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HEALING HORIZONS  
IN ACID REFLUX DISEASE:  
THE MANIFESTATIONS AND  
MEDICAL MANAGEMENT OF GERD

SUPPLEMENT EDITOR AND CME ACTIVITY DIRECTOR:  
JOEL E. RICHTER, MD  
THE CLEVELAND CLINIC

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## HEALING HORIZONS IN ACID REFLUX DISEASE: THE MANIFESTATIONS AND MEDICAL MANAGEMENT OF GERD

SUPPLEMENT EDITOR AND CME ACTIVITY DIRECTOR:  
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### Contents and Faculty

- |  |                   |  |                   |
|--|-------------------|--|-------------------|
| <p><b>GERD pathogenesis, pathophysiology, and clinical manifestations</b></p> <p>PETER J. KAHRILAS, MD<br/>Chief, Division of Gastroenterology and Hepatology, and Gilbert H. Marquardt Professor of Medicine, Northwestern University Medical School, Chicago, Ill.</p> | <p><b>S4</b></p>  | <p><b>The continuum of GERD complications</b></p> <p>M. BRIAN FENNERTY, MD<br/>Professor of Medicine and Section Chief, Gastroenterology, Oregon Health and Science University, Portland, Ore.</p> | <p><b>S33</b></p> |
| <p><b>Extraesophageal symptoms of GERD</b></p> <p>KENNETH R. DEVAULT, MD<br/>Associate Professor of Medicine, Mayo School of Medicine, and Director of Gastrointestinal Research, Mayo Clinic, Jacksonville, Fla.</p>  | <p><b>S20</b></p> | <p><b>Profile and assessment of GERD pharmacotherapy</b></p> <p>PAUL N. MATON, MD<br/>Digestive Diseases Research Institute, Oklahoma City, Okla.</p>  | <p><b>S51</b></p> |

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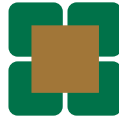
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# GERD pathogenesis, pathophysiology, and clinical manifestations

PETER J. KAHRILAS, MD

## ■ ABSTRACT

Gastroesophageal reflux disease (GERD) is a specific clinical entity defined by the occurrence of gastroesophageal reflux through the lower esophageal sphincter (LES) into the esophagus or oropharynx to cause symptoms, injury to esophageal tissue, or both. The pathophysiology of GERD is complex and not completely understood. An abnormal LES pressure and increased reflux during transient LES relaxations are believed to be key etiologic factors. Prolonged exposure of the esophagus to acid is another. Heartburn and acid regurgitation are the most common symptoms of GERD, although pathologic reflux can result in a wide variety of clinical presentations. GERD is typically chronic, and while it is generally nonprogressive, some cases are associated with development of complications of increasing severity and significance.

**G**astroesophageal reflux disease (GERD), as generally defined, is a common condition that results from the reflux of gastric material through the lower esophageal sphincter (LES) into the esophagus or oropharynx, causing symptoms and/or injury to esophageal tissue.<sup>1</sup> The term encompasses both symptoms and pathophysiologic changes to the esophageal mucosa, which occur as a result of exposure of the distal esophagus to acidic gastric contents after episodes of gastroesophageal reflux.

While most people experience some degree of normal gastroesophageal reflux (ie, retrograde movement of gastric acid contents through the LES into

the esophagus) about once every hour, such episodes are not generally associated with pathologic signs or symptoms. Heartburn may occur, especially after a meal. In most cases, however, such episodes of benign “physiologic” reflux are asymptomatic and characterized by rapid clearance from the distal esophagus.<sup>2</sup>

Pathologic gastroesophageal reflux results in a wide range of symptoms and esophageal pathologic changes characteristic of GERD. Pathologic reflux episodes are more frequent and of longer duration, and they can occur during the day and/or at night. Typically, they lead to chronic symptoms, inflammation, or esophageal mucosal damage.<sup>3</sup> GERD, therefore, is a clinical condition in which the symptoms of gastroesophageal reflux or its effects on esophageal tissue are severe enough to disrupt a patient’s life or cause injury to esophageal tissue.

## ■ CLINICAL OVERVIEW OF GERD

The pathogenesis of GERD is multifactorial. Pathologic reflux is thought to occur when the injurious properties of refluxed gastric acid, bile, pepsin, and duodenal contents overwhelm normal esophageal protective antireflux barriers, such as esophageal acid clearance and mucosal resistance. The primary underlying mechanism causing pathologic reflux appears to be a defective LES, which increases the volume of acidic gastric contents that refluxes into the esophagus. This increase in acid volume tips the balance toward pathologic reflux by overwhelming the normal capacity of the esophageal mucosa to tolerate acid.<sup>4</sup>

A minority of patients with GERD (20%) have, as their primary underlying motility disorder, LES incompetence due to either decreased LES pressure (LESP), increased intra-abdominal pressure (as seen with obesity or pregnancy), or a shorter than normal (< 2 to 5 cm) LES.<sup>3</sup> Many patients with GERD, however, have normal LESP. In this group of patients, frequent transient LES relaxation (TLESR) is often

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found as the underlying cause of pathologic reflux.<sup>5</sup> Although the understanding of TLESRs remains incomplete, one of the main triggers is believed to be gastric distention caused by postprandial fullness or intragastric air. Although TLESRs are not more frequent in GERD, a higher proportion of them are accompanied by acid reflux.

While heartburn and acid regurgitation are the most commonly reported symptoms of GERD, they are not the only associated symptoms. Pathologic acid reflux can result in a wide spectrum of GERD clinical presentations, including dysphagia/odynophagia and noncardiac chest pain. Important extraesophageal symptoms include laryngitis, pharyngitis, chronic sinusitis, dental erosions, asthma, and chronic cough. Laryngeal or pulmonary symptoms, such as laryngitis, hoarseness, noncardiac chest pain, or asthma, can occur as a result of gastric acid reflux into the throat and vocal cords or down into the lungs. Pharyngitis can occur as a result of gastric acid reflux into the back of the throat, causing inflammation. Acid reflux due to GERD can also erode teeth.

While GERD is usually nonprogressive, in a minority of cases disease progression is associated with the development of complications. The range of GERD complications includes esophagitis, bleeding, esophageal erosions and ulcerations, stricture formation, Barrett's esophagus, and adenocarcinoma of the esophagus. Reflux-induced injury to esophageal tissue can result in tissue destruction and the development of esophageal erosions or ulcerations. Esophageal scarring, involving fibrous tissue deposition as a protective response to ulceration, can lead to the development of esophageal stricture. Replacement of ulcerated squamous epithelium by a metaplastic intestinal-type epithelium characterizes the development of Barrett's esophagus.

Barrett's esophagus, a serious complication of reflux esophagitis in severe, long-standing GERD, has been linked to a significant increase in the risk of esophageal adenocarcinoma.<sup>6</sup> In fact, symptomatic reflux has been identified as a strong risk factor for esophageal adenocarcinoma. In a population-based case-control study, a high percentage of esophageal adenocarcinoma cases were attributable to symptomatic reflux.<sup>7</sup> The complications of GERD are discussed in detail in the third article in this supplement.

GERD may also be a temporary condition associated with a specific triggering factor (eg, pregnancy), disappearing once that factor is removed. More typ-

ically, however, GERD is a chronic condition requiring continued management using medications (see the final article in this supplement) and lifestyle modifications. Selected patients with severe disease may benefit from surgery to prevent relapse.

A number of factors have been identified that suggest early recurrence: a hypotensive LES, long-standing symptoms, the need for long-term treatment to achieve initial symptom relief and healing, esophagitis having a high initial endoscopic grade, hiatal hernia, and the presence of persistent symptoms despite endoscopically documented esophagitis healing.<sup>8</sup> Pharmacotherapy, particularly the use of antisecretory agents, has probably modified the natural history of GERD. Proton pump inhibitor (PPI) use, in particular, has had an enormous impact on treatment, in providing significantly improved erosive esophagitis healing rates and better symptom control.<sup>9</sup>

Without maintenance therapy, most patients with erosive GERD, especially those with the greatest disease severity, will experience relapse within 3 months. Prompt recurrence has also been seen among a majority of patients receiving histamine<sub>2</sub>-receptor antagonists (H<sub>2</sub>RAs) for maintenance of esophagitis healing. Among patients with more mild esophagitis, relapse rates of 50% to 90% have been reported.

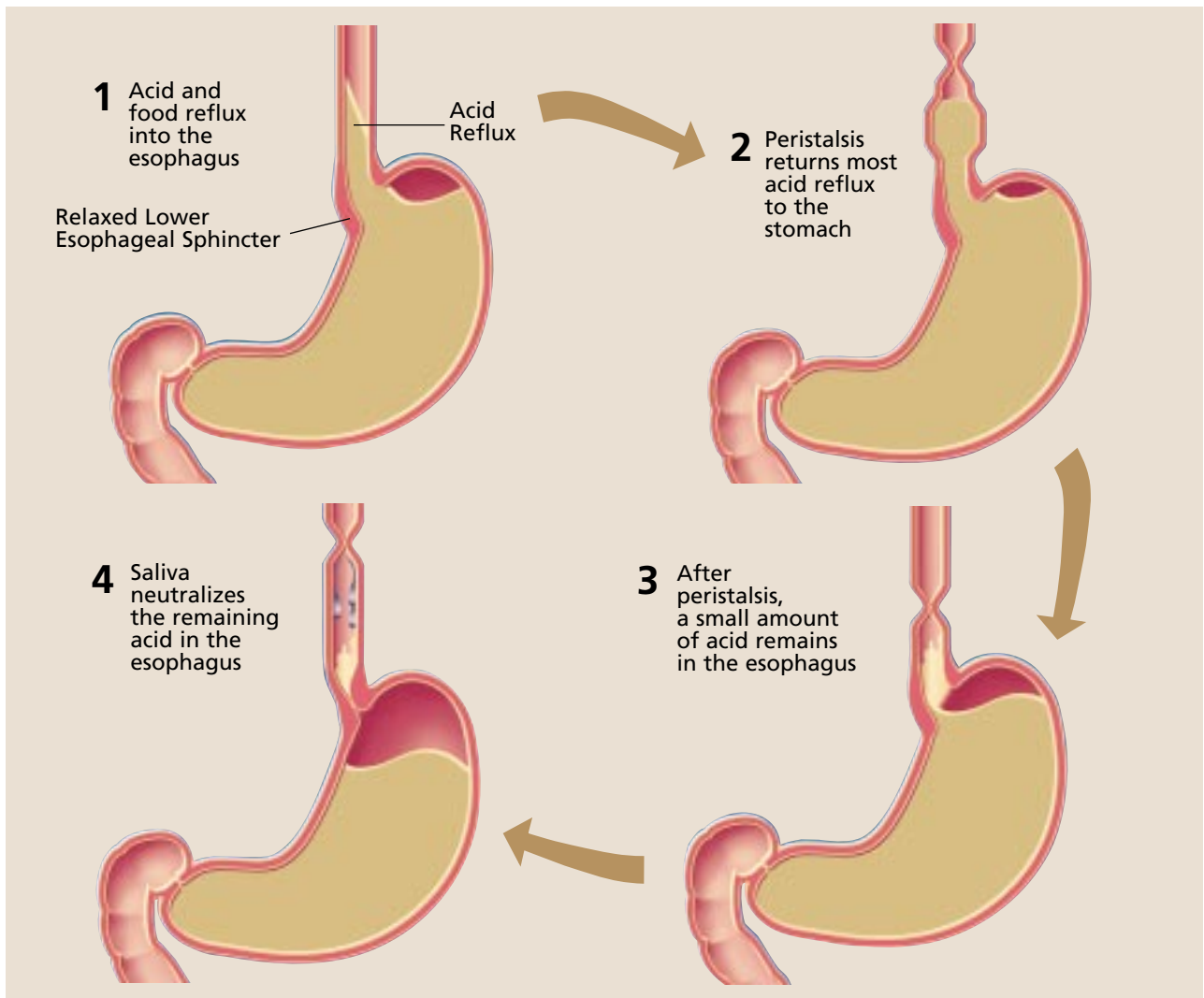
Among patients with nonerosive esophagitis but frequent heartburn, a symptom relapse rate of 75% was seen at 6 months.<sup>10</sup> Additional data from small studies of limited duration suggest that a minority of patients with nonerosive GERD will progress to erosive GERD. This finding needs to be confirmed, however, in larger studies of longer duration.<sup>9</sup> Therefore, an initial negative endoscopy does not preclude the development of erosive disease.

Compared with the pathophysiology, symptoms, and clinical course of GERD, the impact of GERD on quality of life is perhaps less well recognized. Numerous studies have documented how GERD reduces quality of life and the way in which effective treatment can yield significant benefit in measures of patient functioning and well-being.

## ■ PATHOGENESIS AND PATHOPHYSIOLOGY

### A multifactorial etiology

Some degree of gastroesophageal reflux occurs normally in most individuals (**Figure 1**). GERD is thought to develop when a combination of conditions occurs to increase the presence of refluxed



**FIGURE 1.** What happens during nonpathologic reflux.

acid in the esophagus to pathologic levels.<sup>3</sup> Aggressive mechanisms potentially harmful to the esophagus overwhelm protective mechanisms such as esophageal acid clearance and mucosal resistance, which normally help to maintain a physiologically balanced state. In this way, the pathogenesis of GERD is similar to that of other acid-secretory diseases, such as duodenal ulcer disease and gastric ulcer disease.<sup>11</sup>

Among the mechanisms thought to contribute to the development of GERD are TLESRs or decreased LES resting tone, impaired esophageal acid clearance, delayed gastric emptying, decreased salivation, and impaired tissue resistance (**Figure 2**). Recent data also support the importance of the potency of

the gastric refluxate as a contributory factor in some circumstances.<sup>12</sup> A significant defect in any one of these forces can alter the balance from a compensated state to a decompensated one. Manifestations of the decompensated state include symptoms and complications such as heartburn and esophagitis.<sup>13</sup>

Excessive acid reflux due to TLESRs is the most common causative mechanism (**Table 1**).<sup>14</sup> A pathologically decreased LES resting tone is more common among patients with severe GERD, especially those with esophageal strictures or Barrett's esophagus.

Esophageal motility abnormalities (impaired peristalsis) are also commonly associated with severe esophagitis (**Figure 3**).<sup>15</sup> Among both normal individuals and those with GERD, gastric disten-

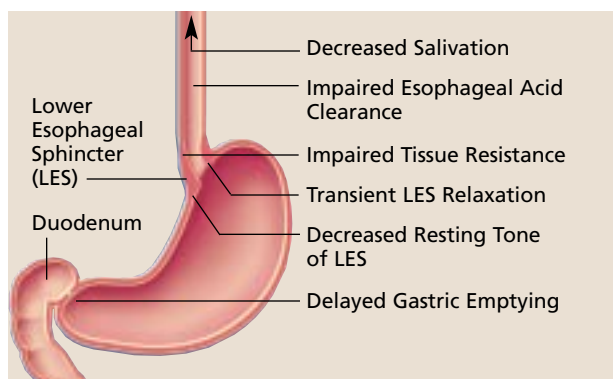


FIGURE 2. Possible etiologic factors involved in GERD.

**TABLE 1**  
Mechanisms of gastroesophageal reflux in normal volunteers and in patients with GERD

Type	Normal volunteers	Patients with GERD
Transient lower esophageal sphincter relaxations (TLESRs)	94%	65%
Transient increase in intra-abdominal pressure	5%	17%
Spontaneous free reflux	1%	18%

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tion is thought to contribute to the increase in reflux by significantly increasing the rate of TLESRs.<sup>16</sup> Thus, it is thought to be the trigger for TLESRs (Figure 4).<sup>17</sup>

Secondary causes of GERD include reflux caused by acid hypersecretory states such as Zollinger-Ellison syndrome; connective-tissue disorders such as scleroderma; gastric outlet obstruction as caused by ulceration and stricture; and delayed gastric emptying due to conditions such as gastric stasis, neuromuscular disease, idiopathic gastroparesis, pyloric dysfunction, duodenal dysmotility, or duodenogastroesophageal bile reflux.

Increased intragastric pressure leading to GERD can be caused by obesity, pregnancy, or disruption of the normal receptive relaxation of the stomach following an increase in gastric volume.<sup>3</sup> Most patients with complicated GERD have a hiatal hernia, which, by displacing the LES segment of the distal esophagus, both reduces LES pressure and impairs acid clearance.<sup>12</sup>

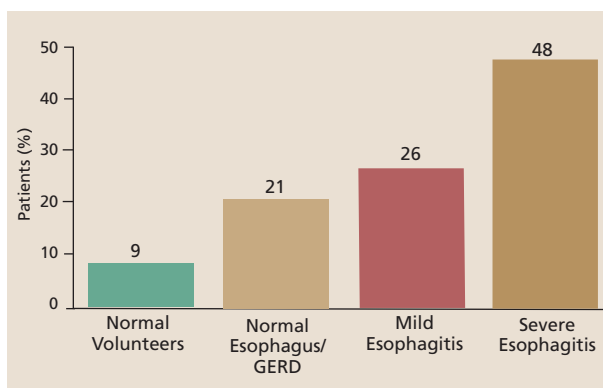


FIGURE 3. Proportion of subjects with esophageal motility abnormalities, by increasing severity of esophagitis. Reprinted from reference 15 with permission from the American Gastroenterological Association.

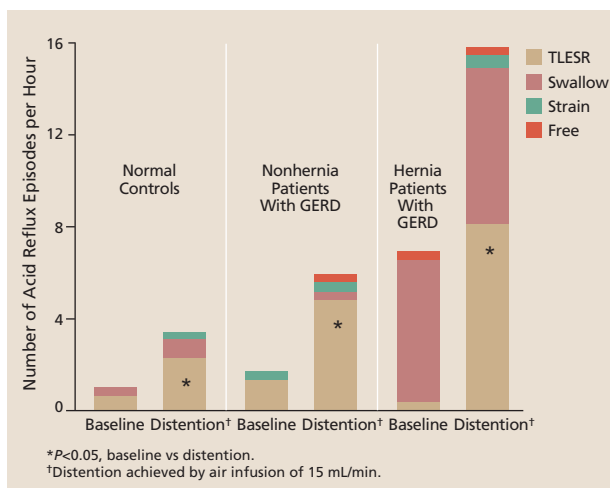


FIGURE 4. Relationship between gastric distention, the number of acid reflux episodes, and the reflux mechanism (TLESR = transient lower esophageal sphincter relaxation). Reprinted from reference 17 with permission from the American Gastroenterological Association.

Once reflux has occurred, impaired acid clearance prolongs exposure of the mucosa to the damaging effects of the refluxate.<sup>16</sup> Diminished peristaltic clearance is seen among approximately one half of patients with severe GERD.<sup>15</sup> Acid clearance is particularly impaired in patients with hiatal hernia.

### Lower esophageal sphincter dysfunction

Perhaps the dominant pattern of dysfunction among patients with mild disease is an increased proportion of TLESRs accompanied by reflux. Patients with more severe disease typically have impaired LES resting tone, associated with a weak sphincter or other factors underlying a persistently reduced LES pressure.

