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CME CREDIT HOURS

KEY POINTS:

Gastroesophageal reflux disease is often a cause of noncardiac chest pain, pulmonary disease (especially asthma), and ear, nose, and throat problems. Aggressive prevention of acid reflux, using either drugs or surgery, is the key to treating these problems.

Ambulatory esophageal pH monitoring is the most accurate diagnostic test for gastroesophageal reflux, but an empirical trial of a proton pump inhibitor may be more practical and cost-effective. Esophageal pH monitoring should be the first study performed in patients with suspected acid related chest pain.

Other tests often used to diagnose acid-related chest pain (such as barium studies, endoscopy, acid-perfusion monitoring, and esophageal manometry) are of little use in diagnosing GERD, as they provide only indirect evidence of the condition and may often give false-negative results.

Extraesophageal presentations of gastroesophageal reflux disease: the case for aggressive diagnosis and treatment

ABSTRACT: Gastroesophageal reflux disease (GERD) has a number of extraesophageal presentations, including noncardiac chest pain, asthma, and laryngitis. Although 24-hour esophageal pH monitoring is the best test to diagnose GERD, an empiric approach to treatment, using an aggressive acid suppression regimen such as a proton-pump inhibitor, may be more cost-effective.

Because gastroesophageal reflux disease (GERD) has many extraesophageal presentations such as noncardiac chest pain, pulmonary disease, and ear, nose, and throat problems (**TABLE**),[1] physicians should keep it in mind when a patient presents with one of these conditions. A careful history usually reveals classic reflux symptoms, but 10% to 45% of patients with GERD deny any previous esophageal complaints. And because many patients with chest pain, asthma, or laryngitis may not be aware of GERD as a possible cause for their complaints, they may present to primary care physicians, cardiologists, pulmonologists, and ear, nose, and throat physicians.

Ambulatory esophageal pH monitoring is the best diagnostic test for GERD because it records episodes of gastroesophageal reflux and also can determine if symptoms occur during these episodes. Other studies, such as barium esophagraphy, endoscopy, and acid-perfusion

TABLE

ATYPICAL PRESENTATIONS OF GASTROESOPHAGEAL REFLUX DISEASE

Noncardiac chest pain

Pulmonary
- Asthma
- Bronchitis
- Aspiration pneumonitis
- Sleep apnea
- Atelectasis
- Pulmonary fibrosis

Ear, nose, and throat
- Hoarseness
- Cough
- Globus sensation
- Halitosis
- Vocal cord granuloma or ulcer
- Laryngeal stenosis
- Laryngeal cancer
- Loss of dental enamel

Chronic hiccups, belching

Reflux dyspareunia

(Bernstein) testing often give false-negative results.

Still, for the patient the important issue is whether the symptoms decrease with antireflux therapy, either medical or surgical. Therefore, many physicians may wish to forego esophageal pH testing in favor of an empirical trial of proton-pump inhibitor therapy.

NONCARDIAC CHEST PAIN

Approximately 20% to 30% of patients with chest pain who undergo cardiac catheterization have normal or insignificantly diseased coronary arteries. Although an esophageal motility disorder was once thought responsible for many of these cases, recent studies suggest that 25% to 50% of patients with noncardiac chest pain actually have GERD.[2,3] This is good news, as GERD is easily treated.

Diagnosing GERD-related chest pain

Clinical clues. I find that many patients with noncardiac chest pain have heartburn, acid regurgitation, or dysphagia. However, the history alone may not reliably distinguish anginal chest pain from reflux-induced symptoms. For example, exercise classically induces angina but also may exacerbate GERD.

Further, GERD and coronary artery disease commonly occur together, and both increase in prevalence with age. Therefore, the two may coexist and even interact. For example, acid reflux pain can increase the heart rate and blood pressure, thereby exceeding the ischemic threshold and producing angina and electrocardiographic changes. In such patients, cardiac medications (nitrates, calcium channel blockers) may actually make the GERD worse.

Problems with conventional tests. Barium studies, endoscopy, and esophageal manometry have little use in diagnosing acid-related chest pain. Although these studies may reveal esophagitis or diminished lower-esophageal sphincter pressure, these findings are only indirect evidence that acid reflux is the cause of the patient's complaints.

