Extraesophageal symptoms of GERD

KENNETH R. DeVAULT, MD

■ **ABSTRACT**

Gastroesophageal reflux disease (GERD) can be the primary cause of, or an aggravating contributor to, a wide variety of conditions affecting extraesophageal structures. As a result, GERD can lead to a number of pulmonary symptoms and diseases, otolaryngologic findings and symptoms, and other extraesophageal manifestations, including dental erosions. Clinicians must be aware of the possibility of these extraesophageal reflux-related conditions, even in the absence of classic esophageal symptoms of GERD. While antireflux therapy is often helpful, response to treatment is less predictable than it is for typical GERD.

Gastroesophageal reflux disease (GERD) can result in the direct regurgitation and aspiration of acidic gastric contents and has been associated with extraesophageal symptoms. GERD can masquerade as a wide variety of conditions affecting extraesophageal structures **(Table 1)**,[1] leading to:

- **Pulmonary symptoms and diseases**, such as asthma, bronchitis, and pulmonary fibrosis
- **Otolaryngologic findings**, such as hoarseness, cough, laryngitis, subglottic stenosis, and laryngeal cancer
- **Other extraesophageal manifestations**, such as sinusitis, pharyngitis, and dental erosions.

For many of these conditions, GERD sometimes can be the primary or principal aggravating cause, although causality is often difficult to establish. Epidemiologically, GERD and many of its extra-

From the Division of Gastroenterology and Hepatology, Mayo Clinic, Jacksonville, Fla.

Address: Kenneth R. DeVault, MD, Director of Gastrointestinal Research, Division of Gastroenterology and Hepatology, Mayo Clinic, 4500 San Pablo Road, Jacksonville, FL 32224.

esophageal manifestations occur frequently and can even occur simultaneously, without a causal relationship. Moreover, the presence of gastric acid in extraesophageal structures has been difficult to document. Many patients with suspected extraesophageal problems do not have classic GERD symptoms, or such symptoms may present too subtly to be detected. For example, more than 50% of patients with reflux-related laryngeal disorders do not have heartburn, regurgitation, or dysphagia.[2]

Data from studies evaluating the role of GERD in extraesophageal manifestations have been somewhat controversial, given that many such studies are small and uncontrolled. In practice, however, positive results associated with antireflux treatment have drawn attention to the role of GERD in extraesophageal complications, making it difficult to ignore a potential association.[3] A number of differences have been described between extraesophageal manifestations and classic GERD manifestations with regard to symptoms, pathophysiology, evaluation, and treatment **(Table 2)**.[4] This review examines the prevalence, pathogenesis, and clinical presentations of extraesophageal manifestations of GERD, and briefly discusses how they are best evaluated and treated, including the role of antireflux therapy.

■ **PREVALENCE AND CLINICAL OVERVIEW**

Relationship to esophageal symptoms

Data demonstrating the high prevalence of GERD and its classic presentations (heartburn and acid regurgitation) have come from population-based surveys. Observational studies have also helped uncover the prevalence of extraesophageal manifestations of GERD in the general population and how they relate to classic GERD symptoms.

Extraesophageal symptoms of GERD are highly prevalent among patients with both frequent and infrequent typical GERD symptoms. In a population-based study in the Midwestern United States, a

TABLE 1
Extraesophageal manifestations of GERD

Pulmonary presentations	Otolaryngologic presentations
Asthma	Hoarseness
Aspiration pneumonia	Chronic cough
Interstitial pulmonary fibrosis	Throat clearing
Chronic bronchitis	Chronic laryngitis
Bronchiectasis	Globus sensation
Neonatal bronchopulmonary dysplasia	Vocal cord ulcers and granulomas
Sudden infant death syndrome	Laryngeal and tracheal stenosis
	Laryngeal cancer
	Mouth soreness
	Halitosis
	Pharyngitis
	Otalgia
	Chronic sinusitis
	Croup
	Stridor
	Dysphonia
	Abnormal taste
	Dental erosions

Adapted from reference 1 with permission from Elsevier.

TABLE 2
General comparisons between esophageal and extraesophageal manifestations of GERD

	Esophageal manifestations	Extraesophageal manifestations
Primary symptoms	Heartburn and regurgitation	Laryngeal and pulmonary
Pathophysiology	Antireflux barrier, acid clearance, esophageal mucosal resistance	Multifactorial; laryngeal and pulmonary factors
Esophagitis and Barrett's esophagus	Common	Uncommon
Ambulatory pH monitoring	Very sensitive and specific for GERD	Sensitivity is lower
Response to anti-reflux therapy	Excellent	Less predictable

Adapted from reference 4 with permission from Elsevier.

reliable and valid self-report questionnaire was mailed to an age- and sex-stratified random sample of 2,200 residents of Olmsted County, Minn., aged 25 to 74 years. The survey's purpose was to determine the prevalence and clinical spectrum of GERD in the community, including the frequency of atypical symptoms (noncardiac chest pain, dysphagia, globus, dyspepsia, asthma, bronchitis, history of pneumonia, and hoarseness) among respondents with frequent, infrequent, and no typical reflux symptoms.[5]

History of pneumonia and noncardiac chest pain (23.6% and 23.1%, respectively) had the highest overall prevalence, followed by hoarseness (14.8%), bronchitis (14.0%), dysphagia (13.5%), dyspepsia (10.6%), asthma (9.3%), and globus (7.0%). Globus and a history of pneumonia were more common among women than among men ($P < 0.05$).[5]

Among respondents with noncardiac chest pain,

40% had symptoms for greater than 5 years, and 5% reported severe or very severe symptoms. Symptom severity and frequency were positively associated ($P < 0.01$). Similarly, among respondents with dysphagia, 37% had dysphagia that had lasted more than 5 years, although a higher proportion of respondents (8.3% of those with any dysphagia, and 17.2% of those with frequent dysphagia) reported severe or very severe dysphagia.[5]

Except for asthma and pneumonia, the atypical symptoms were each significantly more common ($P < 0.001$) among respondents with heartburn or acid regurgitation **(Table 3)**.[5] At least one atypical symptom was present in 79.9% of respondents with frequent (at least weekly) typical reflux symptoms, compared with 48.6% of respondents without heartburn and acid regurgitation. In three logistic regression models, typical reflux symptoms were associated with noncardiac chest pain, dysphagia, globus, and dyspepsia. Frequent typical symptoms were associated with noncardiac chest pain, dysphagia, and dyspepsia.[5]

Other population-based data have helped to describe the relationship between GERD manifestations and extraesophageal symptoms. Using a national database to compare the comorbid occurrence of sinus, laryngeal, and pulmonary diseases in

TABLE 3

Frequency of atypical symptoms by frequency of GERD in Olmsted County (Minn.) residents aged 25 to 74 years

Symptom	Frequent* GERD (n = 303)	Infrequent GERD (n = 566)	No GERD (n = 642)	P value[†]
Noncardiac chest pain	37.0%	30.7%	7.9%	< 0.001
Dysphagia	29.4%	18.2%	4.0%	< 0.001
Globus sensation	14.2%	8.7%	2.3%	< 0.001
Dyspepsia	20.8%	12.9%	3.9%	< 0.001
Asthma	11.6%	8.8%	7.9%	Not signif.
Bronchitis	22.4%	15.0%	10.7%	< 0.001
Pneumonia	28.7%	24.7%	24.5%	Not signif.
Hoarseness	23.4%	15.4%	10.7%	< 0.001
Any atypical symptom	79.9%	70.3%	48.6%	< 0.001