**TABLE 2**  
Substances that influence lower esophageal sphincter pressure (LESP)

	Increase LESP	Decrease LESP
<b>Hormones</b>	Gastrin, motilin, substance P	Secretin, cholecystokinin, glucagon, gastric inhibitory polypeptide, vasoactive intestinal polypeptide, progesterone
<b>Neural agents</b>	Alpha-adrenergic agonists, beta-adrenergic antagonists, cholinergic agonists	Alpha-adrenergic antagonists, beta-adrenergic agonists, cholinergic antagonists, serotonin
<b>Medications</b>	Metoclopramide, domperidone, prostaglandin F <sub>2α</sub> , cisapride	Nitrates, calcium channel blockers, theophylline, morphine, meperidone, diazepam, barbiturates
<b>Foods</b>	Protein	Fat, chocolate, ethanol, peppermint

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**Normal LES function.** The LES is a 3-cm to 4-cm segment of tonically contracted smooth muscle located at the gastroesophageal junction. It is one of two muscular valves located at either end of the esophagus that protect the airway from the reflux of injurious gastric contents. The LES is an anatomically complex zone, comprising two components: the true LES in the distal esophagus and the crural portion of the diaphragm. Both the LES and the diaphragm contribute to gastroesophageal sphincter competence. The LES must be dynamic to protect against reflux in a variety of situations, including swallowing, recumbency, and abdominal straining.

In normal digestion, relaxation of the LES prior to contraction of the esophagus allows food to pass through into the stomach. Constriction of the LES prevents regurgitation of stomach contents (food and acidic stomach juices) into the esophagus. Tonic contraction of the LES is a property of the muscle itself as well as its extrinsic innervation. Both myogenic and neurogenic mechanisms are involved in maintaining LES resting tone. LES tone is maintained or increased by release of acetylcholine. Relaxation of the LES occurs in response to nitric oxide release, as seen in response to swallowing.

In the resting state, the LES maintains a high-pressure zone that is 15 mm Hg to 30 mm Hg above intragastric pressures, depending on individual variability. Normal LESP varies with breathing, body position, and movement, in response to intra-abdominal pressure and gastric distention. The crural diaphragm can augment LESP to help prevent reflux during inspiration, when pressure in the intrathoracic region decreases. LESP also exhibits

significant diurnal variation: it is lowest in the daytime and during the postprandial period and highest at night.<sup>3</sup> LESP is also influenced by various drugs, foods, and hormones (Table 2).<sup>13</sup>

**Transient lower esophageal sphincter relaxations.** TLESRs are brief episodes of LES relaxation that are unrelated to swallowing or peristalsis (Figure 5).<sup>18,19</sup> Lasting approximately 10 seconds to 35 seconds, TLESRs decrease LESP to the gastric level.<sup>3</sup> They occur via stimulation of vagal sensory and motor nerves in response to gastric distention.<sup>2</sup> Seen among individuals both with and without GERD, TLESRs do not always result in gastroesophageal reflux. Nevertheless, they are strongly associated with both physiologic and pathologic reflux.<sup>20,21</sup> In experiments involving simultaneous measurement of LESP and esophageal pH, most reflux episodes were found to be caused by spontaneous complete relaxations of an otherwise normal LES.<sup>20</sup>

In fact, TLESRs account for the vast majority of nonpathologic (ie, physiologic) reflux events. Peristalsis returns approximately 90% of refluxed acidic material to the stomach, and the remaining acid is neutralized by swallowed saliva during successive swallows. Among patients with GERD, TLESRs are considered the primary underlying cause of pathologic reflux in the presence of a normal resting tone. Patients with GERD have an equal frequency of TLESRs compared with normal individuals, although they have a higher percentage of TLESRs associated with reflux.<sup>22</sup> Thus, the time that gastric acid remains in contact with the esophageal mucosa is increased in patients with GERD, increasing their risk of symptoms and esophageal injury.

The proportion of reflux episodes due to TLESRs varies with GERD severity. Among healthy individuals, or those with GERD but no esophagitis, reflux occurs almost exclusively during TLESRs. In patients with erosive or ulcerative esophagitis, reflux occurs during TLESRs in only about one third of episodes. Data from a recent study comparing excess reflux among patients with GERD with and without a hiatal hernia show that TLESRs accounted for 32.8% of reflux episodes among patients with a hiatal hernia, compared with 60.2% among those without a hiatal hernia.<sup>23</sup>

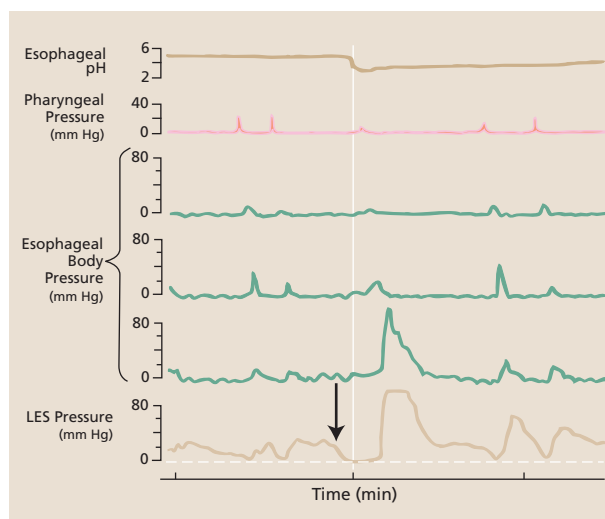
**Decreased LES resting tone.** A minority of patients with GERD have a constantly weak, low-pressure LES, which permits reflux every time the pressure in the stomach exceeds the LESP. Among patients with such a defect, the absolute LESP necessary for GERD is less than 6 mm Hg.<sup>12</sup> A chronically decreased LES resting tone is usually associated with severe esophagitis. Severe impairment in basal LES tone may lead to more severe disease by allowing gastric contents to pass freely into the esophagus when the patient is supine.<sup>8</sup> Similarly, LES defects have been found among many patients with other GERD complications, such as esophageal stricture and Barrett's esophagus.

Factors that decrease LES tone include endogenous hormones (eg, progesterone in pregnancy), medications, and specific foods.<sup>2</sup> In patients with hiatal hernia, the true LES and the crural diaphragm are separated, which impairs acid clearance.

### Increased esophageal acid exposure

Esophageal acid exposure is the percentage of time within a 24-hour period in which esophageal pH is less than 4. The degree of esophageal mucosal injury and the frequency and severity of symptoms such as heartburn, regurgitation, and pain are determined by the degree and duration of esophageal acid exposure. Esophageal acid exposure, in turn, is related to the pH of the refluxed gastric material.<sup>24</sup>

Among most patients with mild disease, esophageal acid exposure occurs predominantly during postprandial periods.<sup>21</sup> The pattern of esophageal acid exposure, in fact, has been linked to increasing GERD severity. Among 401 patients with increased esophageal acid exposure, divided into four groups according to their pattern of reflux (ie, postprandial, upright, supine, or bipositional), the risk of severe GERD increased progressively with the different reflux patterns, from postprandial



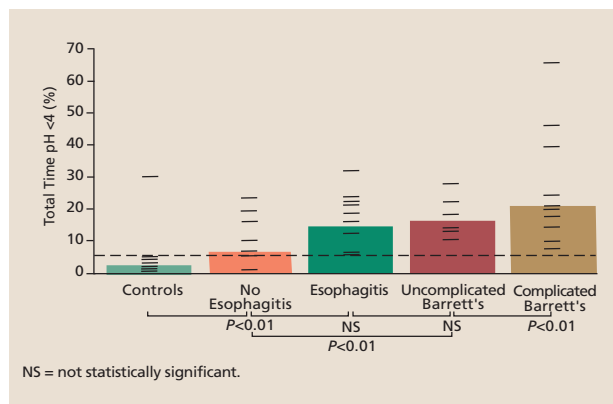
**FIGURE 5.** Gastroesophageal reflux occurring during transient lower esophageal sphincter (LES) relaxations. Shortly before reflux occurs (white vertical line), the LES abruptly relaxes (arrow) without an antecedent swallow. Intra-gastric pressure is indicated by the horizontal broken line. Reprinted from *Gut* 1988; 29:1020–1028,<sup>19</sup> with permission from the BMJ Publishing Group.

to upright to supine to bipositional.<sup>25</sup>

**Normal acid clearance.** The process of normal acid clearance involves peristalsis as well as the swallowing of salivary bicarbonate. Peristalsis clears gastric fluid from the esophagus, whereas the swallowing of saliva (pH of 7.8 to 8.0) neutralizes any remaining acid. Both primary and secondary peristalsis are essential mechanisms of esophageal clearance. Voluntary induced primary peristalsis occurs approximately 60 times per hour. Secondary peristalsis occurs in the absence of a pharyngeal swallow and can be elicited by esophageal distention or acidification, which occurs with acid reflux.<sup>3</sup> Salivation is crucial to the completion of esophageal acid clearance and the restoration of esophageal pH. Gravity also plays an important role in esophageal acid clearance.

**Impaired acid clearance.** Ineffective esophageal acid clearance increases esophageal acid exposure time in patients with GERD. In experimentally induced or spontaneous reflux, patients with GERD have been found to have acid clearance times that are two to three times longer than those of persons without GERD.<sup>13</sup> Impaired esophageal clearance can be caused by an increase in volume of the refluxate. Rarely, impaired esophageal acid clearance may be due to an underlying disease such as scleroderma. In some patients, esophageal body dysfunction can sub-





**FIGURE 6.** Duration during which pH was less than 4 among healthy controls and patients with various grades of GERD. Dashes represent data points for individual subjects; colored bars represent median value for the respective subject group. Horizontal dashed line represents the upper limits of normal acid reflux. Reprinted from reference 28 with permission from the American Gastroenterological Association.

stantially prolong the dwell time of acidic gastric contents in the esophageal lumen.<sup>21</sup>

Two mechanisms of impaired volume clearance have been identified: peristaltic dysfunction and re-reflux. Peristaltic dysfunction is characterized by failed peristalsis and low-amplitude contractions. Failed peristaltic contractions and hypotensive (< 30 mm Hg) peristaltic contractions lead to incomplete esophageal emptying.<sup>26</sup> Decreased amplitude of secondary peristaltic waves and segmental contractions have been demonstrated among some patients with GERD. Peristaltic dysfunction often increases with increasing severity of esophagitis. Re-reflux is associated with certain hiatal hernias, and certain types of hernias also impair esophageal emptying to varying degrees.<sup>13</sup>

The completion of esophageal acid clearance with restoration of esophageal pH depends on salivation. Normally, saliva can neutralize any residual acid coating the esophagus after a secondary peristaltic wave. Acid clearance is prolonged by a reduced salivary rate or by diminished salivary capacity to neutralize acid. Reduced salivation during, or immediately before, sleep accounts for markedly prolonged acid clearance times.<sup>13</sup> Reduced esophageal acid clearance during sleep appears to be a major causative factor in serious forms of GERD.<sup>27</sup> Reduced frequency of swallowing-induced peristalsis during sleep also prolongs esophageal acid exposure.

**Duration of esophageal acid exposure.** The duration of esophageal exposure to acid and other

digestive juices is the primary cause of GERD symptoms and tissue injury. The longer the esophagus is exposed to acid (and also pepsin), the more severe the disease (**Figure 6**).<sup>28</sup> Severe erosive esophagitis and Barrett's esophagus are associated with particularly high levels of acid exposure.

Symptom severity also progressively increases as esophageal acid exposure increases, whether patients have erosive esophagitis or a macroscopically normal esophagus.<sup>21</sup>

A pH of 4 appears to be the optimal threshold for differentiating between aggressive and nonaggressive reflux throughout a 24-hour period.<sup>29</sup> This was demonstrated in a meta-analysis of GERD treatment trials in which gastric acid suppression data were compared with clinical outcomes, showing that greater control of 24-hour intragastric acidity (determined by the length of time that intragastric pH was greater than 4) significantly improved healing rates at 8 weeks ( $P < 0.05$ ).<sup>19</sup> However, symptom relief sometimes requires 24-hour control of intragastric acidity, since GERD patients can experience gastroesophageal reflux at any time of day.<sup>24</sup> These findings are reflected in the treatment goal of antisecretory agents, namely, to reduce esophageal acid exposure. If the intraesophageal pH can be maintained at or above 4 for the majority of a 24-hour period, most patients will remain symptom-free and experience complete healing of erosive lesions.

**Characteristics of the refluxate.** The development of GERD symptoms and the potency of the gastric refluxate (primarily acid and pepsin) in causing mucosal injury are highly dependent on intragastric pH and the amount of time the refluxate is in contact with the mucosa. Esophageal clearance time is also influenced by the pH of the refluxate. The lower the pH, the more time is needed for intraesophageal pH to return to 4 or above.<sup>21</sup>

The relationship between the degree of acidity and pain sensation was explored in a study by Smith and colleagues.<sup>30</sup> They observed a positive correlation between the time elapsed before esophageal pain was experienced and the pH of an infused solution. The most significant difference was found between pH 2 and pH 4. Between these acidity levels, the elapsed time to pain sensation increased progressively, eventually leveling off at a pH greater than 4.<sup>30</sup>

Similarly, the degree of mucosal damage can be markedly accelerated if the luminal pH is less than 2 or if pepsin is present in the refluxate. Studies have shown that the combination of acid and pepsin is

most injurious to esophageal mucosa.<sup>12</sup> The intragastric acidity threshold of pH 4 differentiates between aggressive and nonaggressive reflux in part because gastric refluxate with a pH less than 4 contains active pepsin. The enzymatic activity of pepsin is dependent on pH, and it is activated in an acidic environment. Refluxed bile or alkaline pancreatic secretions, however, may contribute in some cases. Increased amounts of bile acids have been found in the refluxate of GERD patients, especially those with Barrett's esophagus.<sup>12</sup> A recent study indicates, however, that isolated bile reflux does not result in esophagitis.<sup>31</sup> Pepsin is clearly the dominant player. The causative role of bile has not been established.

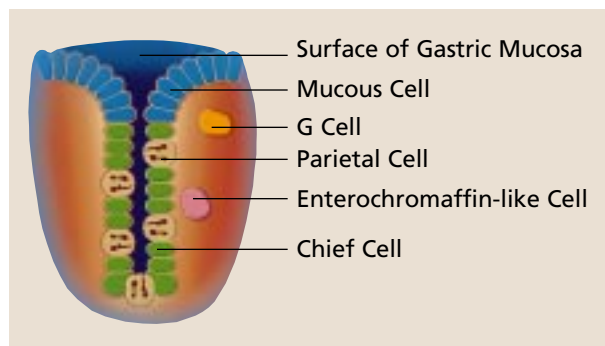
These observations have immediate clinical benefit. Antisecretory drugs have become the principal approach for treating reflux symptoms and esophagitis because they reduce the acidity of gastric juice and the activity of pepsin. They also reduce the volume of gastric juice available for reflux into the esophagus.<sup>32</sup>

The role of hypoacidity has also been demonstrated in new studies suggesting that colonization with *Helicobacter pylori* may protect against severe esophagitis and Barrett's esophagus. This protection is presumed to occur via mechanisms that promote hypoacidity. Eradication of *H pylori*, consequently, may aggravate GERD in susceptible patients.<sup>12</sup>

**Timing of esophageal acid exposure.** Among the majority of patients with GERD who have mild erosive esophagitis or no endoscopic abnormality, most reflux occurs after meals. Relatively little reflux occurs during the night. With increasingly severe cases of esophagitis, acid exposure progressively increases, primarily because of an increase in nocturnal reflux. Nighttime is also the longest period of unbuffered gastric acid secretion, owing to reduced acid neutralization by salivary bicarbonate during sleep. In addition, esophageal acid exposure clearance is reduced because of sleep's effects on esophageal motility.<sup>21</sup>

### Other etiologic factors

**Delayed stomach emptying.** Delayed gastric emptying is present in 10% to 15% of patients with GERD.<sup>12</sup> It is believed to contribute to the development of a small proportion of cases by increasing the amount of fluid available for reflux and by the associated constant gastric distention. Potential causes of impaired gastric emptying include gastroparesis, as seen in patients with diabetes, and partial gastric



**FIGURE 7.** Schematic presenting a microscopic view of the gastric mucosa.

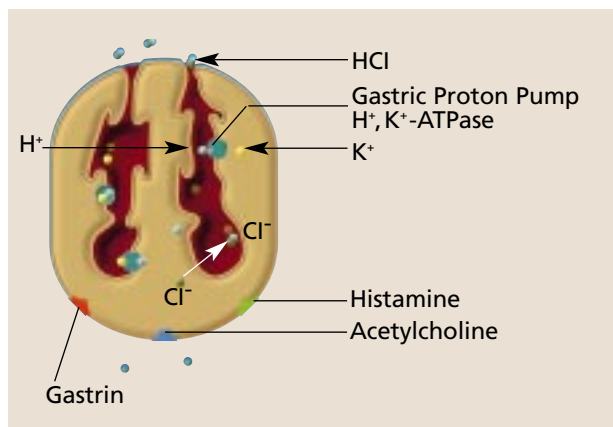
outlet obstruction.<sup>33</sup>

**Impaired mucosal resistance.** The ability of the esophageal mucosa to withstand injury is a determining factor in the development of GERD. Age and nutritional status seem to influence the ability of the mucosa to withstand injury. Esophageal tissue resistance to acid consists of cell membranes and intercellular junctional complexes, which protect against injury by limiting the rate of diffusion of hydrogen ions into the epithelium. The esophagus also produces bicarbonate and mucus. Bicarbonate buffers the acid, and mucus forms a protective barrier on the epithelial surface.

The sensitivity of the esophageal mucosa to damage from acid, pepsin, or bile is rather high. The level of resistance of the esophageal mucosa to acid damage is far less than that of the stomach lining. Esophageal damage occurs because the level of acid and pepsin present exceeds the level of mucosal protection. Pepsin in the acid refluxate can damage the esophageal mucosa by digesting epithelial protein. Enhanced mucosal sensitivity to acid can also be seen in association with chronic heartburn symptoms.<sup>34</sup>

### Gastric acid production and regulation

**Acid production by parietal cells.** Deep within the lining of the stomach lie collections of cells organized into gastric glands, which secrete various substances into the stomach (**Figure 7**), including mucus, hydrochloric acid (HCl), the hormone gastrin, histamine, pepsinogen, and intrinsic factor. Mucous cells, within gastric pits that open onto the surface of the stomach, secrete mucus. Specialized parietal cells, located in the deeper part of the gland, secrete HCl. Parietal cells also are thought to secrete intrinsic factor, which is needed for vitamin



**FIGURE 8.** The gastric proton pump. The  $H^+$ ,  $K^+$ -ATPase molecule, or gastric proton pump, exchanges  $H^+$  for  $K^+$ , which, followed by the passive movement of  $Cl^-$  into the parietal cell lumen, leads to the production of HCl. Acid production within the parietal cell can be stimulated by the binding of gastrin, acetylcholine, or histamine to specific receptors on the cell surface.<sup>42</sup>

$B_{12}$  absorption. G cells, located predominantly in the antrum of the stomach, secrete gastrin. Histamine is secreted by enterochromaffin-like cells, and chief cells secrete pepsinogen.