The acid perfusion (Bernstein) test is little used anymore. Although simple, it lacks sensitivity for detecting GERD as a cause of chest pain. In a study of 75 patients who also underwent 24-hour pH monitoring, the Bernstein test had a sensitivity of only 32%. However, its positive predictive value was excellent (95%). Therefore, if the Bernstein test is positive, further studies are not necessary, but a negative study does not rule out GERD.[4]

Esophageal pH monitoring

Esophageal pH monitoring should be the first study performed in patients with suspected acid-related chest pain.

This test uses a long, thin, transnasal catheter that contains a pH probe or probes, connected to a small, portable recorder that monitors esophageal pH for 24 hours (**FIGURE 1**). This study is typically done on an outpatient basis.

The key to accurate testing is for patients to go about their normal activities, with no restrictions on food, smoking, or alcohol use, in order to have a typical day with a number of chest pain episodes. In order to rule out cardiac causes of chest pain, some physicians perform an exercise treadmill test at the same time they perform the pH testing.

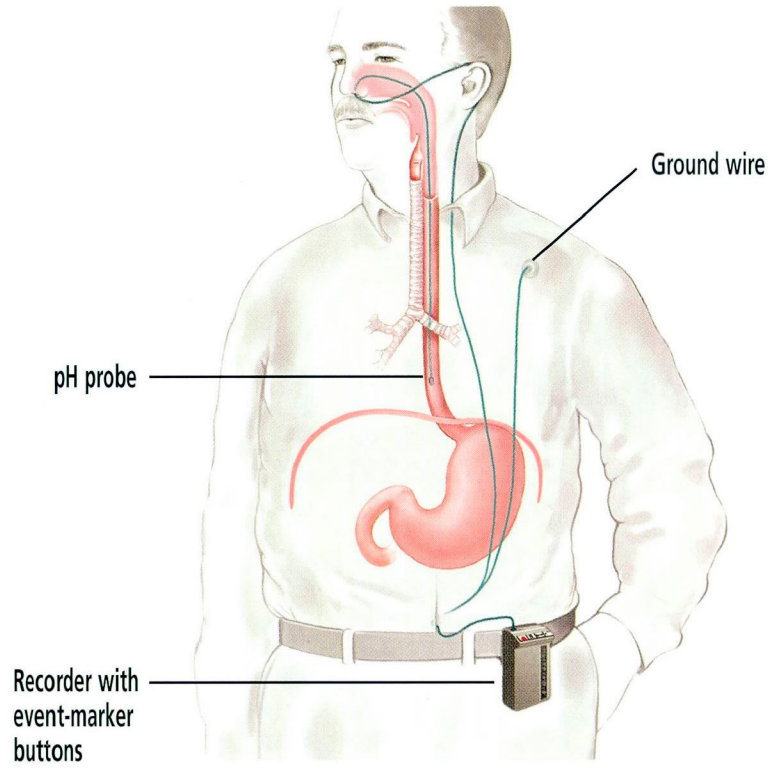
How to interpret esophageal pH results is open to some debate. One method is to calculate the percent of time the pH is less than 4.0 and judge the study abnormal if this percentage is higher than it is for 95% of normal subjects. This is approximately 5% of the total recording time, 1 or 2 percentage points less for the time the patient is supine, and 1 or 2 percentage points more for the time the patient is upright.