* At least weekly.
[†] Based on the usual χ^2 test for a 2×3 contingency table.
Adapted from reference 5 with permission from the American Gastroenterological Association.

patients with and without reflux esophagitis, El-Serag and Sonnenberg[6] evaluated a case population of 101,366 patients with erosive esophagitis or stricture discharged from Department of Veterans Affairs hospitals from 1981 to 1994. They found that patients with reflux esophagitis were at higher risk, compared with hospitalized controls, of having a wide variety of pharyngeal, laryngeal, pulmonary, and sinus conditions **(Figure 1)**.[6] Specifically, erosive esophagitis and esophageal stricture were associated with an increased risk of sinusitis, pharyngitis, aphonia, laryngitis, laryngeal stenosis, chronic bronchitis, asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, bronchiectasis, pulmonary collapse, and pneumonia. Following a multivariate analysis, the strongest statistically significant associations were found with bronchial asthma and pulmonary fibrosis **(Table 4)**.[6]

The most common diagnosis in both the case and the control populations was pneumonia, followed by chronic bronchitis, chronic obstructive pulmonary disease, and bronchial asthma. Much less frequently diagnosed than pulmonary diseases were sinus, pharyngeal, and laryngeal disorders. In this study, as many as 17% of all patients with esophagitis developed an extraesophageal manifestation of the disease. Patients with esophagitis or stricture carried a 15% to 100% increased risk of having extraesophageal diagnoses compared with subjects without esophagitis or stricture.[6]

Endoscopy and esophageal pH monitoring have also been used in prospective studies linking GERD to extraesophageal symptoms. Using such methods, GERD has been diagnosed in as many as 75% of patients with chronic hoarseness,[2] in 78% of patients with laryngeal stenosis,[2] in 70% to 80% of patients with asthma,[7] and in 20% of patients with chronic cough.[8] Endoscopic esophagitis has been found in 30% to 40% of patients with asthma and in approximately 20% of those with laryngitis.[9,10]

Despite the high prevalence of esophagitis in these early studies, many investigators now believe esophagitis to be the clear exception in these patients. This could be due to our increased awareness of extraesophageal GERD, the wide availability of over-the-counter acid suppressants, or some combination of these factors.

Considerations in the elderly. Extraesophageal symptoms of GERD are frequently encountered in the elderly.[11] This is particularly troublesome, since a symptom such as chest pain must be given great respect, particularly in the elderly, and can result in costly and extensive evaluation. It is unclear whether extraesophageal symptoms are more common in the elderly than in younger persons. If so, this finding would not be surprising, since both extraesophageal symptoms and GERD seem to increase in prevalence with age.
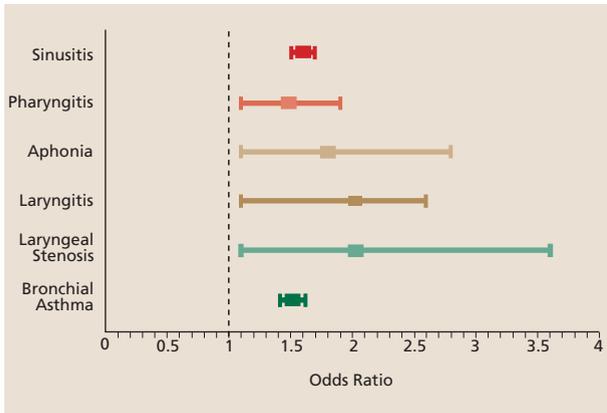
FIGURE 1. Risk of extraesophageal complications in hospitalized patients with erosive esophagitis or esophageal stricture compared with hospitalized controls. Each point represents an odds ratio, depicted with its 95% confidence interval, obtained from a multivariate logistic regression analysis. Reprinted from reference 6 with permission from the American Gastroenterological Association.

TABLE 4
Pulmonary disorders significantly associated with esophagitis or esophageal stricture*

Disorder	Odds ratio	95% CI	P value
Chronic bronchitis	1.28	1.22–1.34	0.0001
Bronchial asthma	1.51	1.43–1.59	0.0001
Chronic obstructive pulmonary disease	1.22	1.16–1.27	0.0001
Pulmonary fibrosis	1.36	1.25–1.48	0.0001
Bronchiectasis	1.26	1.09–1.47	0.0022
Pulmonary collapse	1.31	1.23–1.40	0.0001
Pneumonia	1.15	1.12–1.18	0.0001

* Following multivariate logistic regression analysis. Comparisons are between hospitalized patients with erosive esophagitis or esophageal stricture and hospitalized controls.

Adapted from reference 6 with permission from the American Gastroenterological Association.

Pathophysiology

Proposed mechanisms of extraesophageal symptoms. Two possible mechanisms have been proposed as underlying GERD-related extraesophageal symptoms:

- Microaspiration of gastric contents into extraesophageal structures during reflux episodes
- Stimulation by the gastric refluxate of a vagal reflex arc extending from the esophageal body to the bronchopulmonary and laryngeal systems.

Both mechanisms have been supported by clinical and laboratory data documenting the injurious effects of esophageal acid on extraesophageal structures. Studies using dual-probe esophageal pH monitoring seem to support the reflex arc theory, whereas ambulatory pH studies of patients with suspected extraesophageal complications have demonstrated acid reflux to the proximal esophagus and beyond.[3]

With regard to the first mechanism, physiologic protective mechanisms normally prevent refluxate from entering the pharyngeal and laryngeal space to cause symptoms and tissue damage. A disturbance in any known, or perhaps unknown, protective factor could possibly account for the production of extraesophageal symptoms.[12]

Regarding the second mechanism, embryologic studies show that the esophagus and bronchial tree share a common embryonic origin, having both developed from common tissue of the foregut.[1] It is therefore not surprising that they also share a common neural innervation via the vagus nerve.[1] Acidification of the distal esophagus can stimulate acid-sensitive receptors that could conceivably pro-

duce noncardiac chest pain or interact with pulmonary bronchi and other upper airway structures by a vagally mediated arc.[12]

Neither of these mechanisms is completely understood, nor is its clinical relevance appreciated in the absence of additional outcomes data and more sensitive methods for detecting the movement of gastric refluxate.[3]

Defense mechanisms against extraesophageal symptoms. Defense mechanisms protecting against extraesophageal complications of GERD have been organized into a four-tier system **(Table 5)**.[3] Within this system, each defense mechanism occurs in ascending order from the distal esophagus to the supraesophageal region.

