better), but is much less accurate with mild esophagitis (less than 25%) (12–15). Finally, reflux of barium during radiographic evaluation is only positive in 25–75% of symptomatic patients and is falsely positive in up to 20% of normal controls (15, 16). Patients with hiatal hernias or who reflux barium at fluoroscopy have more acid exposure by ambulatory pH testing, but these findings have poor specificity and sensitivity and should not be used as a screening test for GERD (17). These factors limit the usefulness of barium radiography in the routine diagnosis of GERD and it is not recommended.

Documentation of the presence or absence of esophagitis does not usually determine the initial approach to patients with GERD. Higher grades of esophagitis are more difficult to heal, but once healed can be maintained in remission with medical or surgical therapy (18, 19). The main advantage of knowing a patient has (or had) esophagitis is to confirm the diagnosis of GERD prior to surgical or endoscopic therapy for GERD. Typical esophagitis is essentially diagnostic for GERD.

Endoscopic biopsy is needed to determine the presence of Barrett's epithelium. The issues surrounding the management of Barrett's are covered in another guideline statement (20). Although not proven, this endoscopy probably should be performed after a course of therapy for GERD to allow better identification of Barrett's and to decrease the prevalence of inflammatory changes that are misinterpreted as dysplasia. It is of paramount importance that the esophagogastric junction is well described in the endoscopy report. Biopsies showing intestinal metaplasia, identical to Barrett's, which are obtained from the gastric cardia do not indicate the same malignant potential as biopsies from the esophagus and actually do not even confirm GERD (21). There is no value for histologic examination of normal appearing squamous mucosa to either confirm or exclude pathologic acid reflux (22, 23).

It is critical to understand that while an endoscopy showing clear evidence of Barrett's esophagus or esophagitis confirms the diagnosis of GERD, a normal endoscopy in no way excludes GERD. The majority of symptomatic patients will have a normal endoscopy, which does not necessarily indicate either less severe symptoms or a more easy to control form of GERD (24). In fact, studies of GERD patients without esophagitis have suggested that symptoms are just as difficult and at times more difficult to control (25). The suggestion that only patients with documentable esophagitis should have access to chronic proton pump inhibitor therapy is not supportable, since these patients may well have pathologic amounts of acid reflux that is only controlled with a PPI (26). Symptomatic GERD patients without esophagitis (so called nonerosive reflux disease) should be treated in a similar fashion to those with erosive esophagitis.

DIAGNOSTIC GUIDELINE III: AMBULATORY REFLUX MONITORING

Ambulatory monitoring of the esophagus helps to confirm gastroesophageal reflux in patients with persistent symptoms (both typical and atypical) without evidence of mucosal damage, especially when a trial of acid suppression has failed. It may also be used to monitor the control of reflux in patients with continued symptoms on therapy.

Level of Evidence: III

While endoscopy allows for the evaluation of esophageal mucosa, the presence or absence of mucosal injury does not provide proof that the patient's symptoms are or are not related to GERD. Many patients with typical GERD symptoms and increased esophageal acid exposure do not have esophagitis (27). Patients with symptomatic, but not excessive gastroesophageal reflux have persistence of symptoms and requirements for therapy similar to patients with excessive reflux, but are less likely to have endoscopic findings (28). This "endoscopic negative" form of GERD produces symptoms and illness behavior identical to that of GERD with endoscopic findings (29). Ambulatory pH testing allows both the identification of patients with excess esophageal acid exposure and those with symptoms that correlate with esophageal acid (either with normal or abnormal total acid exposure). Good reproducibility (84–93%) and sensitivity and specificity (96%) have been reported in patients with erosive esophagitis (30, 31). Reasons for concern include the finding of normal acid exposure in up to 29% of patients with documented esophagitis and differences found in the simultaneous acid exposure recorded by two attached probes (32, 33). A recent report repeated pH testing on patients who had an initial negative test (34). If the patient's symptoms had been typical or worse than typical during their first pH test, 22% of second tests were positive, while 55% of studies were abnormal if the patients said their day was "better than typical" during the first test. Despite these limitations, ambulatory pH testing remains the best method to study the actual amount of reflux occurring in a given patient. Ambulatory pH testing while on reflux therapy may also be of benefit in the patient with refractory symptoms (35).