Parietal cells are stimulated to secrete HCl following activation of receptors for histamine<sub>2</sub>, acetylcholine, and/or gastrin. When maximally stimulated, parietal cells can secrete HCl at concentrations that can lower the pH of gastric juice to 1 or less.<sup>35</sup> The stomach produces an average of 2 liters of HCl a day, which, in combination with the protein-splitting enzyme pepsin, breaks down chemicals in food.<sup>35</sup>

During a meal, the rate of acid production by parietal cells increases markedly, mediated by vagus nerves. Stomach distention, hydrogen ion concentration, and peptides send messages through long and short neural reflexes to increase gastrin release, which also increases acid production.

**Acid regulatory pathways.** Acid secretion by parietal cells is controlled by three acid regulatory pathways: the acetylcholine, gastrin, and histamine receptor pathways. These pathways, in turn, are stimulated by food via the vagus nerve. The sight, smell, and taste of food and its physical presence in the mouth, esophagus, and stomach all contribute to the stimulation of gastric acid secretion. Hormones also play a role, as nervous stimulation of cells in the antrum leads to the release of gastrin, which in turn stimulates further acid secretion into the stomach cavity.

Significant interaction and overlap occur among

the three pathways. Acetylcholine release is stimulated by the sight, smell, and taste of food. Digested food in the stomach (containing dietary amino acids and proteins) chemically stimulates the release of gastrin from G cells in the gastric antrum. An elevated gastric pH also stimulates the release of gastrin.<sup>36,37</sup> A low gastric pH inhibits gastrin release by inducing the release of somatostatin from antral D cells, which in turn reduces gastrin release from G cells.<sup>38</sup> Stomach distention, triggering the release of acetylcholine, further stimulates G cells to produce gastrin. Gastrin travels through the bloodstream and binds to the gastrin receptor on the parietal cells, located in the gastric body and fundus. Both acetylcholine and gastrin stimulate enterochromaffin-like cells to release histamine.

The binding of acetylcholine, gastrin, or histamine to its receptor on the parietal cell initiates the process leading to acid production by altering the parietal cell's permeability to calcium ions. The resulting influx of calcium ions increases the intracellular calcium concentration, thereby activating intracellular protein phosphokinases. At the same time, a membrane-bound adenylate cyclase leads to the generation of cyclic adenosine monophosphate, which acts as a second messenger to activate protein phosphokinases.

The final step in gastric acid production occurs via the gastric acid (proton) pump, in the apical membrane of the parietal cell. The low gastric pH maintained by the proton pump allows balance between gastric acidity and mucosal defenses.<sup>39</sup>

**The gastric proton pump.** The hydrogen-potassium adenosine triphosphatase ( $H^+$ ,  $K^+$ -ATPase) molecule, or gastric proton pump, comprises an enzyme system located on the secretory surface of the gastric parietal cell. It has two major components: a larger (alpha) subunit, containing approximately 1,000 amino acids with both transport and catalytic functions, and a smaller (beta) subunit, consisting of about 300 amino acids with structural and membrane-targeting functions.<sup>40</sup>

Each gastric parietal cell contains about 1 million acid pumps in its cytoplasmic membranes. Following the passive movement of potassium and chloride ions into the secretory canaliculus, the pumps are activated by translocation into canaliculi (resulting from the increase in protein phosphokinases described above) and by activation of a potassium and chloride ion transport pathway.<sup>41</sup> The primary function of the activated pump is to exchange

**TABLE 3**  
The spectrum of GERD manifestations

Chest	Pulmonary	Oral	Throat	Ear
Heartburn	Asthma	Tooth decay	Globus sensation	Earache
Regurgitation	Cough	Gingivitis	Hoarseness	
Chest pain	Aspiration		Laryngitis	
Dysphagia/odynophagia				

hydrogen ions from the cytosol of the parietal cell for potassium ions from the secretory canaliculi using energy derived from the splitting of ATP. In the secretory canaliculus, the chloride ions combine with hydrogen ions to form HCl.

Regardless of the stimulus, the physical production of acid from the parietal cell via  $H^+, K^+$ -ATPase is the final common pathway for gastric acid secretion (Figure 8).<sup>42</sup>

Direct inhibition of the proton pump inhibits acid secretion independent of the biochemical pathway involved in its activation. Drugs that target the proton pump are therefore more effective inhibitors of gastric acid secretion than are those that target histamine, gastrin, or acetylcholine receptors on the basolateral surface of the parietal cell. Consequently, PPIs, which inhibit the activity of  $H^+, K^+$ -ATPase, have been found to be more potent inhibitors of gastric acid secretion than other similar treatments (see the final article in this supplement).<sup>43</sup>

## ■ CLINICAL MANIFESTATIONS

### The clinical spectrum of GERD

GERD is characterized by a wide variety of clinical symptoms and presentations, ranging from symptomatic reflux without macroscopic esophagitis to the chronic complications of esophageal mucosal damage.<sup>44</sup> Heartburn is the most common symptom of GERD. In some patients, heartburn may be accompanied by acid regurgitation, odynophagia, and dysphagia. Numerous esophageal manifestations of GERD can occur.

Depending on the extent to which refluxed acid reaches other nearby tissues, other types of symptoms may occur. The spectrum of GERD symptoms, therefore, is diverse (Table 3).

Noncardiac chest pain associated with GERD pre-

sents as unexplained angina-type pain that can resemble a myocardial infarction. A wide range of pulmonary and otolaryngologic symptoms can occur.<sup>45</sup> In addition to laryngitis, pharyngitis, chronic cough, asthma, bronchiectasis, recurrent aspiration syndromes, globus, and dysphagia, extraesophageal manifestations of GERD can include nausea and vomiting and erosive changes in dental enamel.<sup>6,46</sup>

Symptom frequency also varies among patients. Some experience daily or weekly symptoms, while others have GERD symptoms a few times per month. Symptom frequency and severity do not correlate with the degree of esophageal mucosal changes apparent on endoscopy.<sup>47</sup> The most common complication of GERD is esophagitis, and its severity ranges from erythema in early disease to the development of endoscopic erosions or ulcerations of varying severity. More serious complications include obstruction caused by esophageal stricture formation, or Barrett's esophagus (see the third article in this supplement).

Complicated GERD is suggested by a number of early warning signs. Slowly progressive dysphagia, particularly for solids, suggests the presence of peptic strictures. Liquid and solid dysphagia suggests a GERD-related motility disorder. Odynophagia (otherwise, rarely present) suggests inflammation or ulceration, most frequently associated with infectious or pill-induced esophagitis. A GERD-related esophageal motility disorder is more often seen in patients who have associated respiratory symptoms. Occasionally, patients present with occult upper gastrointestinal bleeding or with iron-deficiency anemia. If patients have any of these warning signs, they should undergo prompt evaluation to rule out a diagnosis other than GERD.<sup>48</sup>

### Heartburn and acid regurgitation

Heartburn is the most common symptom of GERD.

Its classic presentation is that of a retrosternal burning sensation that radiates to the pharynx. It usually occurs after meals (typically 30 to 60 minutes after eating) or upon reclining at night. It can also be aggravated by bending over.<sup>33</sup> Many patients can obtain relief by standing upright or taking an antacid to clear acid from the esophagus.

Heartburn is believed to be caused by acid stimulation of sensory nerve endings in the deeper layers of the esophageal epithelium. If an excessive amount of acid reflux enters the esophagus, prolonged contact with the esophageal lining will injure the esophagus and produce a burning sensation. For heartburn to occur, the refluxate must be sufficiently acidic.

Heartburn as the primary esophageal complaint has a high degree of reliability in diagnosing GERD. Many patients, however, have less-specific dyspeptic symptoms and may or may not have heartburn. Increasing frequency of heartburn (from occasional to occurring more than twice per week) suggests GERD. When both heartburn and regurgitation are present, a diagnosis of GERD can be made with greater than 90% certainty.<sup>48</sup> Patients who have both symptoms and acid reflux but normal esophageal acid exposure have been classified as having functional heartburn or "acid-sensitive esophagus." Patients with Zollinger-Ellison syndrome, however, may present with GERD symptoms only. Both heartburn and regurgitation are considered classic symptoms of GERD.<sup>49</sup>

**Acid regurgitation** is the effortless return of acidic gastric contents into the esophagus without nausea, retching, or abdominal contractions. Like heartburn, regurgitation usually occurs after meals, especially after large ones, and may be exacerbated by recumbency, straining, or bending over.<sup>50</sup> If reflux of injurious acidic gastric contents extends beyond the esophagus to the lungs, larynx, pharynx, or oral cavity, extraesophageal GERD symptoms can occur.

### Dysphagia and odynophagia

**Dysphagia** is the perception of impaired movement of swallowed material from the pharynx to the stomach. It affects more than 30% of patients with GERD. Its possible causes include peristaltic dysfunction, inflammation, peptic stricture, or a Schatzki ring.<sup>15</sup> Alternatively, if no physical abnormality is found, the cause may be abnormal esophageal sensitivity to movement of the bolus during peristalsis.<sup>13</sup>

**Oropharyngeal dysphagia** is the perception of

impaired movement of a bolus from the oropharynx to the upper esophagus, whereas **esophageal dysphagia** is the perception of impaired transit through the esophageal body. The distinction can usually be made from a careful history.<sup>33</sup> Among patients with significant GERD, dysphagia is not uncommon and may indicate esophageal stricture. Among those with severe or recent-onset dysphagia, esophageal cancer must be ruled out.

**Odynophagia** is a sharp substernal pain that occurs during swallowing. The pain may be so severe as to limit oral intake. The cause of odynophagia is esophageal ulceration, especially in the setting of infectious esophagitis. It may also be caused by corrosive injury from ingestion of caustic substances or by pill-induced ulcers.<sup>33</sup>

### Noncardiac chest pain

Noncardiac chest pain refers to unexplained substernal chest pain resembling a myocardial infarction without evidence of coronary artery disease. GERD is the most common gastrointestinal cause of noncardiac chest pain. The proximity of the esophagus to the heart and its shared visceral innervation are believed to be underlying factors. Pain is thought to occur as a result of stimulation of chemoreceptors or by esophageal distention. Actual microvascular angina independent of reflux might also be the cause.

Noncardiac chest pain can be sharp or dull and can radiate widely into the neck, jaw, arms, or back. One should also remember that substernal chest pain can be caused by cardiovascular disease. The patient's response to exercise is one aspect of the history that can help distinguish heartburn from heart disease or a myocardial infarction. Pain resulting from heart disease can be aggravated by exercise and possibly relieved by rest. Heartburn is less likely to be associated with physical activity, with the possible exception of bending over, which sometimes exacerbates heartburn.

### Extraesophageal symptoms

Extraesophageal complications of GERD (see the following article in this supplement) have become increasingly well recognized. In up to half of the patients with such symptoms, GERD can be a causative or an exacerbating factor, especially if the symptoms are refractory. Because many of these patients do not experience the classic GERD symptoms of heartburn or regurgitation, the diagnosis is

often overlooked.<sup>33</sup> In many cases, the diagnosis rests on the outcome of empiric treatment.<sup>2</sup>

The most common extraesophageal symptoms associated with GERD are noncardiac chest pain, chronic hoarseness, chronic cough, and asthma.<sup>51</sup> Acid reflux into the lungs causes pulmonary symptoms such as chronic cough, intermittent wheezing, asthma, bronchitis, aspiration or recurrent pneumonia, and interstitial fibrosis. Acid reflux that reaches the mouth can erode dental enamel, causing tooth decay. Other oral symptoms include gingivitis, halitosis, aphthous ulcers, and water brash. Acid reflux into the throat causes sore throat and globus sensation. Vocal cord inflammation can produce chronic posterior laryngitis and hoarseness. Otagia and hiccups are other possible extraesophageal symptoms.<sup>48</sup>

### Symptom relapse and chronicity

We know that patients with reflux esophagitis have a high rate of endoscopic and symptomatic relapse if therapy is discontinued or if the drug dosage is decreased. Patients with higher grades of esophagitis are particularly likely to experience a recurrence if they are not given effective maintenance therapy. Data from numerous studies have yielded a recurrence rate of 80% or more (without maintenance therapy) within 6 months of discontinuing therapy among patients with relatively severe esophagitis.<sup>52</sup>

Acid suppression therapy can control symptoms and heal erosive esophagitis. Because it cannot correct underlying motility problems, however, relapse is common once treatment is discontinued. Even among patients with extraesophageal symptoms, symptom recurrence is common within months of discontinuing therapy. The clinical impression associated with GERD, therefore, is one of chronicity, although the expression of disease chronicity differs among patients. Most patients, particularly those with erosive esophagitis or extraesophageal disease, require continuous medical therapy or surgery for adequate symptom relief.<sup>48</sup>

### ■ EXACERBATING FACTORS

Potential GERD triggers or exacerbating factors include dietary and lifestyle factors (including specific foods, eating habits, obesity, alcohol consumption, smoking, physical activity, and sleeping position) as well as pregnancy, hormones, hiatal hernia, and certain medications.

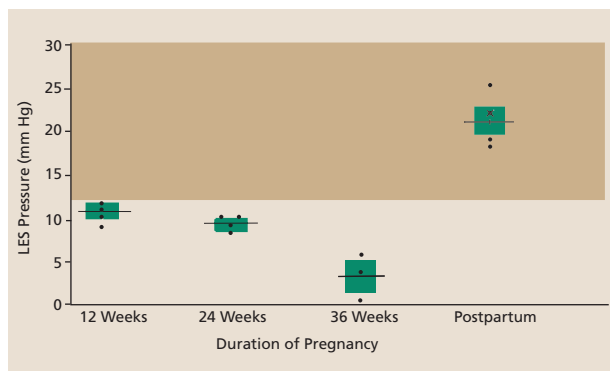
While some of these factors are thought to play a significant and documented role in GERD pathogenesis or pathophysiology, others, primarily dietary and lifestyle factors, lack convincing or consistent documentation of a role in triggering or worsening GERD symptoms. This is because of the nature of the studies conducted, which have been generally small and inconclusive and have yielded conflicting results in different patient groups. The treatment of GERD, however, is oriented toward the individual patient's symptoms, and in practice this includes providing specific advice regarding individual dietary intolerances and lifestyle factors.<sup>53</sup>

A careful history can help to identify specific factors in individual patients, to avoid unnecessarily restricting patients who might not benefit from such measures. Therefore, while little consistent data support the role of lifestyle modifications alone as an effective treatment, avoidance of exacerbating factors can be helpful for individual patients.

### Meals and specific foods

Meals are the major aggravating factor of GERD symptoms, since they stimulate the production of gastric acid available for reflux into the esophagus. Food in general (and large meals in particular) induces TLESRs. Meals eaten within 2 to 3 hours of bedtime (which increase acid availability at nighttime), or with alcohol, can predispose patients to nocturnal reflux.<sup>48</sup> Dietary fat in the duodenum also appears to be a strong reflux trigger, in part by impairing gastric emptying. In a recent study, however, no difference in postprandial LESP and GERD was seen among 12 healthy volunteers after consuming a high-fat meal compared with an isocaloric and isovolumetric low-fat meal.<sup>54</sup> The study authors concluded that it was inappropriate to advise patients to reduce the fat content of their meals, as least with regard to GERD symptom relief.

Specific foods that have been identified as potentially aggravating factors in certain patients include raw onions, chocolate, caffeine, peppermint, citrus juices, alcoholic beverages, tomato products, and spicy foods. Peppermint and chocolate are thought to lower LES tone, facilitating reflux. Citrus juice, tomato juice, and probably pepper can irritate damaged esophageal mucosa. Cola drinks, coffee, tea, and beer can have an acidic pH, lowering LESP to precipitate symptoms. Potential esophageal irritants should be restricted.<sup>48</sup>



**FIGURE 9.** Effect of pregnancy on lower esophageal sphincter (LES) pressure. LES pressure data were recorded from 4 women during pregnancy and the postpartum period. The mean  $\pm$  SEM for each time period is represented by the horizontal bars and green shaded areas. The area shaded in gold represents the range of LES pressures in normal nonpregnant women. Reprinted from reference 60 with permission from the American Gastroenterological Association.

### Body weight

Obesity is thought to be another potential predisposing factor to gastroesophageal reflux or GERD, although data are somewhat conflicting. In a risk-factor analysis of a random sample of 1,524 residents of Olmsted County, Minn., obesity (body mass index  $>30$  kg/m<sup>2</sup>) was found to be a strong risk factor for GERD.<sup>55</sup> In addition to obesity, other risk factors independently associated with frequent (at least weekly) symptoms included family history (suggesting a genetic component to GERD), a history of smoking, frequent alcohol consumption ( $>7$  drinks per week), and a higher degree of psychosomatic symptoms.<sup>55</sup>

A recent population-based study in Sweden among 820 adults conflicts with these findings. The Swedish researchers found no association between body weight and the severity or duration of reflux symptoms. They concluded that weight reduction might not be justifiable as an antireflux therapy.<sup>56</sup> Even so, it is commonly believed that weight reduction and exercise can have a favorable impact on reflux in obese persons. Others have found a significant association between weight loss and improvement of GERD symptoms, and recommend weight loss as a component of first-line management.<sup>57</sup>

### Pregnancy

Pregnancy is the most common condition predisposing to GERD and is generally associated with symptomatic GERD (typically heartburn) rather than

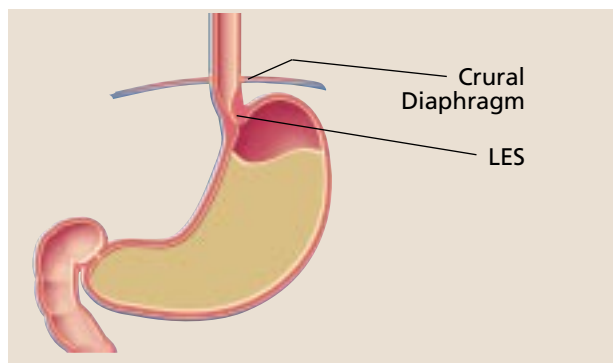
esophagitis.<sup>58</sup> Because heartburn affects approximately two thirds of all pregnancies, it is considered by many to be a normal occurrence during pregnancy. In most cases, symptoms occur for the first time during the pregnancy and subside soon after delivery. Recurrence is also a possibility with subsequent pregnancies. While symptoms may occur throughout the pregnancy, data are conflicting on whether they occur more frequently during the first and second trimesters or during the third.<sup>59</sup>

While the pathogenesis is thought to be multifactorial, the primary pathophysiology of GERD during pregnancy is probably that of decreased LES pressure resulting from the effects of progesterone and estrogen on LES function (Figure 9).<sup>58,60</sup> The two hormones appear to act together, with progesterone acting as a mediator of LES smooth-muscle relaxation and estrogen as a “primer” of LES relaxation.<sup>59</sup> Mechanical factors, such as increased abdominal pressure due to enlargement of the uterus, are believed to play a somewhat smaller role. In most cases, patients can be treated with lifestyle and dietary modifications if symptoms are mild. Otherwise, nonsystemic medications (antacids or sucralfate) can also be safely prescribed for symptom relief. Except for severe or intractable cases, systemic therapy during pregnancy should be avoided.<sup>59</sup>