Junctional structures at the gastroesophageal interface (tier 1) include the lower esophageal sphincter (LES), the crural diaphragm, the sling fibers, and the phrenoesophageal ligament. The LES and the crural diaphragm are discussed in the previous article in this supplement. The sling fibers of the stomach, arranged in a C-shaped fashion with the open side toward the lesser curvature, serve as a "flap valve" to augment LES pressure. The phrenoesophageal ligament helps to anchor the crural fibers to the LES segment.[3]

The esophageal body motor response (tier 2) includes primary and secondary peristalsis and esophageal body tone. The esophageal body clears

TABLE 5

Protective barriers against GERD-induced extraesophageal symptoms

TIER 1
Gastrointestinal junctional structures
- Lower esophageal sphincter
- Crural diaphragm
- Sling fibers
- Phrenoesophageal ligament

TIER 2
Esophageal body motor response
- Primary/secondary peristalsis
- Esophageal body tone
- Acid neutralization by swallowed saliva

TIER 3
Upper esophageal sphincter (UES)

TIER 4
Airway protective reflexes
- Esophago-UES contractile reflex
- Esophagoglottal and pharyngoglottal closure reflexes
- Pharyngeal (second) swallow

Adapted from reference 3 with permission from Elsevier.

90% of gastric refluxate by one or two peristaltic sequences and neutralizes any remaining acid by swallowed saliva. Impaired esophageal peristalsis has a negative impact on volume clearance and on the delivery of saliva to the distal esophagus.[3]

The upper esophageal sphincter (UES) (tier 3) is a circular band of muscle that comprises a high-pressure zone separating the pharynx from the cervical esophagus. Intact LES and UES barriers usually prevent gastroesophageal reflux into the upper airway.[12] While the LES is susceptible to regurgitation of gastric contents in both physiologic and pathophysiologic states, the UES, because of its high basal pressure, usually prevents laryngeal or pharyngeal contact with the gastric refluxate. In addition, UES pressure is augmented when distal reflux results in increased intraesophageal pressure.

Within the supraesophageal region, several reflex mechanisms (tier 4) appear to be a part of an integrated network aimed at preventing aspiration of gastric refluxate.[3] Two reflex actions at the trachea protect the airway during belching and regurgitation. Further protection of the pharynx and airway is provided by the presence of the esophagoglottal closure reflex (occurring with abrupt distention of the esophagus), which also protects the airway from contact with proximal refluxate.[3]

Swallowing also helps to clear refluxate that does not breach the UES.[12] The pharyngeal swallow (Figure 2), triggered by stimulation of the pharynx by fluid, clears the pharyngeal space while also inducing partial closure of the glottis. In addition to these potential pharyngoglottal mechanisms, intrinsic laryngeal reflex mechanisms play an important role in limiting the spread of aspirate and enhancing clearance. Such mechanisms would include the cough reflex and mucociliary action of the bronchotracheal surface.[3]

■ **BRONCHOPULMONARY SYMPTOMS**

In recent decades, GERD has become increasingly recognized as a potential cause of bronchopulmonary symptoms. While most studies have focused on asthma, many other pulmonary disorders have been linked to GERD, including aspiration pneumonia, interstitial pulmonary fibrosis, chronic bronchitis, and bronchiectasis. Pulmonary symptoms related to GERD include shortness of breath, wheezing, and chronic cough.[4] For many patients, pulmonary disorders may be the only indication that GERD is present.[1]

Clinical presentations
Bronchial asthma. The relationship between GERD and asthma is an important one, given the high prevalence of asthma in the United States (estimated at 26 million)[13] and studies showing high rates of GERD among patients with asthma. The prevalence of GERD among asthma patients is estimated to be between 34% and 89%.[14] Estimates vary depending on the group of patients studied and how acid reflux is defined (eg, by symptoms or by 24-hour esophageal pH monitoring).

Clinical presentation. Many patients with asthma report GERD symptoms, including heartburn, regurgitation, and dysphagia. Furthermore, respiratory symptoms related to reflux symptoms have been reported, as has the need for antireflux medication.[15] Alternatively, some patients may have clinically silent GERD, especially in the context of difficult-to-treat asthma.[8]

A high degree of esophageal dysfunction has also been reported among patients with asthma, including esophageal dysmotility, LES hypotension, and a positive Bernstein test.[16] Specific esophageal motility abnormalities in asthma patients include ineffective esophageal motility, with a reported prevalence of 53.3%; nutcracker esophagus, with a prevalence of 7.6%; and low LES pressure, with a prevalence of 15.4%.[17] Endoscopy might also reveal esophagitis or
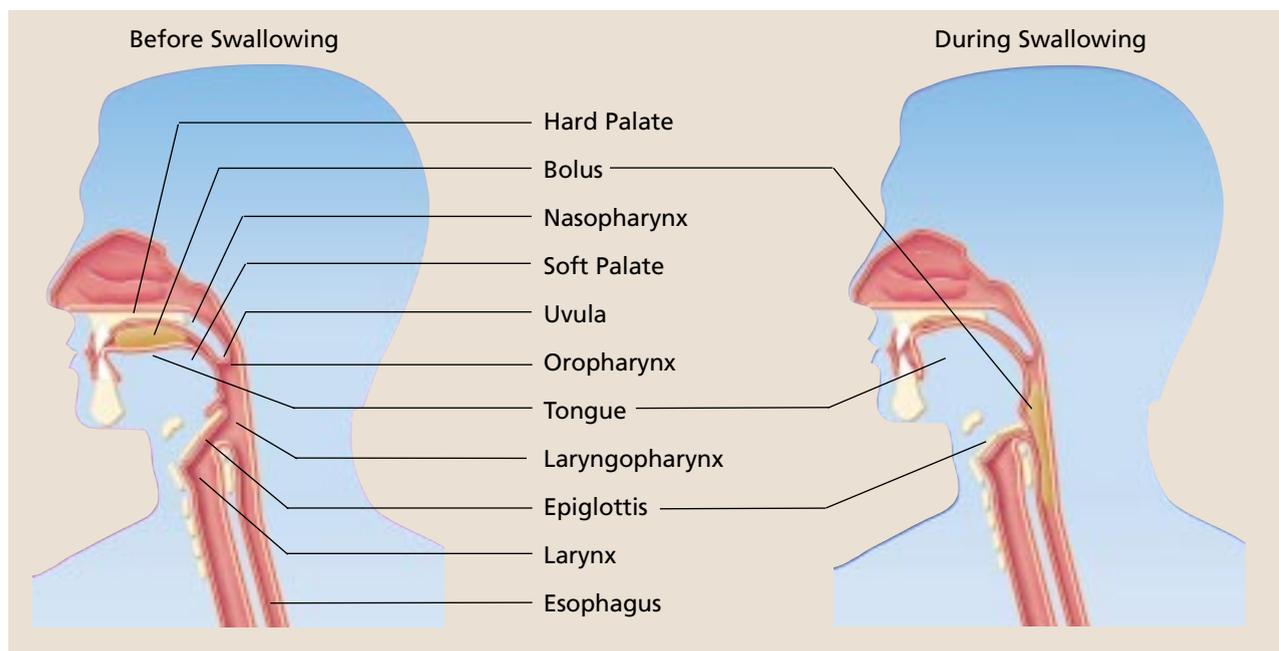
FIGURE 2. Position of esophageal, laryngeal, and pharyngeal structures before and during swallowing.