There have been two recent advances that may alter the management of GERD. Combined impedance and acid testing has been developed (36, 37). This technology allows for the measurement of both acid and nonacid (volume) reflux. This may be particularly important in the patient with persistent symptoms despite an adequate medical trial and allow more efficient monitoring of reflux in patients on therapy. Another new technology is a tubeless method of acid monitoring. This device allows a radiotelemetry capsule to be attached to the esophageal mucosa and monitored without the discomfort of a nasoesophageal tube (38). This decreases patient discomfort, allows for longer (48 h) monitoring, and may improve accuracy by allowing the patient to carry out their usual activities.

DIAGNOSTIC GUIDELINE IV: ESOPHAGEAL MANOMETRY

Esophageal manometry may be used to ensure accurate placement of ambulatory monitoring probes and may be helpful prior to antireflux surgery.

Level of Evidence: III

The accurate placement of esophageal pH probes requires knowledge of the location of the lower esophageal sphincter (39, 40). This usually requires intubation with a manometry catheter and provides an opportunity for full manometry. There now have been several reports that show adequate placement of pH tubes using a combined pH/pressure measurement system, which negates the need for full manometry (41, 42). The new tubeless pH monitoring system uses endoscopic landmarks for placement, which were derived from studies comparing endoscopic to manometric measurements and does not require manometry.

Esophageal manometry to document the presence of effective esophageal peristalsis has been used in patients in whom antireflux surgery is being considered (43). It has been suggested that patients who have ineffective peristalsis may need to either avoid surgery or undergo an alternative (*i.e.*, less tight) procedure (44). Surgeons will often elect to perform a partial fundoplication in patients who have a weaker esophagus by manometry (45). In a series of 107 patients, manometry changed the therapy offered in 10% of patients referred for antireflux surgery (46). These assumptions have recently been challenged by several studies. For example, reflux control was found to be better and dysphagia no more common in several series of patients with weak peristalsis when a complete, as opposed to a partial, fundoplication was performed (47, 48). A recent report of combined impedance and manometry testing suggests that this technique may have the ability to identify which patients with ineffective peristalsis have an esophageal bolus transit abnormality, therefore potentially clarifying which patients have a more significant defect in motility (49). Preoperative manometry is perhaps most useful to exclude rare motility disorders such as achalasia or the aperistalsis associated with disorders such as scleroderma.

TREATMENT GUIDELINE I: LIFESTYLE MODIFICATION

Lifestyle modification may benefit many patients with GERD, although these changes alone are unlikely to control symptoms in the majority of patients.

Level of Evidence: IV

Education of the patient about factors that may precipitate reflux remains reasonable. Numerous studies have indicated that elevation of the head of the bed (50, 51), decreased fat intake (52), cessation of smoking (53), and avoiding recumbency for 3 h postprandially (54) decreases distal esophageal acid exposure although data reflecting the true efficacy of these maneuvers in patients is almost completely lacking.

Certain foods (chocolate (55), alcohol (56), peppermint (57), coffee (58), and perhaps onions and garlic (59)) have been noted to lower LES pressure, although randomized trials are also not available to test the efficacy of these maneuvers. Many authors assume the 20–30% placebo response rate seen in most randomized trials is due to lifestyle changes, but this has not been rigorously tested. The potential negative effect of lifestyle changes on a patient's quality of life has also not been examined.