FIGURE 1

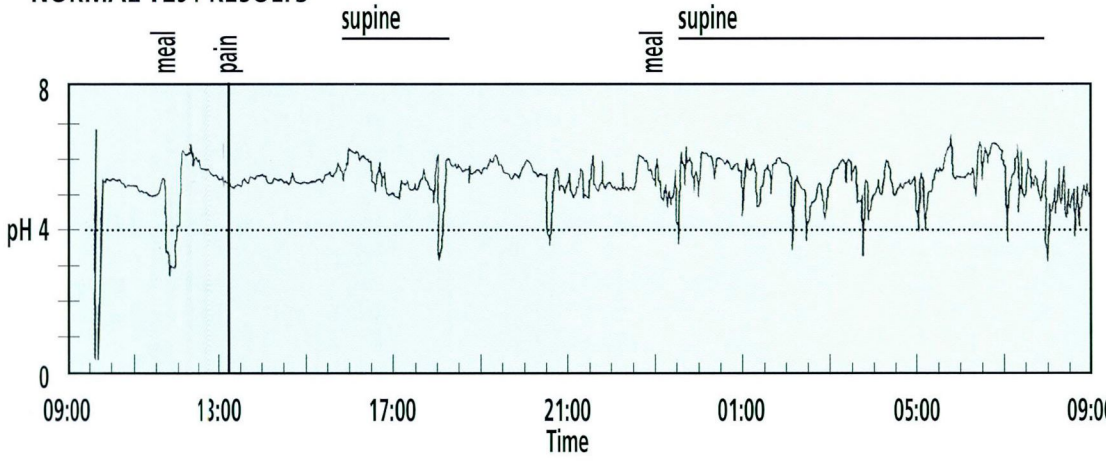
Ambulatory Esophageal pH Monitoring

A portable recorder creates a record of the pH over 24 hours; the patient marks episodes of chest pain or asthma by pressing a button on the recorder.

Below, normal and abnormal recordings. Abnormal reflux times (percent of time the pH is less than 4.0) and symptoms occuring while the pH is less than 4.0 implicate reflux as the cause of symptoms.

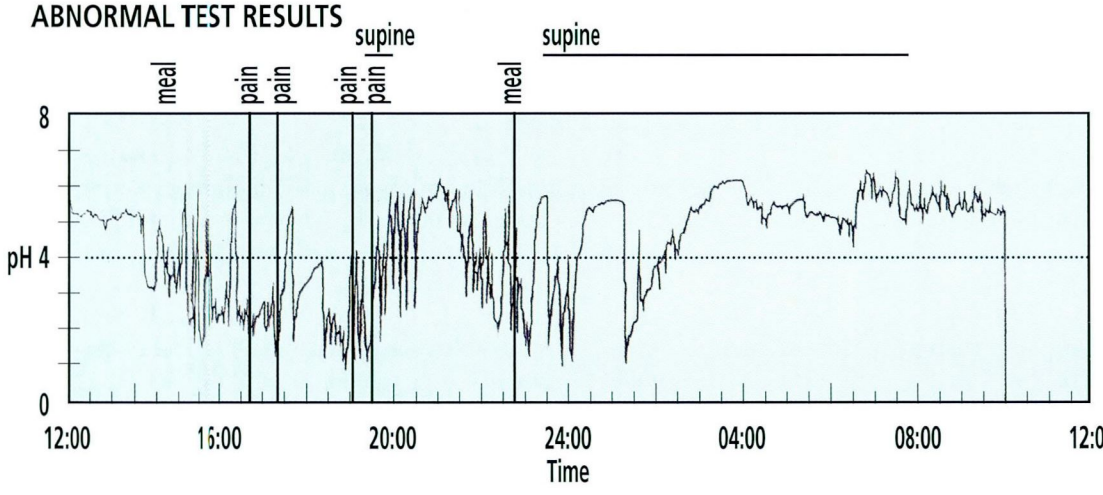


NORMAL TEST RESULTS



	Reflux time, %	
	Patient results	Normal limit
Total	1.5	<5.5
Upright	2.4	<8.5
Supine	0.2	<3.0

ABNORMAL TEST RESULTS



	Reflux time, %	
	Patient results	Normal limit
Total	24.0	<5.5
Upright	26.1	<8.5
Supine	21.5	<3.0

Another method is to calculate the percentage of episodes of chest pain (which the patient records by pushing a button on the pH monitor) that occur while the pH is less than 4.0. How high this percentage (called the "symptom index") must be to be abnormal is also open to question.

I consider *any* concurrent episodes of chest pain and acid reflux a "positive symptom index"—and suggestive of acid reflux as the cause of chest pain.

Studies of pH testing in noncardiac chest pain. In one study[5] in which I participated, half (50 out of 100) of all patients with noncardiac chest pain and normal coronary angiograms had a positive symptom index. (Seventeen patients had no chest pain during the test.) Twenty-four (48%) of the 50 patients with a positive symptom index had normal reflux times; conversely, 11 (30%) of 37 patients with abnormal reflux times had a normal symptom index. Therefore, either an abnormal reflux time or a positive symptom index should suggest that chest pain is GERD-related.