Barrett's esophagus among patients with asthma, although most will not have esophagitis.[7]

Compared with normal controls, patients with asthma have a higher frequency of reflux symptoms, more frequent LES hypotension by manometry, and increased esophageal acid contact times by 24-hour pH monitoring, which further supports the association between GERD and asthma.[18]

Pathogenesis. Bronchospasm is the hallmark of asthma and occurs as a result of several different irritating stimuli to the bronchial airways. Acid reflux may be the only trigger, or it may be one of many contributing factors.[1] Two possible pathophysiologic mechanisms, referred to earlier in relation to all extraesophageal manifestations, have been proposed for GERD-induced asthma. While neither of these mechanisms is completely understood, both appear to be involved in the relationship between GERD and asthma, and their relative effect varies among patients.[1] Both mechanisms might be active in some patients.[18] Furthermore, both involve the vagus nerve and are blunted by vagotomy.

According to the *reflex* theory, stimulation of acid-sensitive receptors by esophageal acid activates a vagal response from the esophagus to the lung, which causes bronchoconstriction. Bronchoconstriction may, in fact, occur in all individuals as a normal protective mechanism in response to intraesophageal acid perfusion.[19] Peak expiratory flow rates apparently return to normal after acid is cleared from the esophagus, although they do so more slowly among patients with asthma.

The *reflux* theory describes the microaspiration of gastric contents into the bronchial tree, which causes direct irritation of the respiratory epithelium and stimulates inflammatory mediators.[1] It is well known that mechanical stimulation of the upper airway or trachea can cause airway resistance.[18] Bronchoconstriction in response to esophageal acidification has been demonstrated in both animal studies[20] and human studies.[21] In animals, acid instilled into the trachea predictably increased airway resistance three to four times.[20]

More recently, investigators found an abrupt decrease in tracheal pH coinciding with bronchoconstriction during episodes of gastroesophageal reflux in patients with asthma and typical GERD symptoms **(Figure 3)**.[22] Further support for the reflux mechanism comes from a recent treatment study showing that proximal acid reflux was a predictor for improvement of asthma symptoms following aggressive acid suppression.[23] A GERD-asthma cycle has been proposed, through which bronchospasm promotes acid reflux, which promotes further bronchospasm. Asthma may also promote GERD as a result of changes in esophageal physiology induced by asthma medications.[1] A large Veterans Administration-based study found, how-
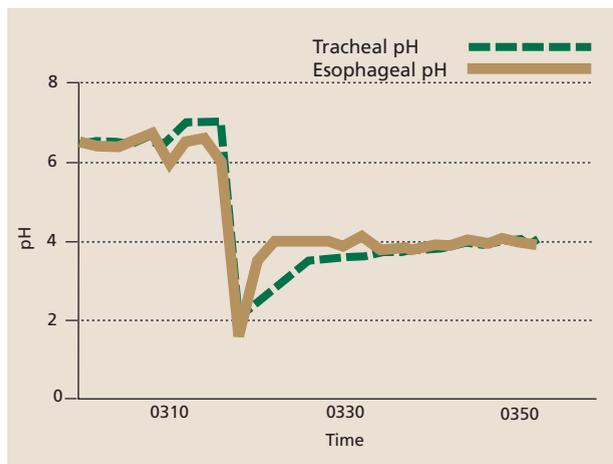
FIGURE 3. Segment from the preoperative tracheal pH (broken line) and esophageal pH (solid line) in a patient with asthma and GERD. Reprinted from reference 22 with permission from the Society of Thoracic Surgeons.

ever, that the GERD-asthma association is independent of bronchodilator use.[7]

Diagnosis. The patient's history is an extremely important part of the diagnosis of GERD-associated asthma, despite the fact that approximately one third of patients with asthma and esophageal dysfunction do not have esophageal symptoms. Certain clinical clues can be helpful in identifying GERD-related asthma, as can selected tests **(Table 6)**.[1] Pulmonary symptoms suggesting reflux include nocturnal cough, as well as worsening of asthma symptoms after eating a large meal, drinking alcohol, or being in the supine position. GERD should be considered in asthmatics who initially present in adulthood, in those without an intrinsic component, and in those not responding to bronchodilator or steroid therapy. An additional clue may be the development of reflux symptoms before the onset of asthma, or heartburn heralding an asthma attack.[1]

Esophageal tests that may be helpful in diagnosis include the barium esophagram, gastroesophageal scintigraphy, and prolonged esophageal pH monitoring. The latter test, considered the gold standard for GERD diagnosis, is the only esophageal test that can directly correlate acid reflux episodes with wheezing or other symptoms of bronchospasm. Nevertheless, confirming an esophageal cause for pulmonary symptoms using this test might still prove difficult.[1] Gastroesophageal scintigraphy has a high specificity, but it also has a low sensitivity, which limits its usefulness in adults.[1]

Irwin and colleagues[8] found that they could usu-

TABLE 6

Clinical clues and tests used in the diagnosis of GERD-associated asthma[1]

Clinical clues
Adult onset of asthma
No family history of asthma
Reflux symptoms preceding asthma onset
Wheezing worsened by meals, exercise, or supine position
Nocturnal cough or wheezing
Asthma worsened by theophylline or beta$_2$-agonists
Asthma requiring prolonged systemic steroid therapy

Esophageal pH monitoring
Best test for GERD-related asthma; > 50% of adults with asthma have abnormal acid reflux
Most episodes of wheezing do not occur during reflux episodes, suggesting that multiple factors are involved

Barium studies
Helpful if they show hiatal hernia or reflux into proximal esophagus
Considerable variation in prevalence of esophagitis

Overnight gastroesophageal scintigraphy
More helpful in children than in adults
Uptake in chest (from stomach) suggests microaspiration

ally determine the cause of difficult-to-control asthma by using a systematic management protocol. While multiple factors were usually involved, the single most common contributory factor proved to be GERD. Moreover, approximately two thirds of affected patients responded favorably to antireflux therapy. The researchers concluded that all difficult-to-control asthma patients should be evaluated for GERD, even if GERD symptoms are minimal or absent.[8]

Treatment. With regard to medical therapy, studies using proton pump inhibitors (PPIs) have had more encouraging results than those using antacids or histamine$_2$-receptor antagonists. The latter have yielded inconsistent effects on asthma symptoms and peak expiratory flow rates. A recent study[23] using omeprazole to treat patients with asthma and GERD over 3 months showed that 73% of patients experienced marked alleviation of asthma symptoms or increases in peak expiratory flow rate. Treatment reduced asthma symptoms by 57% after 3 months **(Figure 4)**. The patients most likely to benefit from the therapy were those with frequent

regurgitation or excessive proximal esophageal acid reflux. At least one third of patients needed 40 mg or more of omeprazole daily.

In a meta-analysis of placebo-controlled studies to evaluate the effects of antireflux therapy on asthma control in patients with GERD, Field and Sutherland[24] found that antireflux therapy improves symptoms and probably reduces the need for asthma medication. Symptoms improved in 69% of patients, and medication use was reduced in 62%. However, lung function was not demonstrably improved in the majority of patients. Only 26% showed improvement in peak expiratory flow, whereas no patient showed improvement on spirometry. The researchers concluded that it was not yet possible to determine which asthma patients will benefit from antireflux therapy.