TREATMENT GUIDELINE II: PATIENT DIRECTED THERAPY

Antacids and over-the-counter (OTC) acid suppressants are options for patient-directed therapy for heartburn and regurgitation. When symptoms persist, continuous therapy is required or alarm symptoms or signs develop, the patient should have additional evaluation and treatment (see above diagnostic guidelines).

Level of Evidence: IV

Antacids and antirefluxants such as alginic acid are useful in the treatment of milder forms of GERD. Antacids (60) and alginic acid (61, 62) have been shown to be more effective than placebo in the relief of symptoms induced by a heartburn promoting meal. In addition, combined antacid/alginic acid therapy may be superior to antacids alone in the control of symptoms (63, 64). There are two long-term trials, which suggest effective symptom relief in approximately 20% of patients using OTC agents (65, 66).

All four of the H2RAs approved for use in the United States are available OTC in doses that have been shown to decrease gastric acid, particularly after a meal. While there are some differences in potency, duration, and rapidity of action, they may be generally used interchangeably. The OTC H2RAs are particularly useful when taken prior to an activity that may potentially result in reflux symptoms (heavy meal or exercise in some patients). Many patients can predict when they are going to suffer from reflux and can premedicate with the OTC H2RAs. Comparisons between OTC H2RAs and antacids are limited. It has been suggested that antacids provide a more rapid response, but gastric pH begins to rise less than 30 min after taking a dose of H2RA so this does not seem to be a major factor. The peak potency of OTC H2RAs and antacids are similar, but the H2RAs have a much longer duration of action (up to 10 h). An OTC formulation of omeprazole has just been introduced in the United States at a dose identical to that available by prescription for the short-term (14 days) treatment of heartburn. It is important that patients visit their physician before using these medications beyond their 14-day indication since some will be at risk for Barrett's esophagus or other upper gastrointestinal pathology and should be evaluated and, if appropriate, referred for endoscopic screening. It is important that physicians and their patients continue to have access to prescription proton pump inhibitors (PPIs) for several reasons including difference in individual response

and differences in FDA indications, dosages, and administration routes for different PPIs.

TREATMENT GUIDELINE III: ACID SUPPRESSION

Acid suppression is the mainstay of therapy for GERD. Proton pump inhibitors provide the most rapid symptomatic relief and heal esophagitis in the highest percentage of patients. Although less effective than PPIs, histamine₂-receptor blockers given in divided doses may be effective in some patients with less severe GERD.

Level of Evidence: I

In the original guideline statement (1), the results of 33 randomized trials including over 3,000 patients with erosive esophagitis are presented. Symptomatic relief can be expected in 27% of placebo treated, 60% of H2RA treated, and 83% of PPI treated patients. Esophagitis healed in 24% of placebo treated, 50% of H2RA treated, and 78% of PPI treated patients. We will not readdress those studies here, but it is clear that while some patients may have relief of symptoms and improvement or healing of esophagitis on H2RAs, PPIs eliminate symptoms and heal esophagitis more frequently and more rapidly than the other agents. Both higher doses and more frequent dosing of H2RAs appear to improve results in the treatment of reflux, but are still inferior to PPIs (67–69). In addition to controlling symptoms and esophagitis, PPI therapy has been shown to normalize the impaired quality of life caused by GERD (70).

Proton pump inhibitors are safe, effective, and have been used for more than a decade in the United States and much longer in Europe and Australia (71). It is becoming increasingly clear that the benefit of chronic PPI therapy in patients with chronic and/or complicated GERD outweighs any theoretical risk. Some concerns have been raised about the possibility of vitamin B-12 deficiency occurring on chronic PPI therapy, although this has only been reported in a few patients (72).