### Hiatal hernia

A hiatal hernia is frequently found among patients with GERD.<sup>47</sup> The proximal stomach is dislocated through the hiatus of the diaphragm into the chest, and the crural diaphragm becomes separated from the LES (Figures 10 and 11).<sup>12</sup> Viewed as part of a GERD continuum, a hiatal hernia is another factor disrupting the integrity of the gastroesophageal sphincter, resulting in increased esophageal acid exposure.<sup>61</sup> It may be a factor in GERD pathogenesis, especially if the patient has severe symptoms. Hiatal hernias are present in more than 90% of patients with severe erosive esophagitis, especially if complications are present, such as esophageal stricture or Barrett’s esophagus.<sup>33</sup> Hiatal hernias, in fact, are found among most patients with Barrett’s esophagus, and they likely contribute to its development.<sup>62</sup> Whether or not the hernia is an initiating factor in GERD, it clearly plays a role in sustaining GERD, accounting for the chronicity of the disease.<sup>63</sup>

Hiatal hernias are thought to promote GERD chronicity via anatomic changes to the gastroesophageal junction that ultimately result in reduced



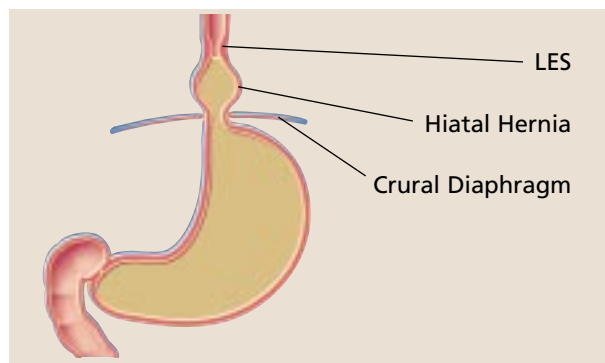
**FIGURE 10.** Normal antireflux barrier containing the lower esophageal sphincter (LES) and the crural diaphragm.<sup>12</sup>

esophageal acid clearance and increased esophageal acid exposure.<sup>63</sup> Depending on their size, hiatal hernias can displace and disable the diaphragmatic sphincter (the crural diaphragm) to increase susceptibility to reflux during sudden increases in intra-abdominal pressure. Large hiatal hernias also impair esophageal emptying during swallowing, thus prolonging acid clearance time.<sup>61</sup> Esophageal acid clearance might also be impaired by diaphragmatic contractions.<sup>3</sup>

### Medications

A wide variety of medications can promote GERD symptoms as a result of their effects on gastric emptying of acid or by reducing LES pressure to promote reflux.<sup>64</sup> The use of hypnotics, neuroleptics, or antidepressants that affect wakefulness, LES tone, salivation, or esophageal motility may induce or exacerbate symptoms. Medications that can decrease LES pressure, leading to reflux, include anticholinergics, sedatives or tranquilizers (particularly benzodiazepines), tricyclic antidepressants, theophylline, prostaglandins, dihydropyridine calcium channel blockers (such as diazepam and alprazolam), alpha-adrenergic blockers, beta blockers, and progesterones. Potassium tablets, non-steroidal anti-inflammatory drugs (NSAIDs), and alendronate can also cause esophagitis.<sup>48</sup>

NSAIDs disrupt tissue resistance, and more-severe cases of esophagitis might be more common among chronic NSAID users. In fact, a small but significant odds ratio of 1.4 for development of reflux esophagitis has been seen among patients with diseases commonly treating using NSAIDs, such as osteoarthritis, back pain, and tension headache.<sup>65</sup> Ingestion of alendronate by patients with osteoporosis can be associated with esophagitis and esophageal ulcer. Damage to the esophagus might occur as a



**FIGURE 11.** Hiatal hernia characterized by separation of the lower esophageal sphincter (LES) from the crural diaphragm.

result of toxicity from the medication itself as well as from nonspecific irritation caused by contact between the pill and the esophageal mucosa, as seen in other cases of pill esophagitis.<sup>66</sup>

### Smoking

The relationship between cigarette smoking and GERD is somewhat unresolved. It has been controversial for decades, since a high statistical association was reported and subsequently challenged.<sup>67</sup>

A number of potentially contributory factors have been identified. Studies show that smoking decreases LES pressure, thereby promoting reflux, and predisposes to strain-induced reflux. Indeed, smoking has been found to be related to an increased number of reflux events in association with deep inspiration and coughing. Smoking might promote the movement of bile from the intestine to the stomach, which would increase the harmful properties of the refluxate. Smoking also prolongs acid clearance by inhibiting the secretion of saliva.<sup>67</sup> This increases the risk of direct esophageal injury, given that saliva secretion is normally a crucial component of the esophageal mucosal defenses.

Nevertheless, smoking is not considered a major risk factor for GERD, despite the impact of both smoking and nicotine on major GERD pathophysiologic factors. However, patients should be cautioned against smoking regardless of its possible contribution to GERD. Smoking cessation, in combination with appropriate pharmacologic therapy, could be beneficial.<sup>67</sup>

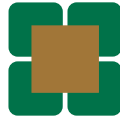
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# Extraesophageal symptoms of GERD

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.

**G**astroesophageal 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),<sup>1</sup> 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-

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.<sup>2</sup>

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.<sup>3</sup> A number of differences have been described between extraesophageal manifestations and classic GERD manifestations with regard to symptoms, pathophysiology, evaluation, and treatment (Table 2).<sup>4</sup> 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

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**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

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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.<sup>5</sup>

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 ( $P < 0.05$ ).<sup>5</sup>

Among respondents with noncardiac chest pain,

**TABLE 2**  
General comparisons between esophageal and extraesophageal manifestations of GERD

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

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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.<sup>5</sup>

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).<sup>5</sup> 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.<sup>5</sup>

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  $\chi^2$  test for a 2×3 contingency table.

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patients with and without reflux esophagitis, El-Serag and Sonnenberg<sup>6</sup> 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**).<sup>6</sup> 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**).<sup>6</sup>

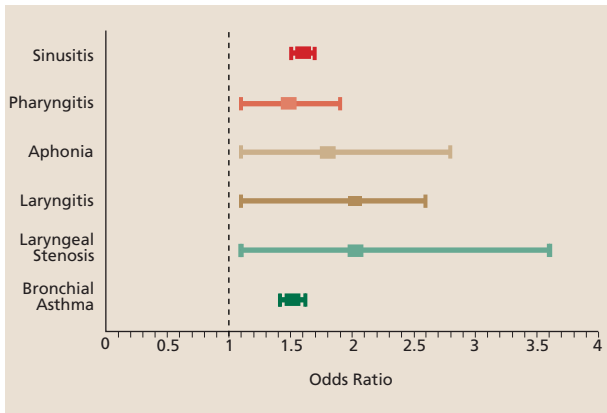
The most common diagnosis in both the case and the control populations was pneumonia, followed by chronic bronchitis, chronic obstructive pulmonary disease, and bronchial asthma. Much less frequently diagnosed than pulmonary diseases were sinus, pharyngeal, and laryngeal disorders. In this study, as 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.<sup>6</sup>

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,<sup>2</sup> in 78% of patients with laryngeal stenosis,<sup>2</sup> in 70% to 80% of patients with asthma,<sup>7</sup> and in 20% of patients with chronic cough.<sup>8</sup> Endoscopic esophagitis has been found in 30% to 40% of patients with asthma and in approximately 20% of those with laryngitis.<sup>9,10</sup>

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.<sup>11</sup> 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.

**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.<sup>3</sup>

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.<sup>12</sup>

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.<sup>1</sup> It is therefore not surprising that they also share a common neural innervation via the vagus nerve.<sup>1</sup> Acidification of the distal esophagus can stimulate acid-sensitive receptors that could conceivably pro-

**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.

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duce noncardiac chest pain or interact with pulmonary bronchi and other upper airway structures by a vagally mediated arc.<sup>12</sup>

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.<sup>3</sup>

**Defense mechanisms against extraesophageal symptoms.** Defense mechanisms protecting against extraesophageal complications of GERD have been organized into a four-tier system (Table 5).<sup>3</sup> 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.<sup>3</sup>

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

<p><b>TIER 1</b> <b>Gastrointestinal junctional structures</b></p> <ul style="list-style-type: none"> <li>• Lower esophageal sphincter</li> <li>• Crural diaphragm</li> <li>• Sling fibers</li> <li>• Phrenoesophageal ligament</li> </ul>	<p><b>TIER 2</b> <b>Esophageal body motor response</b></p> <ul style="list-style-type: none"> <li>• Primary/secondary peristalsis</li> <li>• Esophageal body tone</li> <li>• Acid neutralization by swallowed saliva</li> </ul>
<p><b>TIER 3</b> <b>Upper esophageal sphincter (UES)</b></p>	<p><b>TIER 4</b> <b>Airway protective reflexes</b></p> <ul style="list-style-type: none"> <li>• Esophago-UES contractile reflex</li> <li>• Esophagoglottal and pharyngoglottal closure reflexes</li> <li>• Pharyngeal (second) swallow</li> </ul>

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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.<sup>3</sup>

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.<sup>12</sup> 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.<sup>3</sup> 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.<sup>3</sup>

Swallowing also helps to clear refluxate that does not breach the UES.<sup>12</sup> 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.<sup>3</sup>

## ■ BRONCHOPULMONARY SYMPTOMS

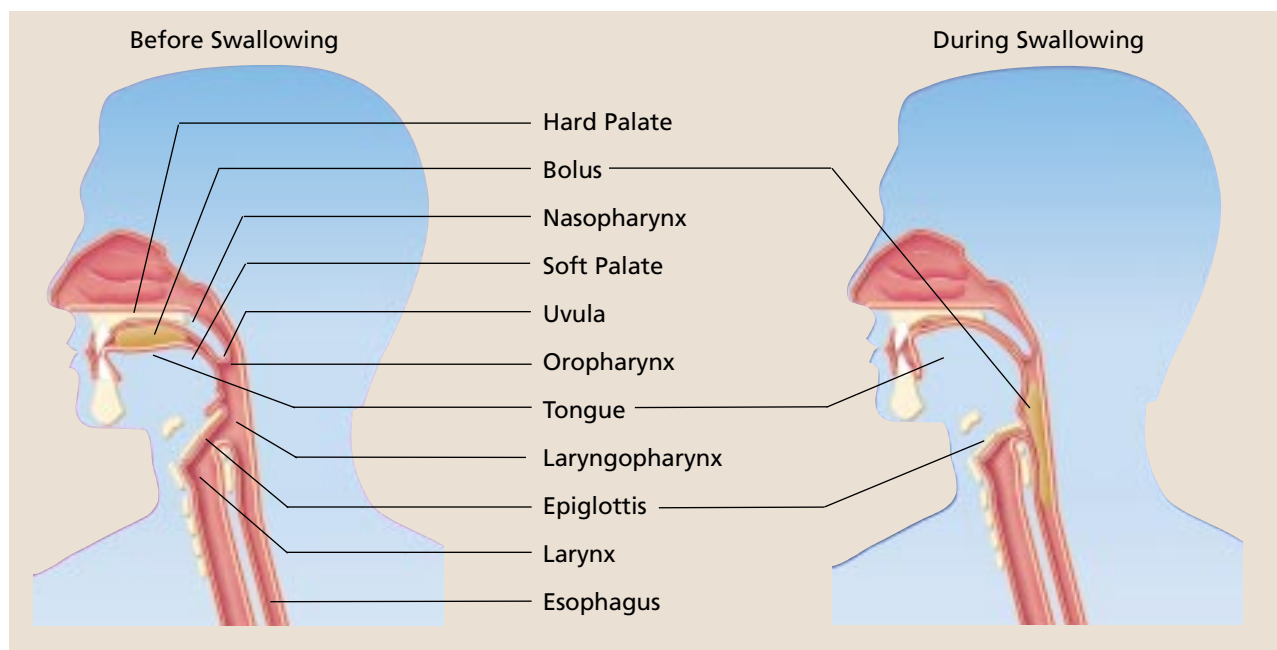
In recent decades, GERD has become increasingly recognized as a potential cause of bronchopulmonary symptoms. While most studies have focused on asthma, many other pulmonary disorders have been linked to GERD, including aspiration pneumonia, interstitial pulmonary fibrosis, chronic bronchitis, and bronchiectasis.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

### 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)<sup>13</sup> 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%.<sup>14</sup> 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.<sup>15</sup> Alternatively, some patients may have clinically silent GERD, especially in the context of difficult-to-treat asthma.<sup>8</sup>

A high degree of esophageal dysfunction has also been reported among patients with asthma, including esophageal dysmotility, LES hypotension, and a positive Bernstein test.<sup>16</sup> 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%.<sup>17</sup> 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.<sup>7</sup>

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.<sup>18</sup>

**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.<sup>1</sup> 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.<sup>1</sup> Both mechanisms might be active in some patients.<sup>18</sup> Furthermore, both involve the vagus nerve and are blunted by vagotomy.

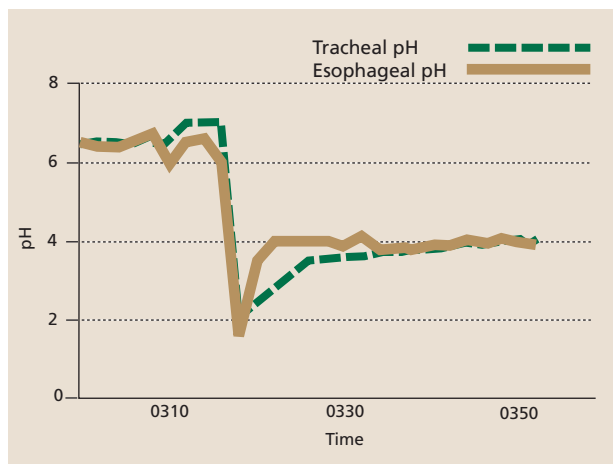
According to the *reflex* theory, stimulation of acid-sensitive receptors by esophageal acid activates a vagal response from the esophagus to the lung, which causes bronchoconstriction. Bronchoconstriction may, in fact, occur in all individuals as a normal protective mechanism in response to intraesophageal acid perfusion.<sup>19</sup> 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.<sup>1</sup> It is well known that mechanical stimulation of the upper airway or trachea can cause airway resistance.<sup>18</sup> Bronchoconstriction in response to esophageal acidification has been demonstrated in both animal studies<sup>20</sup> and human studies.<sup>21</sup> In animals, acid instilled into the trachea predictably increased airway resistance three to four times.<sup>20</sup>

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**).<sup>22</sup> 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.<sup>23</sup> 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.<sup>1</sup> 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.<sup>7</sup>

**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).<sup>1</sup> 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.<sup>1</sup>

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.<sup>1</sup> Gastroesophageal scintigraphy has a high specificity, but it also has a low sensitivity, which limits its usefulness in adults.<sup>1</sup>

Irwin and colleagues<sup>8</sup> found that they could usu-

**TABLE 6**  
Clinical clues and tests used in the diagnosis of GERD-associated asthma<sup>1</sup>

#### 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<sub>2</sub>-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.<sup>8</sup>

**Treatment.** With regard to medical therapy, studies using proton pump inhibitors (PPIs) have had more encouraging results than those using antacids or histamine<sub>2</sub>-receptor antagonists. The latter have yielded inconsistent effects on asthma symptoms and peak expiratory flow rates. A recent study<sup>23</sup> 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

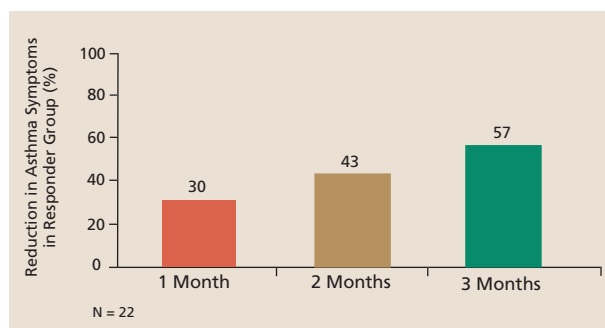
regurgitation or excessive proximal esophageal acid reflux. At least one third of patients needed 40 mg or more of omeprazole daily.

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<sup>24</sup> 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.<sup>1</sup> In a combined analysis of 10 trials, 80% of patients experienced asthma improvement, more than 50% of whom required no further asthma therapy.<sup>18</sup> 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.<sup>25,26</sup>

Field and colleagues<sup>27</sup> 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**<sup>28</sup> 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



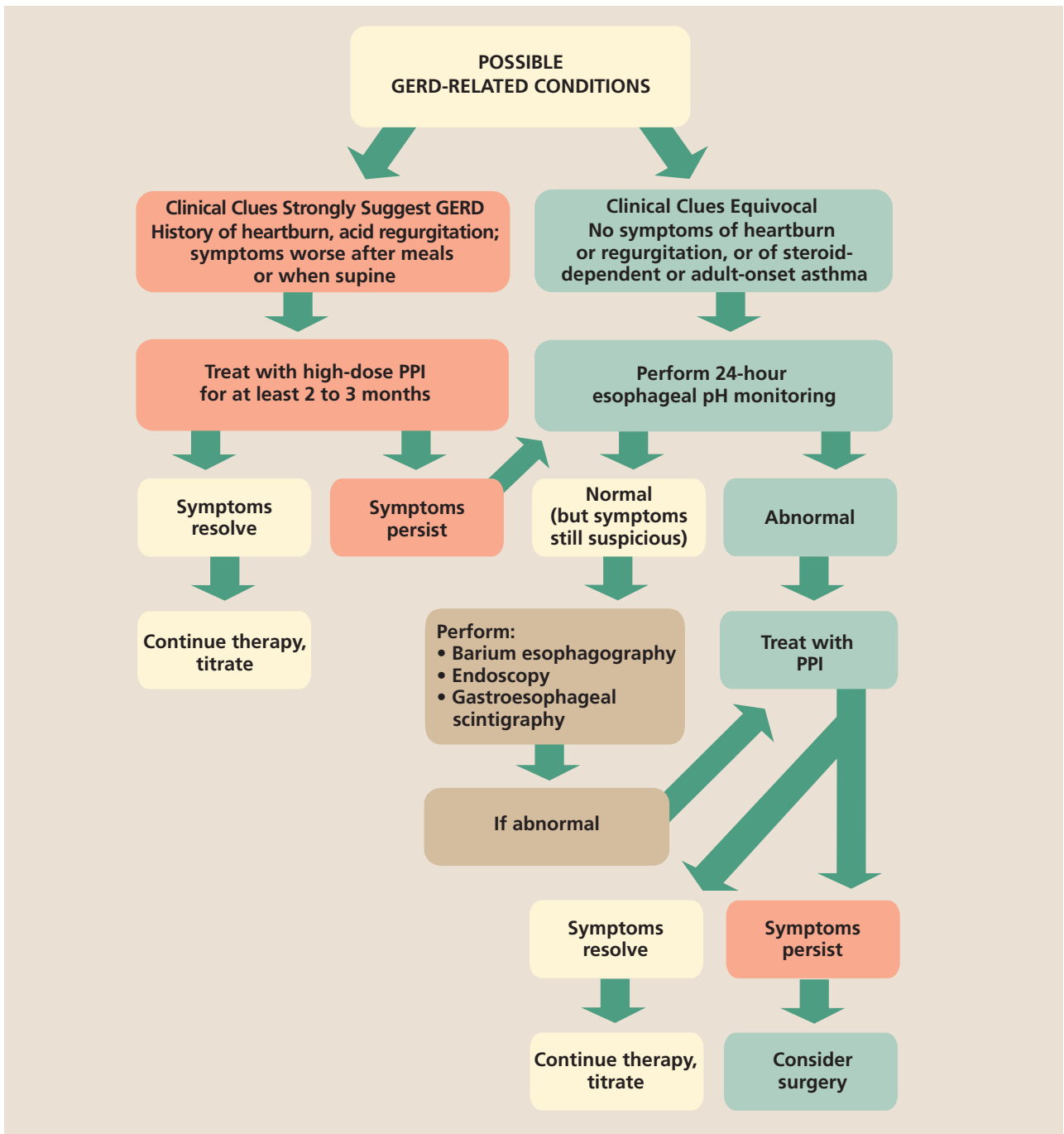
**FIGURE 4.** Reductions in asthma symptoms following treatment with omeprazole.<sup>23</sup>