Surgery is another treatment option, and one that may enable patients to discontinue their asthma medications and decrease or discontinue steroid therapy.[1] In a combined analysis of 10 trials, 80% of patients experienced asthma improvement, more than 50% of whom required no further asthma therapy.[18] Factors identified as predictive of a positive outcome after antireflux surgery included onset of GERD symptoms before respiratory symptoms, asthma improvement on medical therapy, and normal baseline esophageal motility studies.[25,26]

Field and colleagues[27] conducted a meta-analysis of 24 studies (spanning 30 years) examining the effects of antireflux surgery on asthma. Like antireflux medical therapy, antireflux surgery improved asthma symptoms and reduced medication requirements, but it did not improve pulmonary function. GERD symptoms were improved in 90% of patients, asthma symptoms in 79% of patients, and asthma medication use in 88% of patients. Only 27% of patients demonstrated improvement in pulmonary function.

An algorithm can offer practical guidance on the diagnosis and management of possible extraesophageal manifestations of GERD, including asthma. The algorithm presented in **Figure 5**[28] takes into account the usefulness of both diagnostic testing, such as 24-hour ambulatory pH monitoring, and empiric therapy. If the patient's clinical history strongly suggests GERD, empiric PPI therapy is appropriate. If symptoms persist, 24-hour pH monitoring (while the patient continues PPI therapy) is the next step. Patients with an equivocal clinical history for GERD should also undergo 24-hour pH

FIGURE 4. Reductions in asthma symptoms following treatment with omeprazole.[23]

monitoring. If the results of the test are negative, additional diagnostic tests may be required.

Idiopathic pulmonary fibrosis. Repeated episodes of gastric aspiration may provoke interstitial fibrosis. Restrictive lung disease resulting from interstitial fibrosis has been shown in animal studies to result from chronic acid reflux. In a prevalence study of GERD among subjects with definitive or presumptive pulmonary fibrosis, both hiatal hernia and GERD were found to occur more frequently among those with pulmonary fibrosis compared with controls.[29] Important data among elderly subjects have shown a restrictive ventilatory defect among individuals with GERD, in addition to low vital capacity and forced expiratory flow rates.[30,31] GERD has also been found to contribute to pulmonary fibrosis among patients with scleroderma, who often have severe GERD related to LES hypotension and esophageal body dysfunction.[32]

Chronic bronchitis. Patients with chronic bronchitis have been shown in some studies to have a markedly increased prevalence of GERD. In a study of patients with chronic bronchitis and a history of tobacco use, 57% were found to have abnormal amounts of acid reflux.[33]

Aspiration pneumonia. Recurrent aspiration pneumonia is another pulmonary manifestation of GERD. While an association between pneumonia and GERD has been demonstrated by several studies, the actual incidence of aspiration pneumonia due to GERD is unknown. In a small pediatric study, Euler and colleagues[34] reported a history of recurrent pneumonia in 95% of children with pulmonary disease and GERD. The pneumonias reported in this study were slow to resolve, involved multiple lobes in most patients, and were persistent in four children with only right middle lobe involvement. A high prevalence of bronchitis or
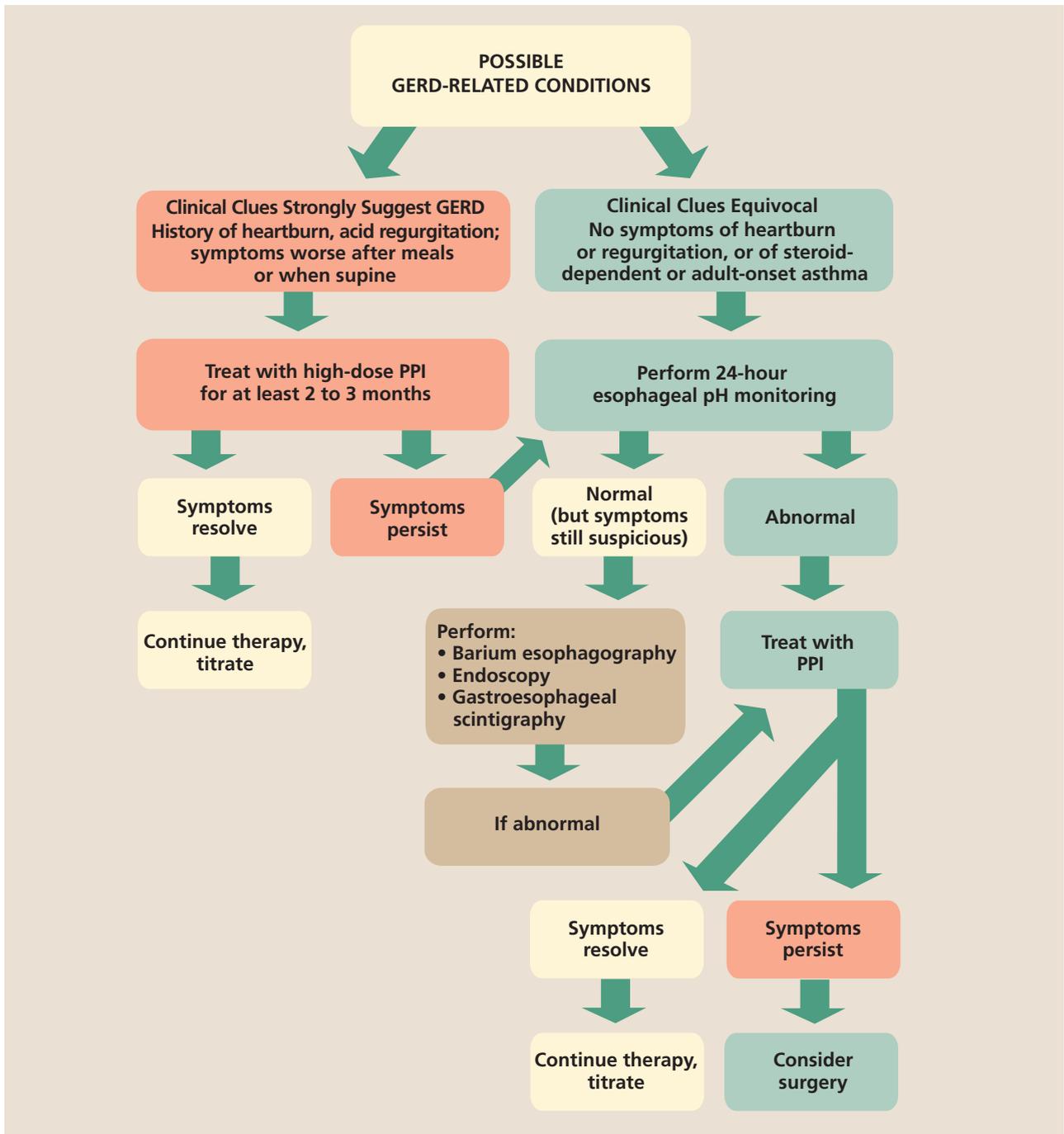
FIGURE 5. Approach to diagnosing and managing GERD-related extraesophageal symptoms, including asthma. Reprinted from reference 28 with permission.

pneumonia has also been found among patients with GERD and interstitial pulmonary fibrosis.[35]

Recurrent lung injury and pneumonia following GERD can result from direct contact with caustic gastric contents or aspiration of bacteria from the upper digestive tract. Dual-probe pH monitoring with the proximal probe positioned in the hypopharynx has indicated that patients with recurrent pneumonia have a higher incidence of reflux. Patients with pulmonary aspiration secondary to