The history may not reliably distinguish angina from reflux-induced symptoms. For example, exercise induces angina but also may exacerbate GERD

We also tested 34 patients who had proven coronary artery disease but atypical chest pain not responding to antianginal therapy.[6] Twenty (59%) of these patients had a positive symptom index and underwent treatment with an H2 blocker in high doses or with a proton-pump inhibitor (omeprazole). After 8 weeks of therapy, two of these patients were asymptomatic, 11 had improved, five had no change in their symptoms, and two were lost to follow-up.

Treating GERD-related chest pain

Even if the history and pH monitoring suggest that acid reflux is the cause of chest pain, aggressive antireflux therapy is the only way to confirm the diagnosis.

In several uncontrolled series, high doses of H2 blockers or omeprazole relieved chest pain in 75% to 80% of patients with abnormal 24-hour pH studies. A recent, placebo-controlled study in 34 patients showed similar results: after 8 weeks of treatment with omeprazole 20 mg twice a day, 13 patients (81%) reported overall symptomatic improvement, vs one patient (6%) in the placebo group.[7]

■ PULMONARY DISEASES

Over the past two decades, physicians have increasingly recognized GERD as a cause of pulmonary diseases.[8] However, it was Sir William Osler in 1892 who first noted the association between worsening asthma and a distended stomach.

Most studies have focused on asthma, and patients with asthma have an increased prevalence of GERD (between 34% and 89%).[8,9] Other GERD-induced pulmonary diseases include aspiration pneumonia, interstitial pulmonary fibrosis, chronic bronchitis, bronchiectasis, and, possibly, cystic fibrosis, neonatal bronchopulmonary dysplasia, and the sudden infant death syndrome.[9,10]

How GERD can cause asthma

There are two theories on how GERD might cause asthma: a vagal reflex and microaspiration.

A vagal reflex. The esophagus and bronchial tree share embryonic foregut origins. Thus, acid in the esophagus could stimulate acid-sensitive receptors, initiating a vagal reflex through shared esophageal and bronchial autonomic nerves.[11] A recent study[12] suggests that intraesophageal acid perfusion causes bronchoconstriction in all persons, possibly as a protective mechanism. Peak expiratory flow rates return to normal after acid is cleared from the esophagus, but more slowly in patients with asthma than in normal subjects.

Microaspiration of gastric contents. In studies in animals, small amounts of acid in the airway (even in the trachea) predictably cause bronchospasm.[13] In addition, asthma medications (theophylline and beta$_2$ agonists) may exacerbate reflux by decreasing lower esophageal sphincter pressure, although this may not occur in all patients.[9]

Diagnosing GERD-related asthma

Clinical clues. The history is extremely

important in diagnosing GERD-related asthma. However, approximately 33% of asthmatic patients with esophageal dysfunction have no esophageal symptoms. Clinical clues include onset of asthma in adulthood; no family history of asthma; reflux symptoms preceding the onset of asthma; wheezing made worse by meals, exercise, or the supine position; nocturnal cough or wheezing; asthma made worse by theophylline or beta$_2$ agonists; and asthma requiring systemic steroid therapy.[8]

Barium studies are helpful if they show a hiatal hernia or reflux into the proximal esophagus. The prevalence of esophagitis varies considerably in patients with asthma and GERD. Sontag et al[14] found endoscopic evidence of esophagitis in 39% of older men with asthma. Middle-aged women with asthma may have a lower prevalence of esophagitis—about 25% in my experience.

Overnight gastroesophageal scintigraphy is more helpful in children than in adults. In this test, a radioactive tracer is placed in the stomach and scans are taken over the chest the next morning; uptake in the chest suggests microaspiration.