There are five available PPIs (omeprazole, lansoprazole, rabeprazole, pantoprazole, and esomeprazole). All of these agents have been demonstrated to control GERD symptoms and to heal esophagitis when used at prescription dosages. There have been several physiologic studies suggesting modest benefits of one agent over another (73–77). The effect of PPIs can be optimized with appropriate dosing. The drugs should always be given prior to meals. Most patients on once-daily PPI should take them prior to breakfast, but a recent study suggested that nighttime acid might be better controlled if the PPI is taken prior to the evening meal (78). In some situations, it is reasonable to use higher than approved doses of PPI, which are then often given in divided doses. Times when this is of particular benefit are during a diagnostic trial for noncardiac chest pain (79), during empiric treatment trial for supraesophageal symptoms of GERD (80), in patients with a partial response to standard dose therapy (5), in patients who

have responded but are having breakthrough symptoms (71), in GERD patients with severe esophageal dysmotility (81), and in patients with Barrett's esophagus (82). When a second dose is added, it should be given prior to the evening meal, not at bedtime.

It is clear that PPI therapy results in the best symptom control and esophagitis healing among our available medical options. It is also clear that some patients (although it is difficult to determine which patients) will do well on the less intense acid suppression resulting from H2RA therapy. Several strategies have been advocated to decrease the cost of GERD therapy by limiting the number of patients taking PPI. These strategies have been examined in many modeling analyses, but have not been well tested in randomized trials. A recent study in a VA population demonstrated that patients who were "PPI dependent" could frequently be managed on less intense therapy (83). They attempted to take 71 patients off PPIs finding that 42% could not be taken off, 42% could be managed with H2RAs, prokinetics, or a combination, and 15% could be taken off medication. It is unclear if these data can be applied to a more generalized population. Modeling studies that use cost as an important endpoint are highly dependent on the assumptions used in constructing the model. Efficacy and safety data support continuous PPI therapy as the most effective management for patients with GERD. The only advantage for using less effective therapy is economic and the current availability of both generic and OTC PPIs makes continuous PPI therapy even more attractive. On-demand therapy with PPIs has not been well studied, but patients tend to do this on their own and it may make economic sense in patients with mild-to-moderate symptoms (84). Once a patient has failed less effective therapy, they should have access to chronic PPI therapy, especially if it is the only medical therapy that keeps them in symptomatic and endoscopic remission.

The benefit of complete acid control in the maintenance of Barrett's esophagus has not been proven, but if this result is desired, many patients will need twice daily PPI therapy at higher than usual doses even when the patients are asymptomatic on lower doses (85, 86). Gastric acid is still secreted, particularly at night, in many patients on twice-daily PPIs (87). The addition of a nighttime H2RA was suggested to suppress this acid, although a recent study found that this effect might not persist over time (88).

TREATMENT GUIDELINE IV: PROMOTILITY THERAPY

Promotility agents may be used in selected patients, especially as an adjunct to acid suppression. Currently available promotility agents are not ideal monotherapy for most patients with GERD.

Level of Evidence: II

Defects in esophagogastric motility (LES incompetence, poor esophageal clearance, and delayed gastric emptying) are cen-

tral to the pathogenesis of GERD (89). If these defects could be corrected then GERD would be controlled, making suppression of normal amounts of gastric acid unnecessary. The frequent Central Nervous System side effects of metoclopramide and bethanechol (drowsiness, irritability, extrapyramidal effects, *etc.*) have appropriately decreased the regular use of these medications (90). Cisapride (91, 92) and domperidone (93) have been demonstrated to produce relief of symptoms. There have been reports of fatal cardiac dysrhythmias associated with the combination of cisapride and several agents that are metabolized by the cytochrome P-450 system (94). These reactions and a more recent suggestion of mechanisms for the production of similar rhythm disturbances while on cisapride alone have resulted in the withdrawal of this agent from regular availability in the United States market (95). Domperidone is a dopamine receptor blocker but unlike metoclopramide does not easily cross the blood-brain barrier and therefore has little central nervous system effect. Domperidone is as effective as metoclopramide and the only significant side effect seems to be hyperprolactinemia in 10–15% of patients. Despite this safety profile, the agent has not been marketed in the United States. Tegaserod is a 5HT3 agonist with promotility and antinociceptive effects. It has been shown to improve esophageal acid exposure (96), but has not been demonstrated to be effective monotherapy in GERD. Finally, baclofen, a GABA receptor type B agonist, has been reported to reduce both the number of reflux episodes and percent time esophageal acid exposure after a single dose of 40 mg (97). The mechanism appears to be suppression of transient LES relaxation (98). This agent has a high side-effect profile and probably will not be routinely used in patients, but there is intensive research ongoing to find a baclofen-like agent with a better side-effect profile. In summary, continued research into the role of promotility agents in GERD is warranted, but acid suppression remains the mainstay of GERD therapy.