GERD might also suffer from an esophageal motor dysfunction affecting all three barriers to aspiration, namely, the LES, the esophageal pump mechanism, and the UES.[36]

■ LARYNGOPHARYNGEAL SYMPTOMS

GERD has been identified as a primary etiologic factor in 10% to 20% of cases of persistent cough, in up to 80% of patients with difficult-to-manage hoarseness, in 25% to 50% of patients with globus sensation, and in a small but definite group of patients with laryngeal cancer.[37,38] The relationship between GERD and these disorders is thought to be so great by some otolaryngologists that they believe GERD may be the major cause of most inflammatory processes in this anatomic region.[1] As many as 50% of patients with GERD-related symptoms, however, do not have classic reflux symptoms, and they primarily present with a cough or sore throat.[2]

The neuroanatomic proximity of the larynx to the proximal esophagus makes it particularly vulnerable to GERD.[39] The most common laryngeal abnormalities noted with GERD are erythema and edema of the cricoarytenoid folds and the posterior portion of the true vocal cords, which are the hypopharyngeal regions closest to the proximal esophagus.[40]

More than 50% of patients with throat symptoms due to acid reflux, however, have normal otolaryngologic findings. The most sensitive test for diagnosing GERD-related otolaryngologic problems is 24-hour esophageal pH monitoring with a dual pH probe **(Figure 6)**.[2,28]

Pathophysiology

Two main pathophysiologic mechanisms are believed to underlie the production of acid-related otolaryngologic symptoms. The first involves a vagally mediated reflex, in which the stimulus is acid in the lower esophagus and the response is chronic repetitive throat clearing and coughing, leading to laryngeal symptoms and lesions. This mechanism for hoarseness and other throat symptoms is difficult to prove given limited evidence.[38] A number of human and animal studies, however, do suggest an important role for direct acid injury to the vocal cord apparatus. These studies also suggest that pepsin rather than acid is the primary injurious agent, given that gastric contents having a pH of 4 were able to markedly damage the laryngeal mucosa.[2]
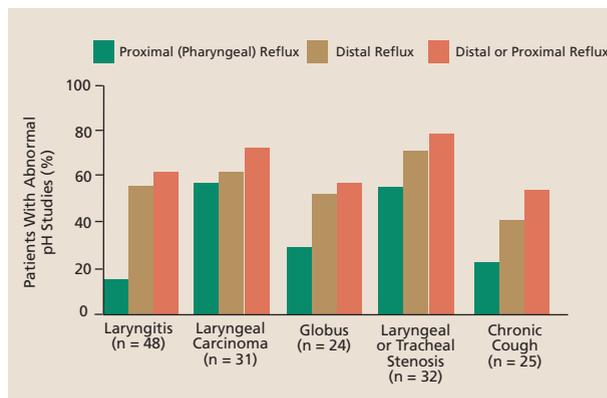

FIGURE 6. Results of proximal and distal esophageal pH monitoring among patients with suspected GERD and extraesophageal symptoms. Reprinted from reference 28 with permission.

The pathophysiology of GERD-related laryngopharyngeal manifestations has been further explained by motility and pH studies. Intermittent esophagopharyngeal reflux, occurring primarily at night when UES pressures are low, appears to be the most likely mechanism by which GERD causes otolaryngologic manifestations.[1] Esophageal dysmotility with poor acid clearance may be another contributing factor. Various researchers have reported a high incidence of esophageal dysfunction and esophageal motility disorders with a high incidence of delayed acid clearance among patients with otolaryngologic symptoms.[28,41]

Clinical presentations

The most commonly associated clinical presentations include hoarseness, chronic cough, throat clearing, globus, chronic laryngitis, and vocal cord granulomas. Reflux laryngitis may be the most prevalent laryngeal symptom.[42] Less commonly seen in association with GERD are laryngeal and tracheal stenosis, laryngeal carcinoma, soreness in the mouth, halitosis, sore throat, otalgia, chronic sinusitis, croup, stridor, dysphonia, and abnormal taste or loss of taste.[1] (Symptoms affecting the oral cavity are discussed separately below.) Often, the medical history alone does not suggest the presence of GERD among persons with laryngopharyngeal symptoms, although a prevalence of 48% has been reported for classic reflux symptoms among patients with otolaryngologic manifestations.[2]

Hoarseness. Hoarseness caused by GERD occurs in approximately 10% of all cases. Studies using 24-hour pH monitoring have been especially helpful in evaluating patients with unresponsive hoarseness,
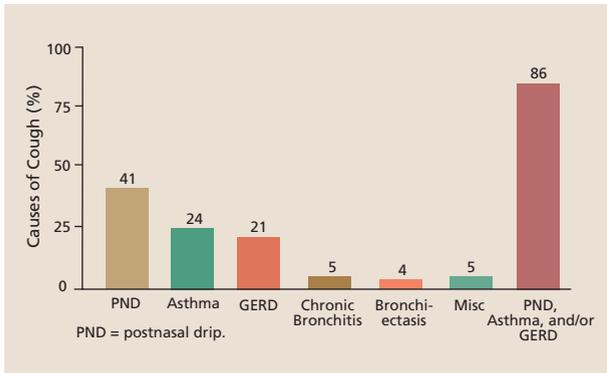
FIGURE 7. The frequency and spectrum of 131 causes of chronic cough persisting for more than 3 months. Reprinted from reference 14 with permission from the American College of Chest Physicians.

FIGURE 8. Mild posterior reflux laryngitis as viewed during upper endoscopy. Epithelial hypertrophy is apparent from the irregular appearance of the interarytenoid space between the vocal cords. In addition, the posterior portion of the vocal cords nearest the esophageal opening appears edematous. Reprinted from reference 1 with permission from Elsevier.

among whom acid reflux was found in 55% to 79% of cases.[40]

Chronic cough. Chronic cough is distinguished from transient acute cough by an arbitrary duration of greater than 3 weeks. Based on an algorithm developed by Irwin and colleagues[43] to determine the cause of chronic cough, GERD was the third-leading cause of chronic cough (after sinus conditions and asthma), accounting for 21% of cases **(Figure 7)**.[14]

Globus sensation. Globus sensation may be associated with GERD in 25% to 50% of cases.[40] Described as an almost constant perception of a lump in the throat, regardless of swallowing, it is more prominent between meals and generally disappears at nighttime. Increased UES pressure might be the cause, but this is unconfirmed.

Chronic laryngitis and sore throat. As many as 60% of cases of chronic laryngitis and sore throat have been associated with acid reflux, which causes symptoms as well as erythema of the posterior vocal cords, contact ulceration, vocal cord polyps, granuloma formation, and subglottic stenosis among patients who have had prior endotracheal intubation.[40]

The most common laryngeal abnormalities seen with GERD-related disease include edema and erythema of the posterior third of the vocal cords, as well as edema, erythema, and epithelial hypertrophy of the posterior glottis **(Figure 8)**.[1] Paradoxically, overt esophagitis is absent among most affected patients. Taking into account the available data, Wong and colleagues[42] have devised a suggested algorithm for the diagnosis of suspected reflux laryngitis **(Figure 9)**. The first step is to rule out other

causes of hoarseness. If hoarseness is present for more than 4 weeks, an otolaryngologic consultation is appropriate.