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.<sup>29</sup> 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.<sup>30,31</sup> 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.<sup>32</sup>

**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.<sup>33</sup>

**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<sup>34</sup> 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.<sup>35</sup>

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.<sup>36</sup>

## ■ LARYNGOPHARYNGEAL SYMPTOMS

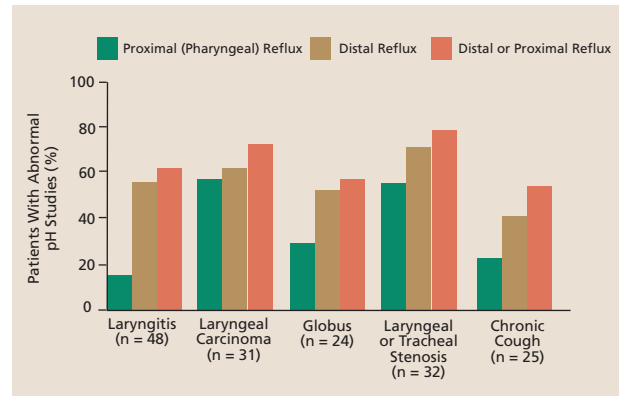
GERD has been identified as a primary etiologic factor in 10% to 20% of cases of persistent cough, in up to 80% of patients with difficult-to-manage hoarseness, in 25% to 50% of patients with globus sensation, and in a small but definite group of patients with laryngeal cancer.<sup>37,38</sup> The relationship 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.<sup>1</sup> 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.<sup>2</sup>

The neuroanatomic proximity of the larynx to the proximal esophagus makes it particularly vulnerable to GERD.<sup>39</sup> 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.<sup>40</sup>

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).<sup>2,28</sup>

### 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.<sup>38</sup> 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.<sup>2</sup>



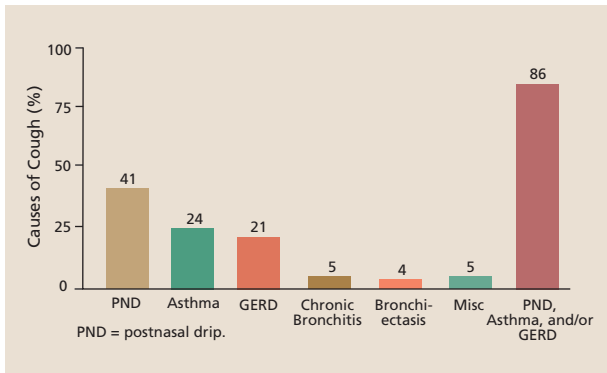
**FIGURE 6.** Results of proximal and distal esophageal pH monitoring among patients with suspected GERD and extraesophageal symptoms. Reprinted from reference 28 with permission.

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.<sup>1</sup> 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.<sup>28,41</sup>

### 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.<sup>42</sup> 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.<sup>1</sup> (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.<sup>2</sup>

**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.

among whom acid reflux was found in 55% to 79% of cases.<sup>40</sup>

**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<sup>43</sup> 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).<sup>14</sup>

**Globus sensation.** Globus sensation may be associated with GERD in 25% to 50% of cases.<sup>40</sup> 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.<sup>40</sup>

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).<sup>1</sup> Paradoxically, overt esophagitis is absent among most affected patients. Taking into account the available data, Wong and colleagues<sup>42</sup> have devised a suggested algorithm for the diagnosis of suspected reflux laryngitis (Figure 9). The first step is to rule out other



**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.

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).<sup>44</sup> 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.<sup>45,46</sup> The “step-up” approach to GERD, however, has been supplanted by an emphasis on initial PPI therapy in most centers. Wong and colleagues<sup>42</sup> 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%.<sup>42</sup> 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.<sup>42</sup>

**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.<sup>47</sup>

## ■ 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.<sup>48</sup>

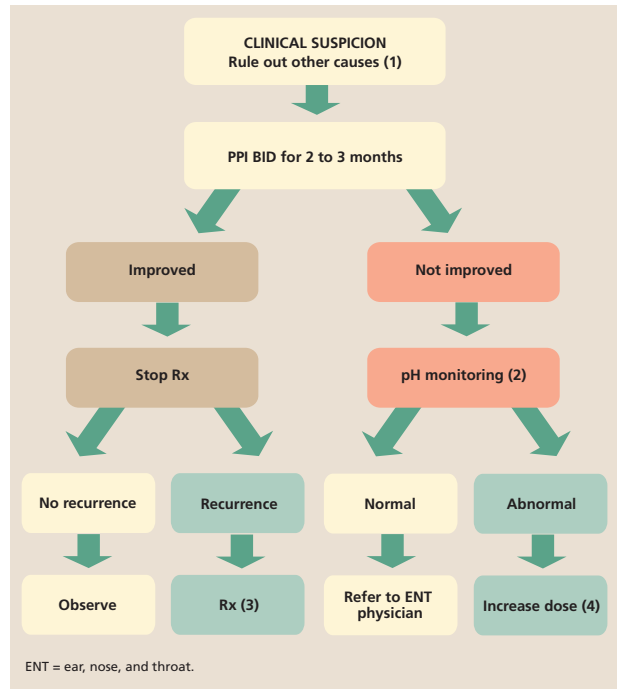
A number of studies have evaluated the relationship between GERD episodes and the loss of tooth structure due to dental erosion. As seen in a cross-sectional study evaluating loss of tooth structure as measured by the Tooth Wear Index (TWI), adults diagnosed with GERD had significantly higher TWI scores compared with controls ( $P = 0.004$ ).<sup>49</sup> 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.<sup>50</sup>

■ 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

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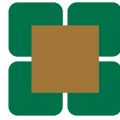


**FIGURE 9.** Algorithm for the evaluation and treatment of hoarseness. (1) ENT evaluation should be done early in the illness. (2) Consider stopping therapy if there is low suspicion of reflux, or consider continuing therapy if there is high suspicion of reflux; use gastric probe to document acid suppression; 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 histamine<sub>2</sub>-receptor antagonist; for medical treatment failure, cautiously consider surgery. Reprinted from reference 42 with permission from the American College of Gastroenterology.

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.

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# The continuum of GERD complications

M. BRIAN FENNERTY, MD

## ■ ABSTRACT

Complications of chronic gastroesophageal reflux disease (GERD) run the gamut from erosive esophagitis to esophageal cancer, but all are linked to repeated exposure of the esophagus to caustic gastric and duodenal acid. Progression from one complication to another is not clearly established across the GERD continuum, although there is a clear progression from the serious complication of Barrett's esophagus to esophageal adenocarcinoma. This review examines the range of complications that can arise from chronic GERD, underscoring the need to view heartburn as a symptom of a potentially serious condition.

It is easy to understand how frequent heartburn and regurgitation can reduce quality of life. Gastroesophageal reflux disease (GERD) symptoms cause discomfort for the sufferer and, in the case of nocturnal reflux, can disturb sleep. For some people who experience mild or moderate GERD, the condition can remain fairly benign and limited to occasional discomfort. For others, GERD symptoms can be signs of serious health problems.

The complications of GERD, from erosions in the esophageal epithelium to esophageal adenocarcinoma, are linked to repeated esophageal exposure to caustic gastric and duodenal juices. Frequent and severe heartburn is often, but not always, an indication of esophageal damage, but damage can occur even in those with mild symptoms or even in the absence of GERD symptoms.

This article explores the complications that arise

from chronic GERD. These include erosive esophagitis, esophageal ulcers, esophageal strictures, and Barrett's esophagus. In addition, GERD complications and hiatal hernia frequently occur as comorbid conditions.<sup>1</sup> Erosive esophagitis is the single most common GERD complication, whereas strictures and ulcers occur more often in combination with other conditions or with each other.

In the case of the more serious GERD complications, namely, Barrett's esophagus and esophageal adenocarcinoma, there is a clear progression from the former to the latter. Indeed, Barrett's esophagus is the only recognized risk factor for esophageal adenocarcinoma.<sup>2</sup> Progression is not as clear, however, with other GERD complications. For example, Winters and colleagues<sup>3</sup> found that the prevalence of Barrett's esophagus was 36.3% (95% confidence interval [CI], 0.20 to 0.52) in patients with erosive esophagitis compared with 12.4% (95% CI, 0.06 to 0.18) in patients with GERD symptoms alone.

The following sections focus on the prevalence and pathology of GERD complications, as well as their appearance in the esophagus, diagnostic signs and symptoms, and other issues in their diagnosis.

## ■ REFLUX ESOPHAGITIS

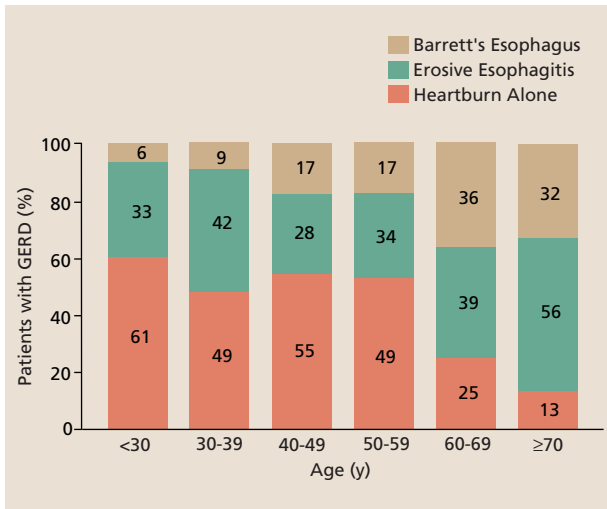
In patients with chronic GERD, the material refluxed into the esophagus can cause epithelial changes, marked by polymorphonuclear or mixed polymorphonuclear and round cell infiltration.<sup>4</sup> In some cases, these microscopic changes occur in an otherwise normal-appearing esophagus. Esophageal inflammation caused by GERD is called reflux esophagitis. For some patients with reflux esophagitis, erosions or mucosal breaks of varying severity can develop in the esophagus. Erosion of the esophageal mucosa, or erosive esophagitis, is a common complication of chronic GERD.

Erosive esophagitis, a visible manifestation of

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**FIGURE 1.** Proportions of GERD patients with heartburn, erosive esophagitis, and Barrett's esophagus according to age group. Reprinted from reference 8 with permission from the American College of Gastroenterology.

esophageal damage caused by refluxate, is considered by many to be synonymous with GERD itself.<sup>5</sup> Some clinicians use the term “nonerosive reflux disease” to denote patients with GERD symptoms who have no visible esophageal damage, and the term GERD to denote patients with visible esophageal damage caused by reflux. In fact, healing of erosive esophagitis was considered a primary end point in most early clinical trials of GERD therapy and continues to be an important measure of treatment efficacy. However, people with nonerosive reflux disease experience GERD symptoms that are as severe as the symptoms of patients with esophagitis, impairing quality of life to the same degree and requiring the same treatment as patients with esophagitis. This article will treat erosive esophagitis as a common GERD complication rather than a symptom.

Erosive esophagitis is difficult to predict clinically, as symptom duration, frequency, and severity are poor indicators of its presence.<sup>6</sup> Moreover, the connections between erosive esophagitis and more serious GERD complications, such as Barrett's esophagus and esophageal adenocarcinoma, are similarly problematic. This section discusses the prevalence, pathology, and endoscopic appearance of esophagitis; evidence of the lack of correlation between GERD symptoms and its presence; and the relationship of this condition with other, more severe GERD complications.

## Prevalence

The population prevalence of erosive esophagitis is difficult to assess. One study in China demonstrated a prevalence rate of 5%, whereas a study in Sweden showed a prevalence rate of approximately 2.4%. In the United States, two prevalence surveys based on physician contacts yielded a rate range of 0.7% to 1.2%.<sup>7</sup>

The only way to positively identify esophagitis is through endoscopy. Therefore, to assess the prevalence of esophagitis in the general population, all individuals would have to undergo this procedure. Usually, only patients who complain of GERD or other upper digestive symptoms undergo endoscopy, and attempts to determine erosive esophagitis prevalence rates for the general population based on studies conducted in patients with GERD symptoms may result in an overestimation of prevalence. In patients with chronic GERD, the prevalence of erosive esophagitis is estimated to be 20%, although some studies have demonstrated even higher rates.<sup>1</sup>

Whereas uncomplicated GERD tends to be more common in women, GERD complications are more common in men.<sup>1</sup> Age is also an important factor in complication prevalence. Collen and colleagues<sup>8</sup> investigated the relationship between age and GERD severity in 228 patients. The proportions of GERD patients aged less than 60 years with heartburn alone or with erosive esophagitis remained relatively consistent among 10-year age groups, averaging 54% (range, 49% to 61%) and 35% (range, 28% to 42%), respectively. However, among patients aged 60 years or older, the proportion of patients with heartburn alone decreased as the prevalence of erosive esophagitis and Barrett's esophagus increased (**Figure 1**). The prevalence of erosive esophagitis and Barrett's esophagus was significantly higher in GERD patients aged 60 years or older: 81%, compared with 47% in younger GERD patients ( $P = 0.000002$ ). Symptom severity, however, did not significantly differ among age groups. These data indicate that, although older patients may not experience more severe GERD symptoms than younger patients do, they may present with more severe GERD complications.

As with GERD in general, esophagitis is more common in whites compared with other ethnic groups.<sup>1</sup> However, there are indications that the prevalence of this complication has been underestimated in Asians or may be increasing. A recent study conducted in 464 Asian inhabitants of Taiwan

found that 14.5% of consecutive patients referred for endoscopy for GERD symptoms had erosive esophagitis.<sup>9</sup> The authors postulated that the increased use of endoscopy as a method of detection, instead of less accurate radiologic studies, might explain this higher-than-expected percentage. They also noted, however, that lifestyle changes in this population could underlie the observed increase in prevalence. This study confirmed a higher prevalence of erosive esophagitis in male versus female patients and in older versus younger patients in this Asian population.

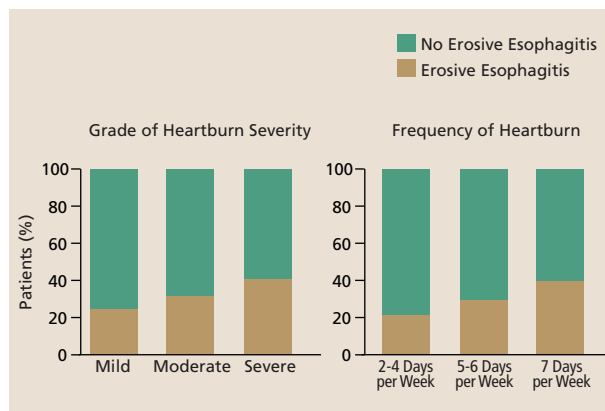
### Etiology and symptoms

In 1935, the idea was postulated that exposure to refluxed material could cause inflammation of and injury to the mucosa of the esophagus. For many years, researchers assumed that hiatal hernia was the main cause of reflux esophagitis. Currently, researchers believe that reflux-related esophagitis is caused by multiple factors and that lower esophageal sphincter pressure (LESP) and hiatal hernia are just two of the many factors in its development. Factors involved in the pathogenesis of reflux-related esophagitis include:

- Impaired esophageal clearance and neutralization mechanisms, which control the amount of time refluxed material remains in contact with esophageal mucosa
- Increased volume and causticity of material that is refluxed into the esophagus
- Impaired ability of the esophageal tissue to resist injury.

The contribution of each of these factors to the pathogenesis of reflux esophagitis varies from patient to patient. Thus, the presence of reflux esophagitis in the patient with GERD symptoms is difficult to predict.<sup>3</sup> Research has found that systemic sclerosis, which results in dysfunction of the LES, correlates with an increased risk of erosive esophagitis.<sup>1</sup> The use of nonsteroidal anti-inflammatory drugs has also been associated with an increased occurrence of this complication, possibly because these drugs seem to impair esophageal tissue resistance to injury by refluxate.<sup>1,6</sup>

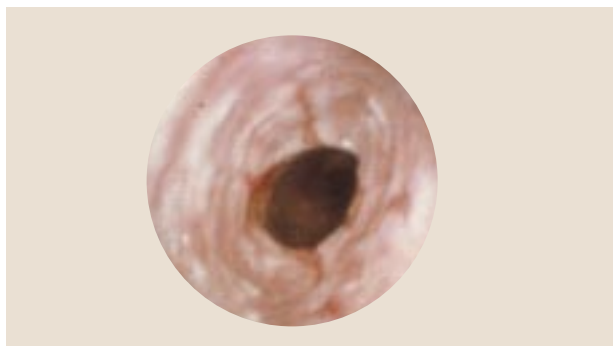
Material refluxed into the esophagus during sleep, when the person is supine, tends to remain in the esophagus for a longer time. Some investigators have postulated that patients with GERD who experience nocturnal reflux are at greater risk of developing esophagitis, because this complication is directly



**FIGURE 2.** Prevalence of erosive esophagitis in a study of 994 GERD patients presenting with varying degrees of heartburn severity and frequency. Reprinted from "Omeprazole 10 milligrams once daily, omeprazole 20 milligrams once daily, or ranitidine 150 milligrams twice daily, evaluated as initial therapy for the relief of symptoms of gastro-oesophageal reflux disease in general practice," by Venables TL, Newland RD, Patel AC, et al, from *Scand J Gastroenterol*, www.tandf.no/gastro, 1997, vol. 32, 965-973, by permission of Taylor & Francis AS.<sup>12</sup>

related to the time of esophageal exposure to caustic refluxed material. However, there is a stronger correlation between the severity of esophagitis and the total time of esophageal exposure to the refluxate than there is between the severity of the esophagitis and the body position at the time of the reflux episode.<sup>10</sup> A study by Orr and colleagues<sup>11</sup> demonstrated that patients with erosive esophagitis had a greater degree of acid reflux and a greater percentage of esophageal acid contact time in both upright and supine positions than did patients without erosive esophagitis. The authors did find that the number of reflux episodes experienced in a recumbent position lasting more than 5 minutes also had predictive value for the presence of esophagitis.