TREATMENT GUIDELINE V: MAINTENANCE THERAPY

Because GERD is a chronic condition, continuous therapy to control symptoms and prevent complications is appropriate.

Level of Evidence: I

The improvement in GERD symptoms noted with the acid suppression produced by full dose PPIs is usually followed by a rapid return of symptoms once it is discontinued (99). Many patients with GERD require long-term, possibly life-long, therapy; therefore maintenance therapy becomes a major concern. Effective maintenance therapy should keep the patient's symptoms comfortably under control and prevent complications. This will vary in each patient and may require only antacids and lifestyle modifications in up to 20% of patients (84). Other patients with chronic reflux (up to 50%) have frequent symptomatic relapses despite appropriate therapy. Patients whose disease has been controlled with PPIs

often will have symptomatic relapses and failure of healing of esophagitis on standard dose, or even higher-dose H2RA and/or prokinetic therapy (100). A full dose of H2RA given once daily, although effective for peptic ulcer disease, is not appropriate for GERD. Reduced doses of PPIs have been consistently shown to be ineffective long-term in the therapy of GERD. This includes alternate day omeprazole (101) or “weekend” therapy (102). A daily dose of omeprazole 10 mg may be superior to standard dose ranitidine (103). Ultimately, whatever dose of medication is needed to control symptoms is the dose that should be used and may include full or even increased dose PPI in many patients.

There are clear data that acid suppression decreases the recurrence of peptic esophageal strictures. Cimetidine 400 mg four times a day did not affect the frequency of the need for dilation (104), but several studies have found that full dose PPIs will lengthen the interval between symptomatic relapses (105, 106). There are no similar data in regards to the prevention or prevention of progression of Barrett’s esophagus. It does not appear that Barrett’s esophagus will regress with either medical or surgical therapy (107, 108). There have been reports of occasional “islands” of squamous epithelium appearing with chronic PPI therapy, but the significance of this is not known (109).

TREATMENT GUIDELINE VI: SURGERY

Antireflux surgery, performed by an experienced surgeon, is a maintenance option for the patient with well-documented GERD.

Level of Evidence: II

Considerable controversy exists over the long-term effectiveness of surgical intervention in GERD and whether it is equal or superior to chronic medical therapy. In the early-published trials of medical *versus* surgical therapy, surgery was shown to be more effective, although both trials used medical therapy that would be considered ineffective today. The initial comparison favored surgical over a rather modest medical therapy (essentially antacids and lifestyle changes) over a 36-month period (110). A comparison of surgery *versus* ranitidine and metoclopramide indicated superiority for the surgical approach (111). The long-term outcome of many of these patients reported that after 10 yr, 92% of the patients randomized to medication were still on medications and 62% of those who were initially treated with surgery were now back on reflux medication (112). A trial that randomized 310 patients between surgery and PPIs found surgery to be slightly superior to omeprazole 20 mg per day at the end of 5 yr, but if dose titration up to 40–60 mg per day of omeprazole were used, the two treatments were equal (113). Proper selection and preoperative evaluation of patients is very important. In a study of 100 patients, the best predictors of a good outcome were; age <50 yr and typical reflux symptoms that had com-

pletely resolved on medical therapy (114). It is also clear that these typical reflux symptoms are more likely to resolve after surgery than the other atypical and supraesophageal symptoms (115).