In a study using dual-probe ambulatory pH monitoring, proximal esophageal acid exposure was found to be significantly increased among subjects with persistent laryngeal symptoms (dysphonia, cough, globus sensation, frequent throat clearing, or sore throat).[44] Nocturnal proximal esophageal acidification might play a particularly important role. It was present in over half of affected patients but in none of the control patients.

Recovery from chronic laryngitis has been reported in patients receiving antireflux therapy in a graduated approach to treatment.[45,46] The "step-up" approach to GERD, however, has been supplanted by an emphasis on initial PPI therapy in most centers. Wong and colleagues[42] evaluated nine methodologically diverse studies using antireflux medications to treat reflux laryngitis. They found that overall symptom improvement rates among the studies ranged from 50% to 90%.[42] Based on the available data, Wong and colleagues have recommended empiric PPI therapy for 2 to 3 months, as shown in the algorithm in **Figure 9**.[42]

Laryngeal cancer. An association between chronic GERD and laryngeal cancer has been reported in four separate case series among patients without the typical risk factors of cigarette smoking or excessive alcohol intake.[47]

■ ORAL CAVITY SYMPTOMS

The effects of GERD on the mouth and salivary glands can result in water brash, which is the spon-

taneous appearance of high volumes of saliva in the mouth, caused by a vagally mediated reflux initiated by esophageal acid. Other effects include gingivitis and dental erosions, both of which are caused by direct contact of gums and teeth with acidic refluxate. Additional clinical presentations involving the oral cavity can include mouth ulcers, otitis/otalgia, and chronic sinusitis.

In a study examining the prevalence of gastroesophagopharyngeal acid reflux among patients with chronic sinusitis, the prevalence of pharyngeal reflux of gastric acid was significantly higher among adults with chronic sinusitis unresponsive to conventional therapy compared with controls.[48]

A number of studies have evaluated the relationship between GERD episodes and the loss of tooth structure due to dental erosion. As seen in a cross-sectional study evaluating loss of tooth structure as measured by the Tooth Wear Index (TWI), adults diagnosed with GERD had significantly higher TWI scores compared with controls ($P = 0.004$).[49] These findings are consistent with those of many studies indicating that dental erosion is the predominant oral lesion associated with GERD. Clinicians should recognize that these lesions usually progress slowly over many years and are not detected by the patient, physician, or dentist until significant damage has occurred to the teeth and overall masticatory system. Preventive measures include control of GERD, as well as referral to a dentist for prompt diagnosis and treatment of oral lesions.[50]

■ CONCLUSIONS

The relationship between GERD and extraesophageal symptoms can be elusive, and classic esophageal symptoms are often absent. A high index of suspicion is necessary to make a diagnosis. Clinicians need to be aware of the possibility of reflux-related conditions. Acid reflux should be considered if signs of GERD are present, if extraesophageal symptoms are unexplained, or if these symptoms are refractory to treatment. While antireflux therapy is often helpful, response to treatment is less predictable than it is for typical GERD. Awareness of the relationship between GERD and related pulmonary and otolaryngologic symptoms is a crucial first step in resolving troubling and usually chronic symptoms.
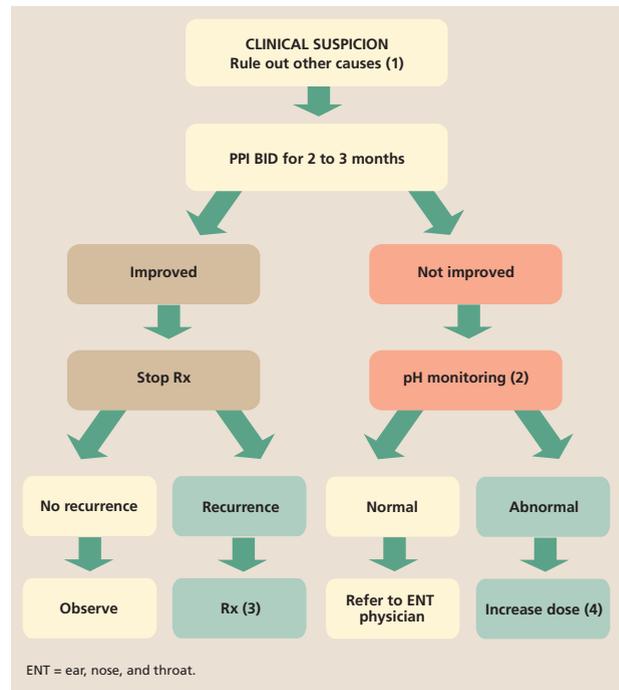

FIGURE 9. Algorithm for the evaluation and treatment of hoarseness. (1) ENT evaluation should be done early in the illness. (2) Consider stopping therapy if there is low suspicion of reflux, or consider continuing therapy if there is high suspicion of reflux; use gastric probe to document acid supression; use pharyngeal probe. (3) Resume treatment, but try to decrease to the lowest dose necessary; consider surgery if long-term treatment is needed. (4) If daytime reflux, increase PPI; if nighttime reflux, add a histamine₂-receptor antagonist; for medical treatment failure, cautiously consider surgery. Reprinted from reference 42 with permission from the American College of Gastroenterology.

■ REFERENCES

1. **Richter JE.** Extraesophageal presentations of gastroesophageal reflux disease. Semin Gastrointest Dis 1997; 8:75–89.
2. **Koufman JA.** The otolaryngologic manifestations of gastroesophageal reflux disease (GERD). A clinical investigation of 225 patients using ambulatory 24-hour monitoring and an experimental investigation of the role of acid and pepsin in the development of laryngeal injury. Laryngoscope 1991; 101:1–78.
3. **Hogan WJ, Shaker R.** Supraesophageal complications of gastroesophageal reflux. Dis Mon 2000; 46:195–232.
4. **Al-Sabbagh G, Wo JM.** Supraesophageal manifestations of gastroesophageal reflux disease. Semin Gastrointest Dis 1999; 10:113–119.
5. **Locke GR III, Talley NJ, Fett SL, Zinsmeister AR, Melton LJ III.** Prevalence and clinical spectrum of gastro-esophageal reflux: a population-based study in Olmsted County, Minnesota. Gastroenterology 1997; 112:1448–1456.
6. **El-Serag HB, Sonnenberg A.** Comorbid occurrence of laryngeal or pulmonary disease with esophagitis in United States military veterans. Gastroenterology 1997; 113:755–760.
7. **Sontag SJ, O'Connell S, Khandelwal S, et al.** Most asthmatics have gastroesophageal reflux with or without bronchodilator therapy. Gastroenterology 1990; 99:613–620.
8. **Irwin RS, Curley FJ, French CL.** Difficult to control asthma. Contributing factors and outcome of a systematic management protocol. Chest 1993; 103:1662–1669.

9. **Larrain A, Carrasco E, Galleguillos F, et al.** Medical and surgical treatment of nonallergic asthma associated with gastroesophageal reflux. Chest 1991; 99:1330–1335.

10. **Sontag SJ, Schnell TG, Miller TQ, et al.** Prevalence of esophagitis in asthmatics. Gut 1992; 33:872–876.

11. **Richter JE.** Gastroesophageal reflux disease in the older patient: presentation, treatment, and complications. Am J Gastroenterol 2000; 95:368–373.