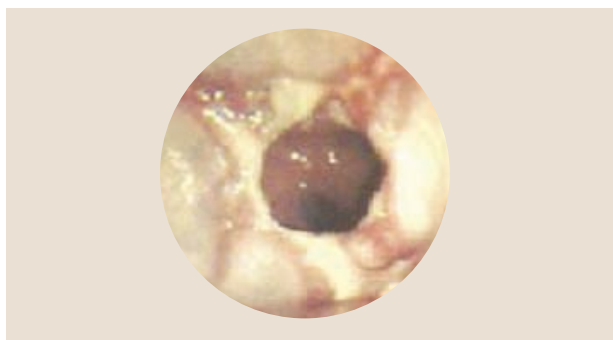
Patients who report having no symptoms or mild symptoms can still demonstrate severe erosive esophagitis on endoscopy. Conversely, patients with severe GERD symptoms often have nonerosive reflux disease. The correlation between the frequency, severity, and duration of symptoms and erosive esophagitis varies from study to study. Venables and colleagues,<sup>12</sup> in a study of 994 patients with chronic GERD symptoms, found that 32% had erosive esophagitis. They noted that, even though most of the study participants did not have erosive esophagitis, the majority indicated that their heartburn was severe enough to disrupt their daily activities. Furthermore, daily heartburn was reported by 49%



**FIGURE 3.** Endoscopic view of **isolated erosions** of the esophageal epithelium.



**FIGURE 4.** Endoscopic view of **confluent erosions** of the esophageal epithelium.



**FIGURE 5.** Endoscopic view of **circumferential erosions** of the esophageal epithelium.

of the participants. **Figure 2** illustrates the relationship of heartburn severity and frequency with the presence of erosive esophagitis in this study. The researchers concluded that the severity or frequency of chronic GERD symptoms is unreliable in predicting the presence of underlying esophagitis.

Voutilainen and colleagues<sup>6</sup> reached this same conclusion in their study of 1,128 patients with GERD referred for endoscopy. They found that the GERD symptoms of heartburn and/or regurgitation had a high specificity (0.87; 95% CI, 0.85 to 0.89)

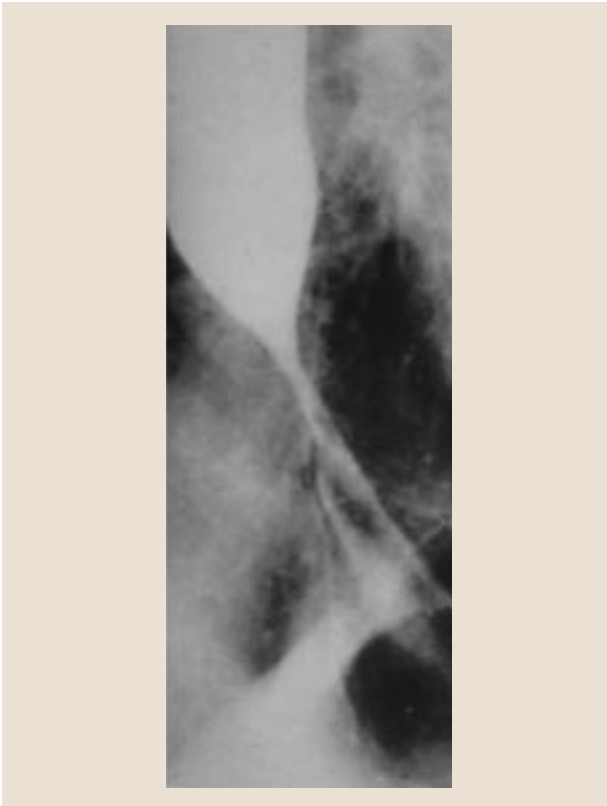
and negative predictive value (0.90; 95% CI, 0.88 to 0.92), but a low sensitivity (0.44; 95% CI, 0.37 to 0.52) and positive predictive value (0.37; 95% CI, 0.31 to 0.44) for the presence of esophagitis. They also found that the majority of patients aged less than 50 years with GERD symptoms did not have esophagitis.

Other studies have found correlations between the severity of specific symptoms and the presence and severity of erosive esophagitis. Lundell and colleagues<sup>13</sup> pooled results from two large studies involving 716 patients (538 in the first, 178 in the second) with GERD symptoms of varying severity. They found that heartburn severity correlated with esophagitis severity ( $P < 0.01$  in the first study;  $P < 0.001$  in the second). In a trial designed to evaluate the causes of Barrett's esophagus, Lieberman and colleagues<sup>14</sup> studied the correlation between the occurrence of GERD symptoms and erosive esophagitis. Of 662 patients with GERD symptoms who underwent endoscopy, 39% had no esophageal inflammation, 44% had erosive esophagitis, and 17% had probable Barrett's esophagus. Sixty-one percent of patients reported daily GERD symptoms, and 39% reported intermittent symptoms of lesser frequency. In this study, the presence of daily GERD symptoms was associated with a greater likelihood of erosive esophagitis ( $P < 0.001$ ), but symptom duration was not associated with an increased likelihood. Forty-seven percent of patients who experienced GERD symptoms for less than 1 year had erosive esophagitis, compared with 42% of those who had GERD symptoms for more than 10 years.

### Appearance

Erosions in the esophageal mucosa appear as areas of "denuded" epithelium. These erosions are classified into three categories<sup>5</sup> to describe the extent of esophageal damage:

- **Isolated erosions.** These are small and unconnected erosions that occur only on the peaks of the mucosal folds (**Figure 3**).
- **Confluent erosions.** These are larger breaks in the esophageal mucosa that occur on the peaks of folds and also between folds. The injury to the esophageal mucosa is more extensive, but it does not encircle the entire esophagus (**Figure 4**).
- **Circumferential erosions.** In this case, the mucosal injury encompasses the entire circumference of the esophagus. Circumferential erosions indicate the most severe form of erosive esophagi-



**FIGURE 6.** Barium esophagram showing a stricture.

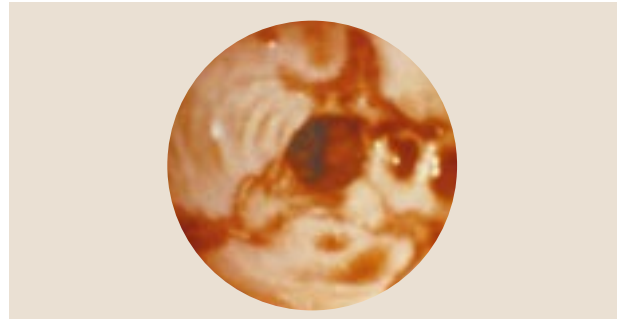
tis. Esophageal injury to this extent often occurs with other complications, such as ulcer, stricture, and Barrett's esophagus (**Figure 5**).

Several classification systems of erosive esophagitis based on the extent of mucosal injury have been developed. The most common methods of classification are discussed elsewhere.<sup>15</sup>

### Uncertain role in disease progression

In the past, practice guidelines recommended aggressive treatment of mild erosive esophagitis to prevent progression to more severe forms. A high prevalence of concurrent GERD complications in patients with esophagitis indicates a close pathophysiologic relationship. However, studies have not shown a definite progression. Instead, patients seem to present with either severe or mild forms and then maintain this phenotypic expression of GERD.

For example, a study conducted by El-Serag and Sonnenberg<sup>16</sup> in US veterans found that 39% of patients were initially diagnosed with esophageal ulcer, a more severe GERD complication, whereas only 22% were diagnosed with esophagitis. In a subsequent study,<sup>17</sup> also conducted in US veterans,



**FIGURE 7.** Endoscopic view of an esophageal stricture and ulceration.

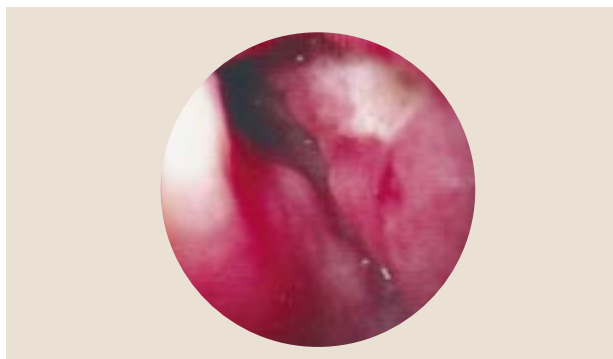
these researchers monitored 29,500 patients with erosive esophagitis but without further complications (ulcer or stricture) and 5,100 patients with esophagitis as well as ulcers or strictures. After 4 years, no patient in the former group had developed ulcers or strictures, whereas 80% of the latter group still had esophagitis and ulcer or stricture.

These findings contradict the logic that repeated and prolonged esophageal exposure to acid reflux, the culprit of initial esophageal injury, causes disease progression. One explanation could be that the most severe grade of esophagitis is reached at onset of the disease.<sup>1</sup> It will be interesting to see how further research into the pathophysiology of this complication resolves this issue.

### ■ ESOPHAGEAL ULCERS AND STRICTURES

Esophageal ulcers and strictures are more-severe GERD complications. The above-mentioned study in US veterans by El-Serag and Sonnenberg<sup>16</sup> found that any GERD complication was 10 times more likely to occur with another GERD complication than without. This was true most often with esophageal strictures and ulcers. Strictures rarely occurred without other GERD complications, and ulcers never occurred as the sole complication. Given these observations, ulcers and strictures behave more like "compound complications" than isolated GERD complications, and both represent the most severe forms of esophagitis. However, this does not implicate or prove a progression to severe esophagitis from milder forms.

**Figure 6** shows a barium esophagram of a stricture, whereas **Figure 7** shows an esophageal stricture, a narrowing of the esophageal lumen,<sup>18</sup> and ulceration. Ulcers are deeper injuries to the esophageal mucosa than the erosions of esophagitis (**Figure 8**) and can cause bleeding in the esophagus.



**FIGURE 8.** Endoscopic view of an esophageal ulcer.

Unlike gastric or duodenal ulcers, esophageal ulcers are not linked to *Helicobacter pylori* infection but are secondary to acid reflux. The prevalence of strictures and ulcers is low in patients with GERD as well as in the general population. This section explores the prevalence, pathology, and symptoms of these two GERD complications.

### Strictures

**Prevalence.** The majority (70% to 80%) of strictures that occur in the distal esophagus are caused by GERD.<sup>18,19</sup> Estimates of the prevalence of strictures in patients with untreated erosive esophagitis range from 7% to 23%.<sup>19</sup> **Table 1** presents the findings of two surveys measuring the prevalence rates of esophagitis, ulcer, and stricture in the general population. The estimated prevalence of erosive esophagitis ranges from 0.7% to 1.2%. In comparison, the prevalence of strictures ranges from 0.07% to 0.12%. Strictures are most prevalent in whites and in men, and prevalence increases with age.<sup>7</sup>

**Etiology and pathology.** The presence of GERD is the most important etiologic factor for an esophageal stricture. Although decreased LES is common in patients with uncomplicated GERD or less severe GERD complications, patients with esophageal strictures tend to have a further decrease in LES. Furthermore, patients with strictures tend to demonstrate more frequent perturbations in motility, such as ineffective peristalsis, which prolongs the duration of esophageal acid exposure. Bile, trypsin, and pancreatic enzymes also play a role in stricture development, and studies have found that strictures are more common in patients with significant alkaline esophageal exposure. Hiatal hernia, found in 85% of patients with esophageal stricture, is another contributing factor to stricture development.

Esophageal strictures form as a result of repeated

**TABLE 1**

Rates of esophagitis, esophageal ulcers, and esophageal strictures from all physician contacts in the United States, based on two 1985 surveys<sup>7</sup>

Survey	Rates per 100,000 population		
	Esophagitis	Ulcer	Stricture
National Disease and Therapeutic Index	1,246	46	125
National Ambulatory Medical Care Survey	797	18	74

damage to the esophageal epithelium, leading to mucosal repair with fibrosis. Initially, inflammation causes the lumen of the esophagus to narrow. During healing, fibrosis occurs as the esophagus builds up type III collagen and scar tissue. Esophageal narrowing caused by scar tissue is irreversible. As a GERD complication, strictures occur most often in the distal esophagus, almost always forming at the squamocolumnar junction. They are usually less than 1 cm long. Esophageal strictures in conjunction with Barrett's esophagus often occur in more proximal locations, as the squamocolumnar junction is displaced to a more proximal area of the tubular esophagus.<sup>19</sup>

**Symptoms.** Dysphagia is the most common symptom of esophageal strictures, although some patients may also present with odynophagia.<sup>18</sup> Patients often report a feeling of food sticking in the throat, even though the stricture is located in the distal esophagus. Patients presenting with dysphagia with liquids either have a narrow stricture or may have a motility disorder. It is difficult to extrapolate the severity of a stricture from dysphagia symptoms, because patients have usually already altered their diet as a result of the stricture. Therefore, patients should be questioned about the kinds of foods with which they experience dysphagia.<sup>19</sup>

In addition to dysphagia and odynophagia, patients with esophageal stricture can present with a variety of esophageal and extraesophageal symptoms. Most patients with esophageal strictures experience heartburn, although it is absent in approximately 25%.<sup>18</sup> Patients with heartburn may report a steady decline in the severity of this symptom because worsening of the stricture may reduce the amount of material refluxed into the esophagus. Extraesophageal

ageal symptoms include chronic cough and asthma. These symptoms are caused by aspiration and are not typical. Food impaction or esophagitis may cause chest pain in patients with strictures. Weight loss is not common, because patients tend to change their diets to accommodate strictures.<sup>19</sup>

### Esophageal ulcers

As shown in **Table 1**, the prevalence of esophageal ulcers in the general population is very low, ranging from 0.018% to 0.046%. Like strictures, GERD-related ulcers increase in prevalence with age and are more prevalent in whites than in other racial groups.<sup>18</sup>

At endoscopy, ulcers appear as deep mucosal injuries and may occasionally bleed. They are not a common complication but may be seen in patients with Barrett's esophagus. In a study conducted in 78 patients with Barrett's esophagus, Murphy and colleagues<sup>20</sup> detected discrete esophageal ulcers in 36 patients over an average 3.3 years of follow-up (range, 1 year to 11 years). The majority of these ulcers were located in the distal esophagus, and 86% occurred within 3 cm of the esophagogastric junction. Gastrointestinal bleeding was present in 24% of patients, and in 76% of these patients, the bleeding was caused by the Barrett's ulcer.

### ■ BARRETT'S ESOPHAGUS

The lining of a normal esophagus is composed of a stratified squamous epithelium, in contrast to the columnar cell-lined epithelium found in the stomach and intestine. Barrett's esophagus is characterized by the presence of a metaplastic columnar epithelium in the tubular esophagus. The cellular changes of Barrett's esophagus appear to develop as a result of disordered repair following damage by caustic material refluxed from the stomach.<sup>21</sup>

In patients with Barrett's esophagus, GERD is often severe and may be complicated by esophageal ulcer, hemorrhage, and stricture. Although relatively few patients with GERD develop Barrett's esophagus, this condition merits attention because it is a major risk factor for the development of esophageal adenocarcinoma. This section discusses the pathophysiology, prevalence, and diagnosis of Barrett's esophagus, as well as its progression to dysplasia and adenocarcinoma.

### Pathophysiology

Barrett's esophagus is defined as the replacement of the normal squamous epithelium of the esophagus

**TABLE 2**  
Endoscopic findings from the GORGE study:  
Relation between erosive esophagitis, duration of GERD symptoms, and probable Barrett's esophagus

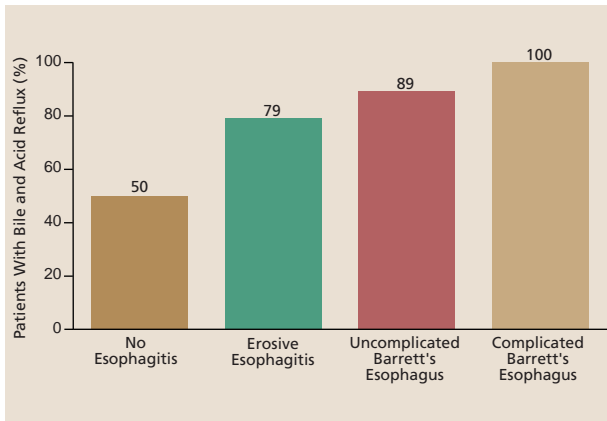
Duration of symptoms (yr)	Number of pts	Pts with esophagitis	Pts with probable Barrett's esophagus
< 1	127	47%	4%
1–5	236	53%	11%
5–10	81	48%	17%
> 10	140	42%	21%

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with a metaplastic columnar epithelium. The exact mechanism of this process is not known. However, evidence has linked Barrett's esophagus to repeated and prolonged exposure of the esophageal mucosa to gastric material refluxed into the esophagus. Pluripotential stem cells then appear to differentiate into columnar epithelium during the repair process.<sup>22</sup> Therefore, exposure of the esophagus to acid reflux seems to both precipitate and facilitate development of the metaplastic columnar epithelium.<sup>21</sup>

This process would seem to suggest that the presence of erosive esophagitis is a risk factor for Barrett's esophagus. Csendes and colleagues,<sup>23</sup> in a study of 376 patients with GERD symptoms, found that erosive esophagitis occurred in 64% of participants with short-segment Barrett's esophagus and in 80% of those with traditionally defined, or long-segment, Barrett's esophagus. However, studies investigating a progressive relationship between erosive esophagitis and Barrett's esophagus have not been able to establish a clear link. In the GORGE study<sup>14</sup> of 662 patients with GERD symptoms who underwent endoscopic examination, a history of erosive esophagitis was not found to be an independent risk factor for Barrett's esophagus. Of patients who experienced GERD symptoms for less than 1 year, 47% had erosive esophagitis, although only 4% of this group had probable Barrett's esophagus on endoscopy. However, among patients who experienced GERD symptoms for more than 10 years, only 42% had erosive esophagitis on endoscopy, but 21% had probable Barrett's esophagus (**Table 2**).

Although patients with Barrett's esophagus have

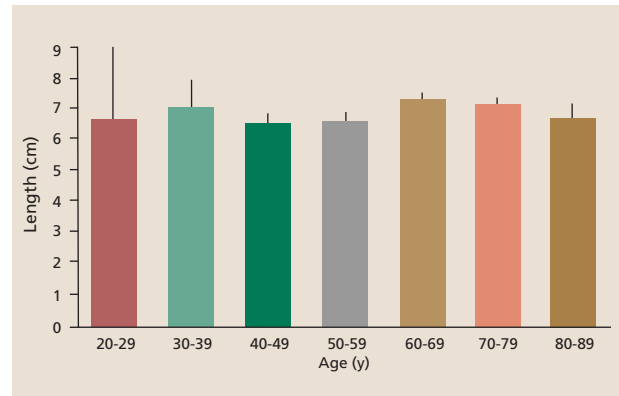


**FIGURE 9.** Prevalence of gastric acid reflux combined with duodenogastric reflux in patients with GERD, by degree of GERD severity. Reprinted from reference 26 with permission from the American Gastroenterological Association.

increased esophageal acid exposure, hypersecretion of gastric acid does not seem to be related to Barrett's esophagus. Studies that compared patients with Barrett's esophagus to patients with erosive esophagitis alone found no difference in several acid output measures (basal acid output, gastrin-stimulated peak output, and pepsin output).<sup>24</sup>

The composition of the refluxed material in patients with Barrett's esophagus also has been investigated, particularly the role of duodenal secretions in esophageal injury. Some researchers have postulated that pancreatic enzymes, bile salts, and lysolecithin are important in the development of intestinal metaplasia and esophageal adenocarcinoma. When acid is present, damaging agents of bile salts are potentiated, and the salts are better able to penetrate into the esophageal mucosa.<sup>25</sup>

Vaezi and Richter<sup>26</sup> measured esophageal acid and bile exposure in patients with GERD ( $n = 30$ ), patients with Barrett's esophagus ( $n = 20$ ), and 20 control subjects. The refluxed material of most patients with GERD comprised both acid and bile (Figure 9). The percentage of time that esophageal pH was less than 4 and that the bilirubin level was 0.14 or greater increased gradually with increasing disease severity, as did fasting gastric bile acid concentrations. Most episodes of duodenogastric reflux (79% to 91%) occurred when the pH of the esophagus was less than 4. Also, there was a significant correlation between the percentage of time that esophageal pH was less than 4 and the percentage of time that the bilirubin absorbance level was 0.14 or greater ( $P < 0.01$ ).<sup>26</sup>



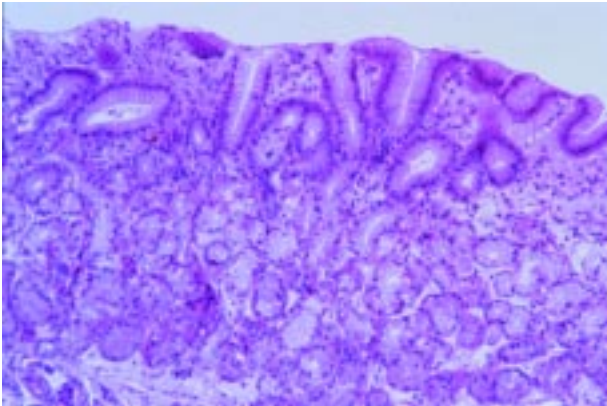
**FIGURE 10.** Mean length of segments of Barrett's esophagus among different patient age groups. Lines indicate standard error of the mean. Reprinted from reference 27 with permission from the American Gastroenterological Association.