If typical reflux esophagitis is not present endoscopically, ambulatory pH testing should be performed. Controversies related to the use of manometry to guide antireflux surgery are discussed in the above section on manometry. Delayed gastric emptying has been reported to increase the rate of complication following an antireflux surgery, but the utility of the routine preoperative use of these tests is not clear (116).

The medical therapy of GERD has focused on the neutralization of refluxed acid from the stomach. It is clear that there are other injurious factors involved. The possibility of duodenogastroesophageal reflux has been raised as an additional indication for the surgical repair of the LES in patients with GERD (117). While it appears that control of acid decreases the injury in patients who reflux duodenal contents (118, 119), certain of these patients may benefit from antireflux surgery although objective evidence of this type of reflux is difficult to obtain preoperatively.

Controversy exists in regards to the durability of these repairs with at least one group suggesting deterioration in both LES pressure and endoscopic histology back toward the presurgical level 5–6 yr postoperatively (120). A group of 55 patients who had undergone laparoscopic Toupet fundoplication were studied a mean of 2.9 yr after surgery and 67% reported heartburn, 33% regurgitation, and 33% regular use of prescription GERD medications. On the other hand, another group suggested that more dysphagia occurred with a full Nissen fundoplication and that the partial, Toupet fundoplication controlled reflux with less dysphagia (121). The advent of a laparoscopic approach to antireflux surgery has resulted in an increase in patient acceptance of this technique (122, 123). A recent study found significantly lower cost and shorter lengths of hospital stay with the laparoscopic approach, although patient satisfaction was similar between the open and laparoscopic groups (124). The only adverse effect of switching from an open to laparoscopic approach appears to be an increase in dysphagia in those treated laparoscopically (125). This approach may not be possible in some patients who have had previous surgery and may be less effective in the very obese (126). The decreased postoperative morbidity involved in this approach should not change the indications or evaluations for surgery, but does make this option more attractive for some patients whose alternative would be long-term medical therapy (127). However, postoperative symptoms are common and include dysphagia (128), difficulty with belching, increased flatulence, and diarrhea (129).

Choosing a patient for surgery remains something of a paradox. Patients who respond fully to PPIs appear to be the best candidates for surgery, but one wonders how advisable it is to subject a well-controlled patient to the morbidity of antireflux surgery. Some patients who are refractory to medical

therapy (especially those with nocturnal regurgitation) will benefit from surgery, but there are not clear data to help predetermine which patient will benefit most. An equal, perhaps more important factor in determining the outcome of antireflux surgery is the experience of the surgeon. Many more complications and poorer outcomes occur in low volume centers (130).

TREATMENT GUIDELINE VII: ENDOSCOPIC THERAPY FOR GERD

Endoscopic therapy controls symptoms in selected patients with well-documented GERD.

Level of Evidence: III

A great deal of excitement had been generated by the introduction of techniques designed to control reflux endoscopically. There are three broad categories of endoscopic therapy: radiofrequency application to the LES area, techniques designed to decrease reflux using endoscopic sewing devices, and techniques using an injection into the LES region. Radiofrequency application (Stretta; Curon Medical, Fremont, CA) is designed to increase the reflux barrier of the LES. The open-label, 1-yr follow-up of the first cohort of patients treated with this technique has been recently reported (131). The symptom score related to heartburn improved initially in most patients and this improvement persisted. A total of 34% of patients were back on PPIs and an additional 38% were regularly taking antacids at 1 yr. A sham treatment controlled trial has also recently been completed (132). Heartburn quality of life, median heartburn score, and SF 36 physical quality of life were improved more with active treatment compared to sham therapy. On the other hand, there were no differences noted in acid exposure nor in the percentage of patients who were able to discontinue daily medications (47% after active treatment, 37% after sham treatment, NS). Reported complications have included: death (two early in the experience with the technique), perforation, and hemorrhage.