Esophageal pH monitoring is the best test for GERD-related asthma. More than 50% of adults with asthma (perhaps 70% to 80%) have abnormal amounts of acid reflux. However, most episodes of wheezing do not occur during episodes of acid reflux, suggesting that multiple factors incite asthma episodes in such patients.[8]

Treating GERD-related asthma

Initial studies with antacids and H2 blockers showed inconsistent effects on asthma symptoms and peak expiratory flow rates.[15–19] However, studies using proton-pump inhibitors were more encouraging.[20,21]

For example, we recently gave 30 consecutive patients with asthma and GERD increasing doses of omeprazole (20 to 60 mg daily) until 24-hour pH monitoring showed the acid reflux was under control, and then continued this therapy for 3 months. Overall, 73% of patients showed marked alleviation of asthma symptoms or increases in peak expiratory flow rate. Patients with frequent regurgitation or excessive proximal esophageal acid reflux were more likely to benefit from this therapy. However, at least one third of the patients required 40 mg or more of omeprazole per day.[21]

Surgical studies reinforce the importance of treating acid reflux aggressively. Of 110 patients with asthma and GERD who underwent antireflux surgery in five studies, 34% became free of asthma symptoms afterward, 42% were improved, and 24% were unchanged.[8] More important, many patients were able to discontinue their asthma medications and decrease or stop steroid therapy.

EAR, NOSE, AND THROAT SYMPTOMS AND DISEASE

There is increasing evidence that GERD commonly causes ear, nose, and throat (ENT) problems.[22]

Hoarseness is caused by GERD in an estimated 10% of all cases. Studies (particularly using 24-hour pH monitoring) in patients with unresponsive hoarseness found that 55% to 79% had acid reflux.

Chronic laryngitis and difficult-to-treat sore throat are associated with acid reflux in as many as 60% of patients. Acid reflux not only causes symptoms but produces erythema of the posterior vocal cords, vocal cord polyps, vocal cord granulomas, and, in patients with prior endotracheal intubation, subglottic stenosis.

Chronic cough. GERD is the third-leading cause of chronic cough (after sinus problems and asthma), accounting for 20% of cases.[23]

Globus sensation (a feeling of choking or a lump in the throat, more prominent between meals and generally disappearing at nighttime) may be caused by GERD in 25% to 50% of cases.

Laryngeal cancer. Most alarming, four separate cases series of 10 to 20 patients each reported an association between chronic GERD and laryngeal cancer in patients without the common risk factors of smoking or excessive alcohol intake.[24]

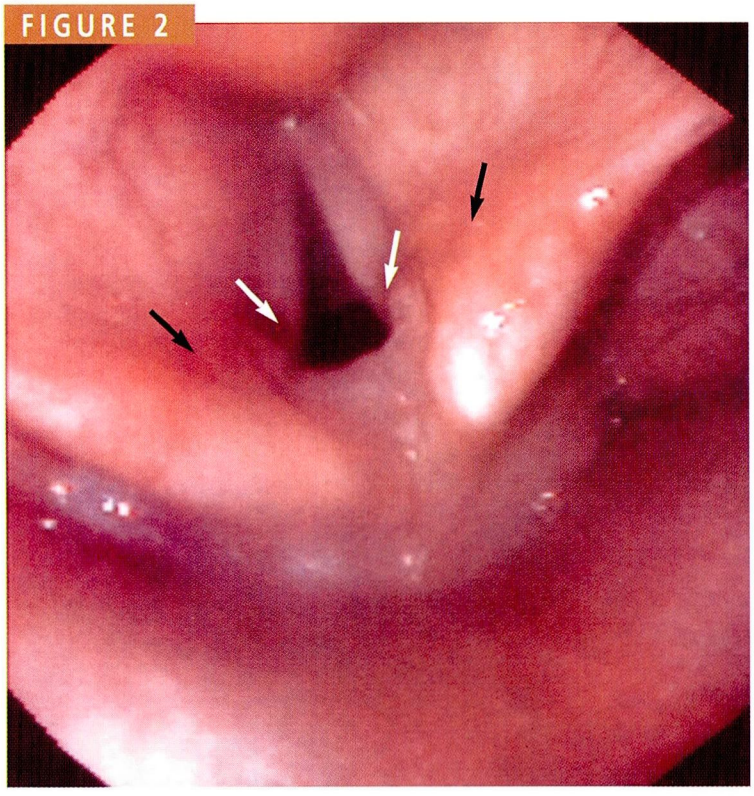
Dental erosions are particularly common in patients with bulimia; however, seven of 10 patients in our laboratory who had evidence of proximal reflux by pH testing had dental erosions.[25]