Although Barrett's esophagus is essentially an acid-reflux-facilitated process of epithelial damage followed by abnormal cellular repair, the condition is rarely progressive. Instead, it tends to develop to its fullest extent early on. The reason for this lack of progression is not known.<sup>21</sup> In a study involving 377 patients diagnosed with Barrett's esophagus from 1976 to 1989, Cameron and Lomboy<sup>27</sup> found that the length of the segment of Barrett's esophagus did not vary significantly among age groups (Figure 10). Barrett's was defined as extension of the columnar epithelium at least 3 cm from the distal esophagus. Also, in 101 patients who underwent follow-up endoscopic examinations (average follow-up interval, 3.2 years), no significant progression of Barrett's esophagus was noted.

### Histology

The types of columnar epithelium found in the esophagus fall into three categories<sup>21,22</sup>:

- **Gastric fundic-type epithelium**, which is lined with pits composed of mucus-secreting cells. The glandular layer underneath is composed of chief and parietal cells (Figure 11).
- **Gastric junctional-type (or cardiac-type) epithelium**, which has a foveolar surface. There are no parietal cells, and the glands are composed almost entirely of mucus-secreting cells (Figure 12).
- **Specialized intestinal metaplasia (or specialized columnar epithelium)**, which is required for a diagnosis of Barrett's esophagus and is the only one of these three types of columnar epithelium linked to an increased risk of esophageal adenocarcinoma. It has a villiform surface and mucus-



**FIGURE 11.** Fundic-type epithelium, lined with pits composed of mucus-secreting cells. The glandular layer underneath consists of chief and parietal cells.

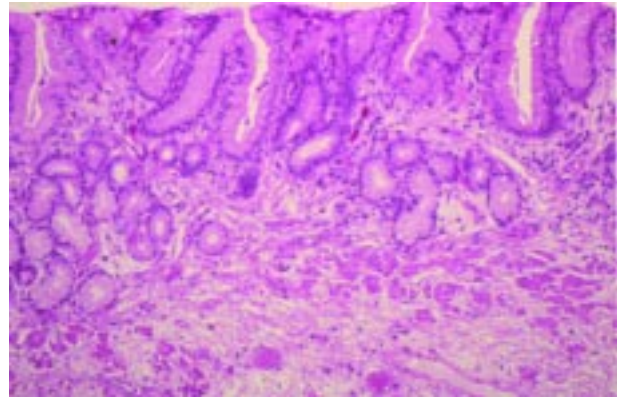
secreting goblet and columnar cells lining intestinal-type crypts. Chief and parietal cells are usually absent (**Figure 13**).

The different types of epithelia occurring in Barrett's esophagus look the same on endoscopy, and histologic examination must be performed to differentiate them. Although gastric fundic-type and junctional-type epithelia are sometimes histologically indistinguishable from normal gastric mucosa, specialized intestinal metaplasia is easily identified.<sup>21</sup>

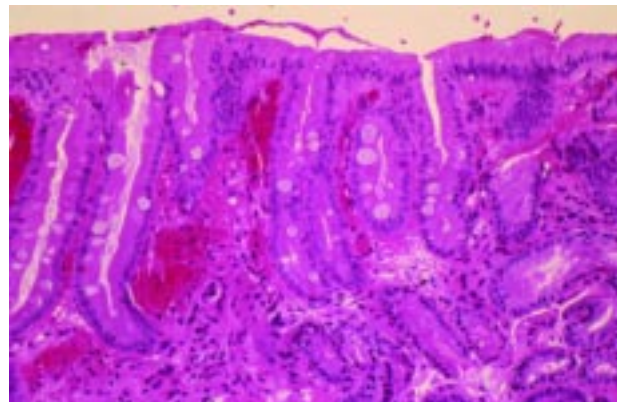
### Prevalence

The overall prevalence of Barrett's esophagus is unknown. Its estimated prevalence in the general population is 0.41% to 0.89%,<sup>24</sup> although studies in specific populations have shown higher rates.

Cameron and colleagues<sup>28</sup> conducted a population-based study in Olmsted County, Minn., comparing the prevalence of clinically detected Barrett's esophagus with autopsy findings. The study analyzed the number of county residents who had been clinically diagnosed with Barrett's esophagus from 1968 to 1986. The researchers found that, as of January 1, 1987, the age-adjusted and sex-adjusted prevalence rate was 22.6 cases of Barrett's per 100,000 individuals in the population (95% CI, 11.7 to 33.6 cases). The researchers then prospectively reviewed the autopsy records of Olmsted County residents over an 18-month period ending in September 1987. Using the same diagnostic criteria, the autopsy data yielded a prevalence rate of 376 cases of Barrett's per 100,000 residents (95% CI, 95 to 967 cases)—a 21-fold increase (95% CI, 5 to 54). These findings suggest that, for every case of



**FIGURE 12.** Junctional-type or cardiac-type epithelium, with its characteristic foveolar surface. No parietal cells are present, and the glands consist almost entirely of mucus-secreting cells.



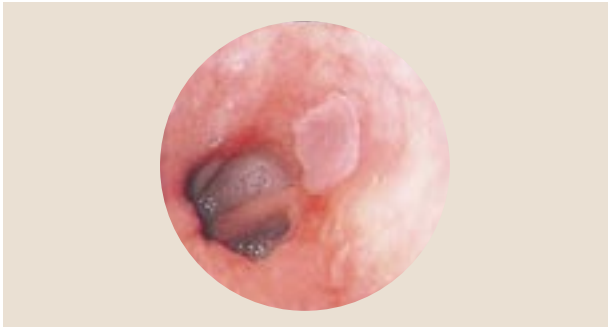
**FIGURE 13.** Specialized intestinal metaplasia, characterized by a villiform surface and mucus-secreting goblet and columnar cells lining intestinal-type crypts. This is the only type of columnar epithelium linked to an increased risk of esophageal adenocarcinoma.

Barrett's esophagus that is detected antemortem, 20 cases are not detected.

Differences in the parameters used to diagnose Barrett's esophagus also lead to changes in prevalence estimates. In a study of 650 adults in Japan, Azuma and colleagues<sup>29</sup> found that when the traditional diagnostic measures were used (segments of columnar epithelium 3 cm or greater in length), the prevalence rate of Barrett's esophagus was 0.62%. However, when they included the prevalence of short-segment Barrett's esophagus (segments less than 3 cm), the rate was 15.7%.

Barrett's esophagus is most common in white males, appearing less commonly in black and Asian populations.<sup>25</sup> Studies have placed the prevalence of Barrett's esophagus in Hispanic populations at a rate comparable to that in whites. Moreover, a recent study in a Taiwanese population demonstrated a





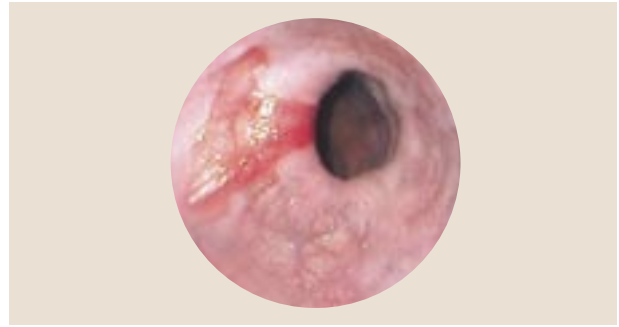
**FIGURE 14.** Endoscopic view of columnar epithelium in the distal esophagus showing a white, pearly patch of squamous epithelium within Barrett's esophagus.

prevalence rate of 2%, suggesting that prevalence may be increasing in populations where the condition previously was thought to be unusual.<sup>24</sup>

Estimates of the prevalence of Barrett's esophagus in patients with chronic GERD symptoms range from approximately 10%<sup>30</sup> to as high as 20%.<sup>14</sup> The prevalence of Barrett's esophagus in this population has been linked to the duration of GERD symptoms. In the GORGE study,<sup>14</sup> 4% of patients who had symptoms for less than 1 year had Barrett's esophagus. For patients who had symptoms for 1 year to 5 years, the odds ratio for Barrett's esophagus was 3.0 (95% CI, 1.2 to 8.0). The odds ratio increased to 6.4 (95% CI, 2.4 to 17.1) for patients who had symptoms for more than 10 years.

### Diagnostic issues

Estimates of the average age of the Barrett's patient at diagnosis vary. One common estimate is 55 years.<sup>25</sup> In their population study, Cameron and Lomboy<sup>27</sup> found that the mean age at development of Barrett's esophagus was 40 years, but the mean age at diagnosis was 63 years. One explanation for this gap could be related to symptomatology. Barrett's esophagus is impossible to differentiate from uncomplicated GERD based on symptoms alone,<sup>25</sup> and the signs of Barrett's esophagus can be detected only by endoscopy. A positive diagnosis is made after histologic examination of biopsy samples from the esophagus reveals the presence of intestinal-type epithelium. Patients with GERD symptoms who have Barrett's esophagus develop those symptoms at an earlier age, have more-severe nocturnal reflux, and suffer from more complications, such as stricture, ulcer, and bleeding.<sup>25</sup> Although most patients with Barrett's esophagus are referred for endoscopy for GERD symptoms, there are no antecedent esophageal symptoms in an



**FIGURE 15.** Endoscopic view of a red, velvet-like tongue of columnar epithelium among normal pink, glossy epithelium, typical of Barrett's esophagus.

estimated 25% of cases.<sup>21</sup> In these cases, Barrett's esophagus is discovered when the patient is referred for endoscopy for unrelated conditions.

Also, many patients with Barrett's esophagus appear less sensitive to pain caused by acid reflux. Impaired sensitivity to acid reflux may further hamper efforts to detect Barrett's esophagus. This decreased sensitivity may be age-related or caused by the presence of columnar epithelium.<sup>25</sup>

**Appearance.** When viewed through an endoscope, the normal squamous epithelium lining the esophagus appears pearly white.<sup>21</sup> Columnar mucosa appears as a salmon-pink-colored epithelium. In most cases of Barrett's esophagus, the columnar epithelium consists of salmon-pink-colored, velvety tongues extending upward from the gastroesophageal junction.<sup>31</sup> **Figures 14 and 15** present typical endoscopic images of columnar epithelium and Barrett's esophagus. Patches of squamous epithelium appear pearly white among the darker columnar epithelium. The esophagus terminates at the gastroesophageal junction, which appears as a pinched closure at the end of the esophagus coinciding with the beginning of the gastric folds. The presence of hiatal hernia, erosive esophagitis, and other GERD complications can make it difficult to fix the exact location of this junction visually on endoscopy.<sup>31</sup>

**Short-segment vs long-segment Barrett's esophagus.** In the late 1950s, when Barrett's esophagus was first defined as an acquired condition separate from other gastroesophageal abnormalities, such as tubular-shaped hiatal hernia, the length of columnar epithelium required for a diagnosis of Barrett's esophagus was determined to be at least 3 cm.<sup>32</sup> Recent emphasis, however, has been placed on the presence of any length of intestinal-type metaplastic epithelium rather than any specific length of the

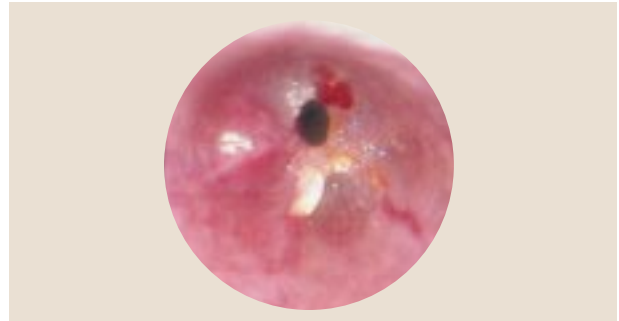
columnar epithelium segment. Endoscopic evidence of segments of columnar epithelium less than 3 cm in length in the distal esophagus, paired with histologic findings of intestinal-type mucosa, indicates short-segment Barrett's esophagus. Among patients undergoing routine endoscopy, prevalence rates of Barrett's esophagus 3 cm or more in length are around 1%, but the reported prevalence increases when shorter segments are included, ranging from 6% to 36%.<sup>25</sup>

Short-segment Barrett's esophagus shares many clinical features with traditional, or long-segment, Barrett's esophagus. Patients with GERD symptoms and increased esophageal acid exposure have an increased likelihood of developing short-segment Barrett's esophagus.<sup>31</sup> However, a study by Weston and colleagues<sup>33</sup> of 237 patients undergoing routine endoscopy found that acid reflux symptoms were present in only about half (53%) of patients with histologically confirmed short-segment Barrett's esophagus. Hiatal hernia was present in a majority of these patients (84%).

The degree and incidence of most abnormalities in patients with short-segment Barrett's seem to fall between those of patients with long-segment Barrett's esophagus and patients without Barrett's esophagus. For example, patients with short-segment Barrett's esophagus have increased LESP compared with patients with long-segment Barrett's esophagus, but decreased LESP compared with patients without Barrett's esophagus. Patients with short-segment Barrett's esophagus also experience less esophageal acid exposure than the former group, but more than the latter group.<sup>25</sup>

Detection of short-segment Barrett's esophagus is complicated by its proximity to the gastric cardia in the very distal esophagus (**Figure 16**). Fixing the exact location of the gastroesophageal junction and comparing it with the squamocolumnar junction is the initial step in recognizing Barrett's esophagus. Intestinal metaplasia of the esophagus is histologically indistinguishable from intestinal metaplasia of the gastric cardia. If the junction is not precisely identified endoscopically and the endoscopist is not exact with the location of the biopsy, a patient who has intestinal metaplasia of the gastric cardia could be misdiagnosed with short-segment Barrett's esophagus.

Short-segment Barrett's esophagus can be missed when small segments of columnar mucosa in the distal esophagus are not recognized visually during



**FIGURE 16.** Endoscopic view of short-segment Barrett's esophagus present with Los Angeles grade B erosive esophagitis.

endoscopy, when biopsy samples are not targeted accurately from affected areas, or when biopsy specimens are accidentally taken from the gastric cardia.<sup>31</sup>

Research findings indicate some risk of esophageal adenocarcinoma developing in segments of Barrett's esophagus of less than 3 cm (short-segment Barrett's esophagus), but the results are inconclusive in patients with specialized intestinal metaplasia of the gastric cardia. As a result, controversy has arisen over the exact parameters of Barrett's esophagus. Some researchers narrow the definition based on length of segment and location of intestinal metaplasia. Long-segment Barrett's is used to denote the presence of columnar epithelium of greater than 3 cm; short-segment Barrett's is used when the segments of columnar epithelium extend up from the esophagogastric junction less than 3 cm into the distal esophagus. The term "intestinal metaplasia of the cardia" (or CIM) is used when the metaplasia is confined to the gastric cardia.<sup>32</sup>

**Guidelines for diagnosis.** The American College of Gastroenterology published guidelines for the diagnosis, surveillance, and management of Barrett's esophagus in 1998.<sup>34</sup> In these guidelines, the traditional definition of Barrett's esophagus, which restricted the length of the segment of abnormal cells to 3 cm or greater, was replaced by a definition (**Table 3**) with two key points:

- The change in the esophageal epithelium, regardless of how far the segment extends up from the esophagogastric junction into the distal esophagus, can be recognized on endoscopy
- Histologic examination confirms the presence of intestinal metaplasia.

Endoscopic examination is recommended for patients with chronic GERD symptoms, particularly patients who are aged 50 years or older, as Barrett's esophagus is most common in this age

**TABLE 3**  
Evolving definition of Barrett's esophagus\*

Old definition	New definition
"≥ 3 cm of columnar lining or intestinal metaplasia in the esophagus"	"A change in the esophageal epithelium of any length that can be recognized at endoscopy and is confirmed to have intestinal metaplasia by biopsy"

\* According to the American College of Gastroenterology guidelines for diagnosis.<sup>34</sup>

group. The guidelines also point out the high prevalence of Barrett's esophagus in asymptomatic persons and recommend close examination of the distal esophagus for all patients undergoing endoscopy for any indication.<sup>34</sup>

A definitive diagnosis of Barrett's esophagus requires histologic confirmation. Numerous biopsy samples should be taken from the suspect areas to detect intestinal metaplasia. To rule out the presence of dysplasia, four-quadrant biopsies of the columnar epithelium should be taken at 1-cm to 2-cm intervals.<sup>32</sup> Various methods, including jumbo biopsy and balloon and brush cytology,<sup>25</sup> have been advocated for obtaining optimal results. Currently, the guidelines include only standard biopsy sampling.<sup>34</sup>

### Development of dysplasia in Barrett's esophagus

Although the presence of intestinal metaplasia alone is a precancerous condition, the chances of a patient developing esophageal adenocarcinoma are even greater if high-grade dysplasia is present. Barrett's esophagus without dysplasia progresses to high-grade dysplasia in 5% of patients at 5 years. In contrast, low-grade dysplasia progresses to high-grade dysplasia in 25% of patients at 5 years.<sup>35</sup>

Not every patient with Barrett's esophagus goes on to develop adenocarcinoma, but for those who do, neoplastic progression in Barrett's esophagus follows a multiple-step process. As exposure to refluxed material continues to irritate the metaplastic columnar epithelium, low-grade dysplasia can develop, progressing to high-grade dysplasia, and finally to adenocarcinoma.<sup>32</sup>

In nondysplastic columnar metaplasia, the cells are mucus-producing with uniform-size nuclei close to the basement membrane. In high-grade dysplasia, the cells produce little or no mucus; have enlarged,

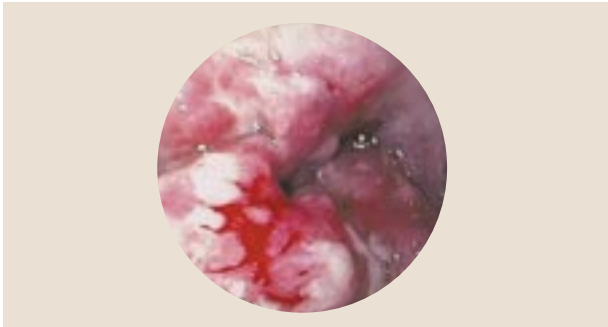
pleomorphic nuclei; are stratified on the basement membrane; and have irregular-shaped glands. (In the case of adenocarcinoma, the cells penetrate the basement membrane into the wall of the esophagus.)<sup>36</sup> The natural history of high-grade dysplasia in Barrett's esophagus is uncertain. In many cases, high-grade dysplasia rapidly progresses to carcinoma. However, in some cases, it does not progress and can actually regress. For intermediate grades of dysplasia, progression to adenocarcinoma is less frequent.<sup>35</sup>

There are problems inherent in grading dysplasia, including the subjectivity of the assessment method and lack of correlation between biologic behavior of the lesion and the grade of dysplasia.<sup>22</sup> Low-grade dysplasia also can be confused with inflammatory atypia.<sup>26</sup> Furthermore, interobserver agreement, at 85% when differentiating high-grade dysplasia and carcinoma from low-grade, indefinite, and negative dysplasia, falls to 72% when diagnosing low-grade dysplasia and to 58% when diagnosing indefinite dysplasia.<sup>25,34</sup>

Any segment of metaplasia is capable of developing into dysplasia.<sup>32</sup> However, a study by Weston and colleagues<sup>37</sup> conducted in 152 patients with either short-segment or long-segment Barrett's esophagus found that dysplasia was more common in the latter group. The incidence of dysplasia at diagnosis was 8.1% in patients with short-segment Barrett's esophagus, compared with 24.4% ( $P < 0.007$ ) in patients with long-segment Barrett's esophagus. Dysplasia also developed at a significantly faster rate in patients with the long-segment form, with two cases developing in patients with short-segment Barrett's esophagus compared with six cases in patients with the long-segment form ( $P < 0.05$ ). Cameron and Carpenter<sup>38</sup> found that dysplasia occurs in patches and in varying degrees of severity in Barrett's esophagus and develops in many areas at the same time. Large patches form when smaller patches converge, instead of spreading out from one site.