12. **Fennerty MB.** Extraesophageal gastroesophageal reflux disease: presentations and approach to treatment. Gastroenterol Clin 1999; 28:861–873.

13. **American Lung Association.** Prevalence based on revised National Health Interview Survey. Available at: www.lungusa.org/data/data_102000.html. Accessed January 16, 2003.

14. **Harding SM, Richter JE.** The role of gastroesophageal reflux in chronic cough and asthma. Chest 1997; 111:1389–1402.

15. **Field SK, Underwood M, Brant R, et al.** Prevalence of gastroesophageal reflux symptoms in asthma. Chest 1996; 109:316–322.

16. **Kjellen G, Brundin A, Tibbling L, et al.** Oesophageal function in asthmatics. Eur J Respir Dis 1981; 62:87–94.

17. **Fouad YM, Katz PO, Hatlebakk JG, Castell DO.** Ineffective esophageal motility: the most common motility abnormality in patients with GERD-associated respiratory symptoms. Am J Gastroenterol 1999; 94:1464–1467.

18. **Richter JE.** Gastroesophageal reflux disease and asthma: the two are directly related. Am J Med 2000; 108(suppl 4a):153S–158S.

19. **Schan CA, Harding SM, Haile JM, et al.** Gastroesophageal reflux-induced bronchoconstriction: an intra-esophageal acid infusion study using state of the art technology. Chest 1994; 106:731–737.

20. **Tuchman DN, Boyle JT, Pack AI, et al.** Comparison of airway responses following tracheal or esophageal acidification in the cat. Gastroenterology 1984; 87:872–881.

21. **Mansfield LE, Stein MR.** Gastroesophageal reflux and asthma: a possible reflex mechanism. Ann Allergy 1978; 41:224–226.

22. **Donnelly RJ, Berrisford RG, Jack CI, et al.** Simultaneous tracheal and esophageal pH monitoring: investigating reflux-associated asthma. Ann Thorac Surg 1993; 56:1029–1034.

23. **Harding SM, Richter JE, Guzzo MR, et al.** Asthma and gastroesophageal reflux: acid suppressive therapy improves asthma outcome. Am J Med 1996; 100:395–405.

24. **Field SK, Sutherland LR.** Does medical antireflux therapy improve asthma in asthmatics with gastroesophageal reflux? Chest 1998; 114:275–283.

25. **Perrin-Fayolle M, Gormond F, Braillon G, et al.** Long-term results of surgical treatment for gastroesophageal reflux in asthmatic patients. Chest 1989; 96:40–45.

26. **DeMeester TR, Bonavina K, Iascone C, et al.** Chronic respiratory symptoms and occult gastroesophageal reflux: a prospective clinical study and results of surgical therapy. Ann Surg 1990; 211:337–345.

27. **Field SK, Gelfand GA, McFadden SD.** The effects of antireflux surgery on asthmatics with gastroesophageal reflux. Chest 1999; 116:766–774.

28. **Richter JE.** Extraesophageal presentations of gastroesophageal reflux disease: the case for aggressive diagnosis and treatment. Cleve Clin J Med 1997; 64:37–45.

29. **Mays EE, Dubois JJ, Hamilton GB.** Pulmonary fibrosis associated with tracheobronchial aspiration. Chest 1976; 69:512–515.

30. **Raiha IH, Ivaska K, Sourander B.** Pulmonary function in gastro-oesophageal reflux disease of elderly people. Age Aging 1992; 21:368–373.

31. **Raiha I, Manner R, Hietanen E, et al.** Radiographic pulmonary changes of gastro-oesophageal reflux disease in elderly patients. Age Aging 1992; 21:250–255.

32. **Johnson DA, Drane WE, Curran J, et al.** Pulmonary disease in progressive systemic sclerosis. Arch Intern Med 1989; 149:589–593.

33. **Ducolone A, Vandevenne A, Jouin H, et al.** Gastroesophageal reflux in patients with asthma and chronic bronchitis. Am Rev Respir Dis 1987; 135:327–332.

34. **Euler AR, Byrne WJ, Ament ME, et al.** Recurrent pulmonary disease in children: a complication of gastroesophageal reflux. Pediatrics 1979; 63:47–51.

35. **Tardif C, Nouveu TA, Denis P, et al.** Surgical treatment of gastroesophageal reflux in ten patients with severe asthma. Respiration 1989; 56:110–115.

36. **Patti MG, Debas HT, Pellegrini CA.** Esophageal manometry and 24-hour pH monitoring in the diagnosis of pulmonary aspiration secondary to gastroesophageal reflux. Am J Surg 1992; 163:401–406.

37. **Gaynor EB.** Otolaryngologic manifestations of gastroesophageal reflux. Am J Gastroenterol 1991; 86:801–805.

38. **Champion GL, Richter JE.** Atypical presentations of gastroesophageal reflux disease: chest pain, pulmonary, and ear, nose, throat manifestations. Gastroenterologist 1993; 1:18–33.

39. **Toohill RJ, Kuhn JC.** Role of refluxed acid in pathogenesis of laryngeal disorders. Am J Med 1997; 103(5A):100S–106S.

40. **Ohman L, Olofsson J, Tibbling L, et al.** Esophageal dysfunction in patients with contact ulcer of the larynx. Ann Otol Rhinol Laryngol 1983; 92:228–230.

41. **Ossakow SJ, Etta G, Cotturi T, et al.** Esophageal reflux and dysmotility as the basis of persistent cervical symptoms. Ann Otol Rhinol Laryngol 1987; 96:387–392.

42. **Wong RKH, Hanson DG, Waring PJ, Shaw G.** ENT manifestations of gastroesophageal reflux. Am J Gastroenterol 2000; 95(8 suppl):S15–S22.

43. **Irwin RS, Corrao WM, Pratter MR.** Chronic persistent cough in the adult: the spectrum and frequency of causes and successful outcome of specific therapy. Am Rev Respir Dis 1981; 123:413–417.

44. **Jacob P, Kahrilas PJ, Herzon G.** Proximal esophageal pH-metry in patients with "reflux laryngitis." Gastroenterology 1991; 100:305–310.

45. **Kamel PL, Hanson D, Kahrilas PJ.** Prospective trial of omeprazole in the treatment of posterior laryngitis. Am J Med 1994; 96:321–326.

46. **Hanson DG, Kamel PL, Kahrilas PJ.** Outcomes of anti-reflux therapy in the treatment of chronic laryngitis. Ann Otol Rhinol Laryngol 1995; 104:550–555.

47. **Ward PH, Hanson DG.** Reflux as an etiologic factor of carcinoma of the laryngopharynx. Laryngoscope 1988; 98:1195–1199.

48. **Ulualp SO, Toohill RJ, Hoffman R, Shaker R.** Possible relationship of gastroesophagopharyngeal acid reflux with pathogenesis of chronic sinusitis. Am J Rhinol 1999; 13:197–202.

49. **Gregory-Head BL, Curtis DA, Kim L, Cello J.** Evaluation of dental erosion in patients with gastroesophageal reflux disease. J Prosthet Dent 2000; 83:675–680.

50. **Lazarchik DA, Filler SJ.** Dental erosion: predominant oral lesion in gastroesophageal reflux disease. Am J Gastroenterol 2000; 95(8 suppl):S33–S38.