Results of the endoscopic sewing techniques have also been reported. Six months after treatment with the first endoscopic sewing device (Endocinch; Bard, Murray Hill, NJ), 62% of 64 patients in the initial report were off PPIs (133). Extended follow-up of a small number of these patients (39) has been presented as an abstract, which suggested that less than 25% of patients were able to remain off medications for 2 yr (134). Most recently, early data from the full thickness plication device (NDO Surgical, Mansfield, MA) have been reported with 74% of 64 studied patients able to be off PPI therapy at 6 months (135). Finally, injection of a nonresorbable polymer (Enteryx, Boston Scientific, Natick, MA) has been reported to control GERD symptoms and allow 74% of patients to discontinue PPI therapy at 6 months and 70% to discontinue at 12-month follow-up (136, 137).

All of these techniques seem to produce an improvement in reflux symptoms, although significant changes in lower

esophageal sphincter pressure have not been documented and less than 35% of patients have been demonstrated to have normalization of their intraesophageal acid exposure (measured with ambulatory pH testing). When the results of the available studies (both published manuscripts and abstracts) are critically examined, many issues remain unresolved including: long-term durability and safety, efficacy of these procedures performed outside of clinical trials, and efficacy in atypical presentations of GERD, among others. Systematic reviews of the radiofrequency (138), endoscopic sewing (139), and injection techniques (140) were unable to identify any clear indications for these techniques, but did support their use in clinical trials and outside of clinical trials in certain well-informed patients who have well-documented GERD that is responsive to PPI therapy.

TREATMENT GUIDELINE VII: REFRACTORY GERD

GERD that is refractory to medical therapy is rare. The diagnosis should be carefully confirmed, preferably with ambulatory pH testing, prior to antireflux surgery.

Level of Evidence: IV

The vast majority of patients will have their symptoms and mucosal disease controlled with medical therapy for GERD (71). When a patient presents with either typical or atypical symptoms of GERD refractory to therapy, the diagnosis should be reconsidered. This may involve an ambulatory pH study, either on or off therapy, additional endoscopic and manometric evaluations, and consideration of testing and therapeutic trials for other conditions that may produce symptoms similar to GERD. It is also clear that some patients do not respond to traditional, approved doses of PPIs and that increasing the dose and particularly dosing the medication twice daily is appropriate in those patients (78). Refractory GERD is often used as a rationale for antireflux surgery and even for the development of some of the endoscopic techniques. The available data suggest that patients who do the best with surgery are those who previously responded to medical therapy, not the refractory patient (114). The endoscopic techniques have not been adequately studied in patients who are refractory to medications.

AREAS IN NEED OF ADDITIONAL STUDY

GERD has been extensively studied and we continue to see a steady improvement in our understanding of the condition. Despite this, many questions remain to be answered, including:

- (i) Will impedance monitoring and "tubeless" pH monitoring change our approach to subsets of GERD patients?
- (ii) Will esophageal manometry prior to antireflux surgery be abandoned or perhaps be replaced by impedance

- testing? If motility testing is abandoned, will a partial or complete fundoplication become the operation of choice?
- (iii) How will the availability of OTC and generic PPIs change the face of GERD for both primary care and gastroenterology?
 - (iv) Will new promotility agents be developed to address the underlying physiological defect in GERD?
 - (v) Will the results from endoscopic therapy of GERD improve and become more attractive options?
 - (vi) There are many questions related to Barrett's esophagus covered extensively in other guidelines, but some of these include:
 - (a) Is there an appropriate public health benefit for Barrett's screening and surveillance?
 - (b) Do patients who have their GERD diagnosed and controlled with medication still eventually need a "once in a lifetime" endoscopy to exclude Barrett's esophagus?
 - (c) Will less invasive (small caliber, unседated) endoscopy allow for more cost-effective screening for Barrett's esophagus in GERD patients?

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