Aggressive antireflux therapy is the only way to confirm the diagnosis of acid reflux chest pain

How GERD can cause ENT symptoms

The most likely etiology for acid-related ENT symptoms is microaspiration. Studies in animals[22,26] and humans[27] found that intermittent acid reflux can damage the larynx, particularly in the presence of pepsin. The acid reflux most likely occurs at night, when upper esophageal sphincter pressure is low.[27]

FIGURE 2



Hypopharynx in a patient with chronic cough and hoarseness. Note the erythema of the cricoarytenoid folds (black arrows) and bilateral red streaks posteriorly on the true vocal cords (white arrows).

Abnormalities of motility in the proximal esophagus and dysfunction of the upper esophageal sphincter may also contribute.

Diagnosing GERD-related ENT problems

As many as 50% of patients with GERD-related ENT problems do not have classic reflux symptoms, often presenting to their physicians simply with a sore throat or cough.[22] Further, barium esophagraphy and esophageal manometry are not usually helpful in diagnosing GERD.

A thorough laryngeal examination should be the first study performed. This can be done either by an ENT specialist or by a gastroenterologist at the time of upper gastrointestinal endoscopy.[22]

The most common laryngeal abnormalities observed with GERD are erythema and edema of the cricoarytenoid folds and the posterior portion of the true vocal cords, which are the hypopharyngeal regions in closest proximity to the proximal esophagus (**FIGURE 2**). However, more than 50% of patients with throat symptoms due to acid reflux have normal ENT findings.

Twenty-four-hour esophageal pH monitoring with a dual pH probe (one low in the esophagus and another in the hypopharynx or just below the upper esophageal sphincter) is the most sensitive test for diagnosing GERD-related ENT problems.[22,28] Testing with a single, distal probe might miss some patients with GERD: Koufman[22] studied 182 patients with suspected GERD and upper aerodigestive tract symptoms and found that 62% had abnormal reflux during 24-hour pH monitoring. Of those with abnormal findings, 20% had normal distal studies but abnormal proximal studies (**FIGURE 3**).

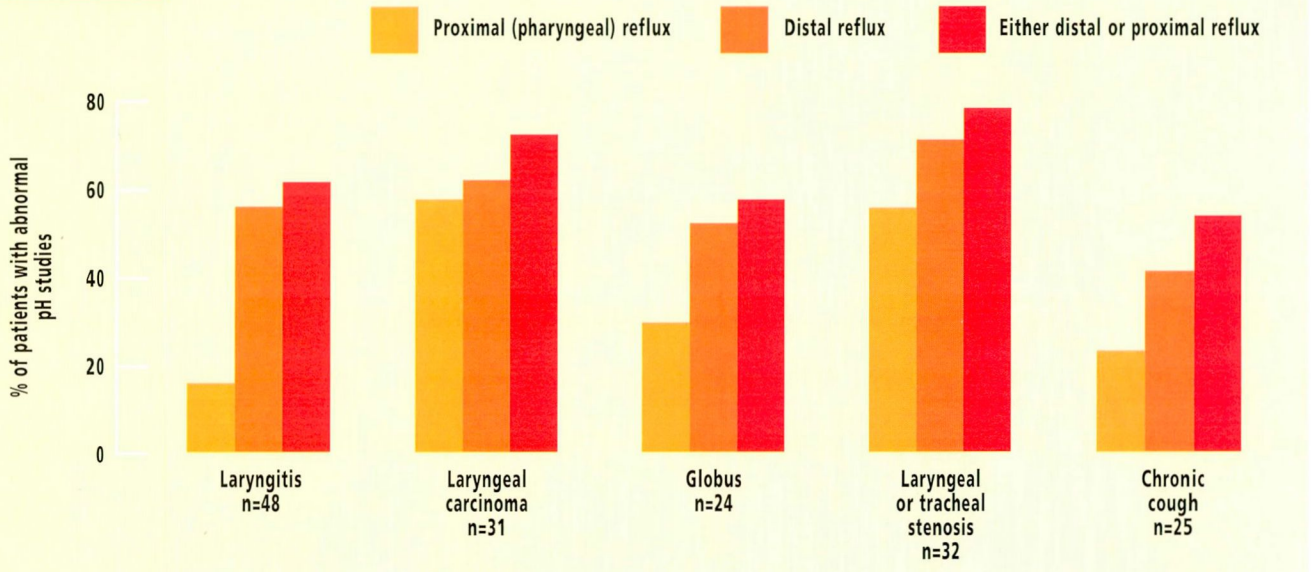
Treating GERD-related ENT problems

There is a striking absence of good studies of treatment in GERD-related ENT problems. Anecdotal studies suggest that GERD-related chronic cough and hoarseness abate over 3 to 6 months with treatment with antacids, H2 blockers, and metoclopramide. However, two recent studies with omeprazole suggest that patients with GERD-related ENT complaints need more potent acid suppression (ie, with a proton-pump inhibitor rather than an H2 blocker), continued longer.[29,30]

Kamal et al[29] treated 15 patients who had laryngeal symptoms and reflux laryngitis, giving them omeprazole 40 mg at bedtime for at least 6 months. Only three patients had esophagitis at entry. Two patients could not tolerate omeprazole and had their treatment changed to H2 blockers in high doses instead. Three other patients had their omeprazole dosage increased to 40 mg twice a day, after esophageal pH monitoring at 12 weeks demonstrated persistent proximal acid reflux. Laryngeal symptoms abated significantly, but more slowly than did esophageal symptoms. Reflux laryngitis took even longer to resolve.

Recently, we compared the effects of omeprazole 20 mg twice a day and placebo in a double-blind, randomized study in 39

FIGURE 3



Proximal and distal esophageal pH monitoring results in patients with suspected GERD and upper aerodigestive symptoms. Nearly 70% of these patients have abnormal reflux, but 20% of these may have a normal distal esophageal pH profile. Note the marked amount of proximal reflux in patients with laryngeal cancer and laryngeal or tracheal stenosis. Data from Koufman, reference 22.

patients. Treatment lasted 8 weeks. Overall, ENT symptoms decreased in 78% of the patients receiving omeprazole, vs 25% of patients taking placebo, and the difference was statistically significant. Similarly, abnormal findings on ENT examinations decreased or resolved in 60% of patients taking omeprazole, compared with none of the patients receiving placebo.[30]

A PRACTICAL APPROACH

My approach to suspected extraesophageal manifestations of GERD is to perform diagnostic tests, particularly ambulatory 24-hour pH monitoring, to determine if the patient actually has GERD. If these tests are positive, I would assess the importance of GERD to the extraesophageal symptoms with a trial of aggressive acid suppression.

However, an empirical trial of acid suppression might accomplish the same goals and be more practical and cost-effective. The algorithm (**FIGURE 4**), based on my clinical experience, incorporates both testing and empirical therapy. This approach balances the expense of high doses of proton-pump inhibitors (more than $600 for 3 months' therapy) vs the cost (approximately $400), availability, and discomfort of ambulatory esophageal pH monitoring.

If clinical clues strongly suggest GERD

If the clinical history strongly suggests GERD, an empirical trial with a proton-pump inhibitor is appropriate (eg, omeprazole 20 mg twice a day or lansoprazole 30 mg twice a day for at least 2 to 3 months). Most patients with GERD-related chest pain respond in 1 to 2 months, but patients with GERD-related asthma or ENT complaints usually need at least 3 months of aggressive antireflux therapy.

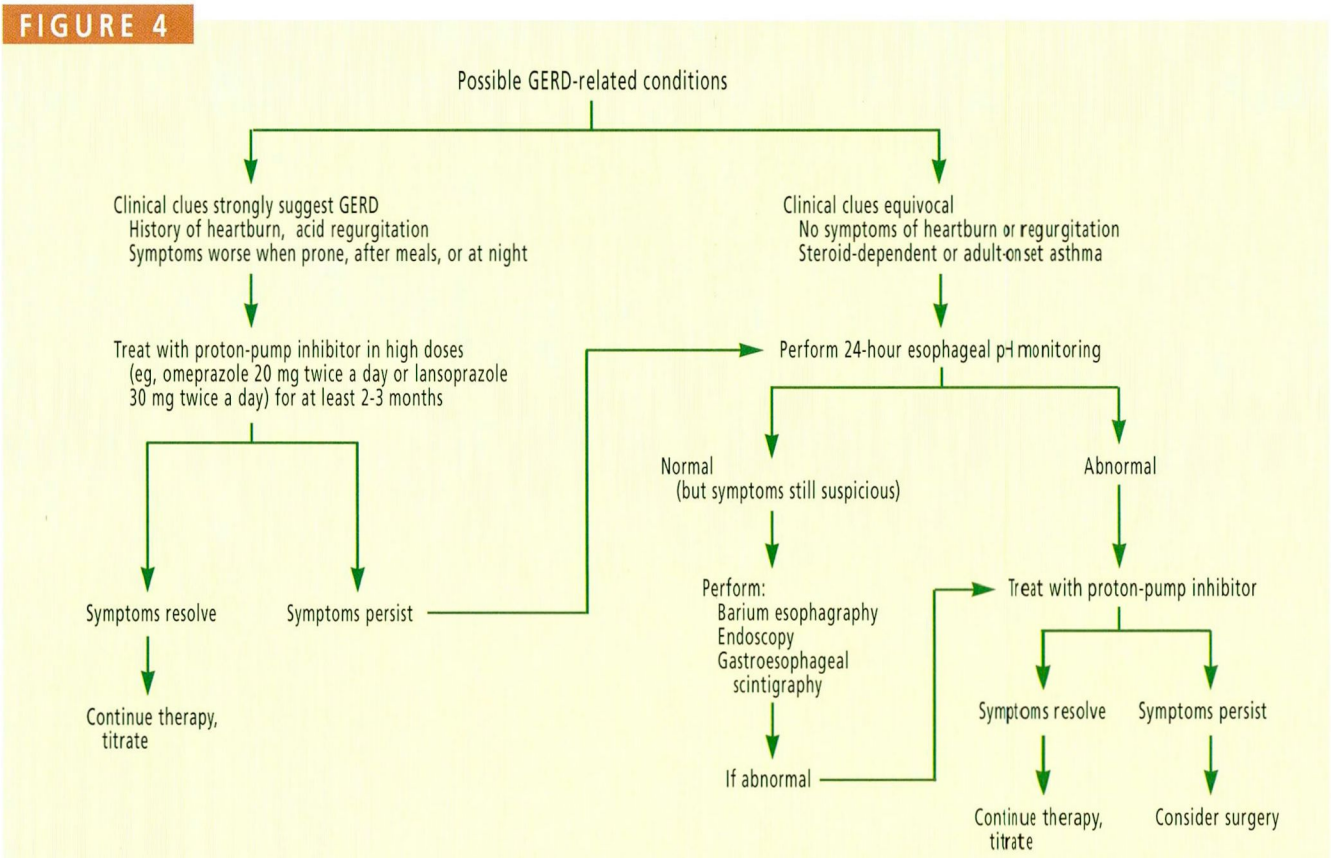
If the extraesophageal symptoms resolve during this therapy, the long-term treatment plan should include gradual titration downward of the acid-suppression therapy, possibly with the addition of a promotility drug, or antireflux surgery.

If the symptoms persist. Patients who have partial or no relief of extraesophageal symptoms after 3 months should undergo 24-hour pH monitoring while still taking the proton-pump inhibitor. In my experience, approximately 25% of such patients require more aggressive acid suppressive therapy, ie, higher doses of the proton-pump inhibitor. The rest (those with normal pH profiles) can be deemed partial responders or nonresponders, and other causes for their complaints investigated.

If clinical clues are equivocal

On the other hand, patients with only equivocal historic clues suggesting GERD may

FIGURE 4



A practical approach to diagnosing and managing possible GERD-related problems.

benefit from ambulatory 24-hour pH monitoring first to confirm the existence of excessive acid reflux. If this test is negative and the physician still suspects GERD, other studies (barium swallow, endoscopy, nuclear scintigraphy) may be required to diagnose the cause of the symptoms. ■

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