### ■ ESOPHAGEAL ADENOCARCINOMA

Once a rare condition and still relatively uncommon in the general population, the incidence of esophageal adenocarcinoma is rising in the United States and Europe.<sup>39</sup> Barrett's esophagus is the only recognized risk factor for this type of esophageal cancer. Barrett's esophagus, unfortunately, has no symptoms to distinguish it from GERD, and as many as 25% of patients with long-segment Barrett's esophagus have no esophageal symptoms.<sup>21</sup>



**FIGURE 17.** Endoscopic view of esophageal adenocarcinoma.

As a result, esophageal adenocarcinoma (**Figure 17**) is often detected when patients with the cancer present with dysphagia and weight loss. Cancer in patients presenting with these symptoms is usually incurable. Median survival is 2 years, and fewer than 10% of these patients survive for 5 years.<sup>2</sup>

Strong associations have been drawn between GERD and a patient's risk of developing esophageal adenocarcinoma. This section discusses these associations, the growing prevalence of this type of esophageal cancer, and the cellular process by which adenocarcinoma develops from Barrett's esophagus.

### Prevalence and increasing incidence

In the mid-20th century, the overwhelming majority of cancers of the esophagus were squamous cell carcinomas. In fact, esophageal adenocarcinoma occurred so rarely that experts questioned its existence.<sup>21</sup> Over the past 20 years, however, while the incidence of squamous cell carcinoma has stayed constant, the incidence of adenocarcinoma of the esophagus and esophagogastric junction has risen fivefold—a growth rate exceeding that of any other cancer.<sup>40</sup> Esophageal cancer (both adenocarcinoma and squamous cell cancer) occurs at a rate of 3.3 per 100,000 individuals in the population.<sup>39</sup> Adenocarcinoma currently accounts for about half of all esophageal cancers in the United States.<sup>21</sup>

Esophageal adenocarcinoma is most prevalent in white males. In 1975, the incidence of adenocarcinoma per 100,000 person-years in the United States was 0.7 for white males and 0.4 for black males. However, by 1995, the incidence had risen to 3.2 for white males but only to 0.6 for black males. **Table 4** breaks down ratios of esophageal adenocarcinoma incidence rates among different age groups of white males over a recent 20-year period. For men aged less than 65 years, the rate of adenocarcinoma doubled over this period; for men aged 65 years or older, the

**TABLE 4**  
Ratios of esophageal adenocarcinoma incidence rates in white males, by age

Age (yr)	1974 to 1980*	1981 to 1987	1988 to 1994
< 55	1.0	1.4	2.3
55–64	1.0	1.3	2.3
65–74	1.0	2.4	4.5
≥ 75	1.0	1.9	3.8

\* Baseline incidence.

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rate increased approximately threefold to fourfold.<sup>41</sup>

A comparison of the incidence of esophageal adenocarcinoma with the incidence of colon cancer in white and black males in the United States helps to put these figures in perspective. According to the Surveillance, Epidemiology, and End Results Cancer Statistics Review, the colon cancer rate for the years 1975 to 1995 was fairly steady, averaging 58.48 per 100,000 person-years for white males and a comparable 57.67 per 100,000 person-years for black males.<sup>42</sup>

The reasons underlying the increased incidence of esophageal adenocarcinoma in the general population are largely unknown and are under investigation. Lagergren and colleagues<sup>43</sup> compared the use of drugs that relax LES, thus promoting reflux, such as anticholinergics, with the incidence of adenocarcinoma. In patients who had used these types of drugs for 5 or more years, the incidence rate ratio of adenocarcinoma was 3.8 when compared with patients who had never taken these types of drugs. The authors estimated that, assuming a causal relationship, approximately 10% of all cases of esophageal adenocarcinoma occurring in the population could be attributed to drugs that relax LES.

Other researchers have suggested that adenocarcinoma incidence is increasing as a result of the declining rates of *H pylori* infection. They suggest that *H pylori* has a protective effect against patients developing Barrett's esophagus, esophageal adenocarcinoma, or both.<sup>40</sup>

### Symptoms and association with GERD

Daly and colleagues<sup>44</sup> recently conducted a multicenter US study of 3,466 patients diagnosed with esophageal cancer to evaluate which symptoms

**TABLE 5**  
Symptoms at diagnosis of esophageal cancer

Symptom	Number of patients	Percentage of patients*
Cervical adenopathy	190	5.5
Chronic cough	375	10.8
Dysphagia	2,566	74.0
Heartburn	712	20.5
Hematemesis	195	5.6
Hemoptysis	126	3.6
Odynophagia	574	16.6
Shortness of breath	418	12.1
Weight loss	1,974	57.3
Other	1,046	30.2

\* Among all patients reported from diagnosing institutions (n = 3,466).

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these patients presented with, as well as cancer stage distribution and treatment modalities. Patients were mostly men (74.2%) and mostly white (76.8%). Approximately 30% had used tobacco previously, and 53% currently either smoked cigarettes or used tobacco in other forms. More than half of the patients reported that they did not drink alcohol, and the large majority of patients averaged fewer than two drinks per day. **Table 5** lists the symptoms with which patients presented. Most patients reported dysphagia (74%), followed by weight loss (57.3%) and GERD (20.5%). In this study, the 1-year disease-specific overall survival rate for esophageal cancer was 43%.

Chronic reflux has been identified as the main cause of Barrett's esophagus. Because Barrett's esophagus is significantly linked to esophageal adenocarcinoma, it seems logical that chronic GERD has the potential to play an important role in the pathogenesis of esophageal adenocarcinoma.

Lagergren and colleagues<sup>39</sup> conducted a case-control population-based investigation of the connection between GERD and adenocarcinoma of the esophagus and gastric cardia in 1,438 patients in Sweden. The 451 patients with adenocarcinoma represented 85% of all eligible cases of adenocarcinoma in Sweden. Among participants who experi-

enced heartburn and reflux symptoms at least once per week, the risk for developing adenocarcinoma was nearly eight times that in participants who did not experience these symptoms. The authors also found that increased severity and duration of symptoms correlated with increased risk of adenocarcinoma (**Table 6**). For example, a person with a reflux-symptom score (a measure of symptom severity) of 1 to 2 points had an odds ratio of 1.4 for adenocarcinoma. However, a person with a reflux-symptom score of 4.5 to 6.5 points had an odds ratio of 20.0.

Another investigation of the relationship between adenocarcinoma and GERD symptoms, conducted by Chow and colleagues,<sup>45</sup> yielded comparable results. The investigators collected data from the medical records of 196 patients with adenocarcinoma matched with 196 controls. Patients with a history of GERD symptoms for 1 year to 5 years had an odds ratio for developing adenocarcinoma of 1.2. However, patients who had symptoms for 5 years or more had an odds ratio of 2.5.

### Pathophysiology from Barrett's esophagus

In patients with Barrett's esophagus in the United States, esophageal adenocarcinoma incidence rates range from 1 case in 100 patient-years to 1 case in 200 patient-years—a 30-fold to 125-fold increase in risk from that of the general population.<sup>2</sup> These estimates are obviously very wide ranges. In an attempt to more precisely fix the incidence rates, Drewitz and colleagues<sup>46</sup> conducted a study in all patients undergoing endoscopy at a Veterans Affairs Medical Center between January 1982 and April 1995. They calculated an incidence rate of 1 case per 208 patient-years. Although this study population was 98% male, these findings are similar to those from a study by O'Connor and colleagues<sup>47</sup> conducted in 91 male and 45 female patients from The Cleveland Clinic's Barrett's esophagus registry. The incidence rate in this study was 1 case per 285 patient-years, a slightly lower but similar figure.

Nevertheless, the risk of developing esophageal adenocarcinoma from Barrett's esophagus does seem to vary with gender. Menke-Pluymers and colleagues<sup>48</sup> studied characteristics of patients with benign Barrett's esophagus and patients with esophageal adenocarcinoma arising from Barrett's esophagus. In the former group, the male-to-female ratio was 1.2:1, whereas it was 3.1:1 in the group with malignant disease.

Esophageal adenocarcinoma incidence and

TABLE 6

Risk of esophageal adenocarcinoma according to the frequency, severity, and duration of GERD symptoms

	Number of controls (%)	Number of pts with adenocarcinoma (%)	Adjusted odds ratio (95% CI)
<b>Frequency of reflux symptoms</b>			
No symptoms	685 (84)	76 (40)	1.0
1 time per week	95 (12)	37 (20)	5.1 (2.8–9.4)
2–3 times per week	16 (2)	35 (19)	6.3 (3.8–10.3)
>3 times per week	24 (3)	41 (22)	16.7 (8.7–28.3)
<b>Reflux-symptom score</b>			
No symptoms	685 (84)	76 (40)	1.0
1–2 points	58 (7)	10 (5)	1.4 (0.7–3.0)
2.5–4 points	43 (5)	39 (21)	8.1 (4.7–16.1)
4.5–6.5 points	34 (4)	64 (34)	20.0 (11.6–34.6)
<b>Duration of reflux symptoms</b>			
No symptoms	685 (84)	76 (40)	1.0
< 12 years	41 (5)	31 (16)	7.5 (4.2–13.5)
12–20 years	67 (8)	42 (22)	5.2 (3.1–8.6)
> 20 years	27 (3)	40 (21)	16.4 (8.3–28.4)

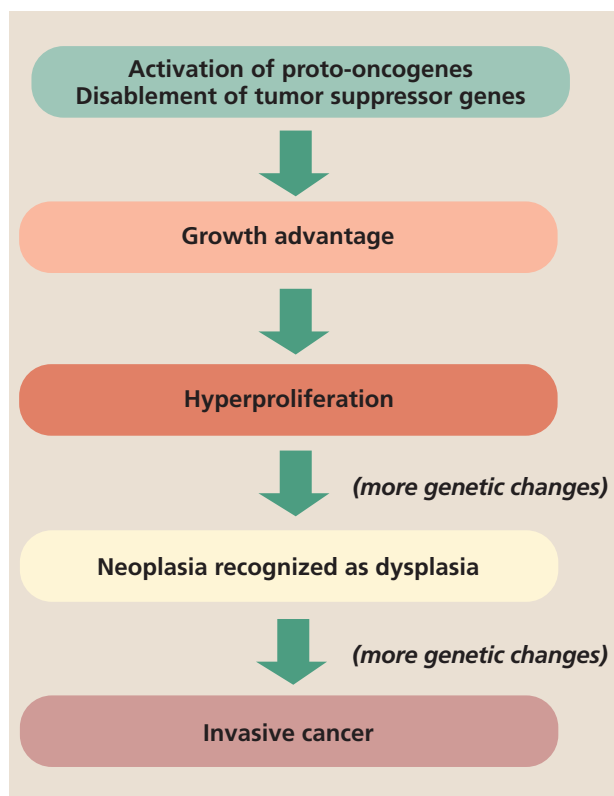
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prevalence rates vary depending on the length of the Barrett's esophagus segment. For patients with endoscopically obvious (long-segment) Barrett's esophagus, esophageal adenocarcinoma develops at rates ranging from 1 case per 46 patient-years of follow-up to 1 case per 441 patient-years of follow-up. For patients with short-segment Barrett's esophagus, the risk is not clearly defined. However, a study conducted by Hamilton and colleagues<sup>49</sup> found that, of 39 patients with esophageal adenocarcinoma that developed from Barrett's esophagus, 19 (49%) had short-segment Barrett's esophagus.

Weston and colleagues<sup>50</sup> conducted a prospective, multivariate analysis of the factors that predicted the development of multifocal high-grade dysplasia and esophageal adenocarcinoma in 108 patients with Barrett's esophagus. Patients newly diagnosed with Barrett's esophagus were followed for a mean of 39.9 months (range, 12 to 101 months). Five patients developed multifocal high-grade dysplasia, and 5 patients developed esophageal adenocarcinoma. The incidence for both of these conditions was 1 per 71.9 patient-years. Chi-square analysis revealed that progression from Barrett's esophagus to multifocal high-grade dysplasia and esophageal adenocarcinoma was associated with the presence of hiatal hernia ( $P = 0.02$ ), the length of the Barrett's esophagus seg-

ment ( $P = 0.001$ ), and the presence of dysplasia at diagnosis or at any time during the follow-up period ( $P < 0.001$ ). Logistic regression analysis supported these associations. Progression from Barrett's esophagus to multifocal high-grade dysplasia and esophageal adenocarcinoma was associated with hiatal hernia size ( $P < 0.02$  for hernias 3 cm or greater), the length of the Barrett's esophagus segment ( $P = 0.009$  for segments 2 cm or greater), and the presence of dysplasia at diagnosis ( $P < 0.0001$ ) or at any time during follow-up ( $P < 0.03$ ).

Barrett's esophagus with or without dysplasia is a premalignant condition. Cameron and Carpenter,<sup>38</sup> in their study of dysplasia in Barrett's esophagus, noted that cancer can develop anywhere esophageal intestinal metaplasia occurs. This finding contrasts with the idea that cancer develops only near the squamocolumnar junction at the most proximal extent of the Barrett's epithelium. **Figure 18** roughly outlines the proposed developmental process of esophageal adenocarcinoma in Barrett's esophagus. This process begins with genetic changes that can activate proto-oncogenes, impair tumor-suppressor genes, or both. Abnormal cells begin to grow, and, after more genetic changes, autonomous cell growth, or neoplasia, occurs. Accumulating DNA abnormalities lead to malignancy and invasion of



**FIGURE 18.** Possible sequence of genetic changes resulting in adenocarcinoma from Barrett's esophagus. Reprinted from reference 21 with permission from Elsevier.

surrounding tissue. Dysplasia occurs before this final malignant stage and can be recognized histologically.<sup>21</sup> Numerous studies have focused on the genetic changes that are markers for predicting and preventing the development of esophageal adenocarcinoma, including p53 alterations, cyclin D1 overexpression, and DNA ploidy.

**p53 Alterations.** The protein product related to this gene helps to inhibit cellular proliferation and is involved in cell cycle regulation, DNA repair, and apoptosis. As Barrett's esophagus progresses to esophageal adenocarcinoma, p53 alterations become more pronounced. In one study, 5% of patients with intestinal metaplasia had p53 alterations. For indefinite or low-grade dysplasia, 15% of patients had alterations; for high-grade dysplasia, 45% of patients had alterations; and for adenocarcinoma, 53% had p53 alterations.<sup>40</sup> From these data, one would assume that p53 could be a biomarker to help predict a patient's risk of developing esophageal adenocarcinoma from Barrett's esophagus. However, in a prospective study by Bani-Hani and colleagues<sup>51</sup> of

307 patients with Barrett's esophagus, p53 positivity was not a statistically significant marker for increased risk of esophageal adenocarcinoma (odds ratio = 2.99;  $P = 0.197$ ).

**Cyclin D1 overexpression.** In other cancers, modification of messenger ribonucleic acid stability, disruption of promoter structure, and amplification of a special chromosomal region cause cyclin D1 overexpression. However, the relationship between this gene's overexpression and esophageal adenocarcinoma has not been clarified. The above-mentioned study by Bani-Hani et al<sup>51</sup> also investigated the link between cyclin D1 overexpression and the pathology of esophageal adenocarcinoma in Barrett's esophagus. Of the 307 patients with Barrett's esophagus, 12 developed adenocarcinoma. Of these patients, 8 (67%) had biopsy specimens that stained positive for cyclin D1 before carcinoma development. The odds ratio for this group was 6.85 ( $P = 0.0106$ ). Comparatively, in patients with Barrett's esophagus that did not progress to adenocarcinoma, only 14 of 49 biopsy specimens (29%) stained positive for cyclin D1. The study authors noted the distinct possibility that some of these "control" patients could go on to develop esophageal adenocarcinoma. One patient who tested positive for cyclin D1, but who did not develop esophageal adenocarcinoma during the 9 years of the study, did go on to develop adenocarcinoma at a later date.

**DNA ploidy.** With neoplastic proliferation, the DNA ploidy of the cell changes. Cells are normally diploid (with the exception of germline cells); however, aneuploidy is observed in 63% of high-grade dysplasia in Barrett's esophagus.<sup>40</sup> Reid and colleagues<sup>52</sup> found that, among 13 patients with two cellular ploidy abnormalities (aneuploidy and increased G2-cell population), 9 developed high-grade dysplasia or adenocarcinoma. These proliferative changes were absent in patients who did not have high-grade dysplasia or esophageal adenocarcinoma. These data suggest that abnormal nuclear DNA content is an important part of the progression of adenocarcinoma from intestinal metaplasia.

### Summary and implications

Esophageal adenocarcinoma is one of the most lethal cancers. One reason the prognosis is usually poor is that the cancer is often not detected until widespread metastases are already present. This poor prognosis underlies the need for further research into the developmental process of

esophageal adenocarcinoma and the need for vigilant, aggressive monitoring of patients with Barrett's esophagus and chronic GERD.

## ■ CONCLUSIONS

The sometimes tenuous relationship between GERD symptoms and complications presents interesting diagnostic challenges. Patients with daily heartburn may have no esophageal injury from refluxed material. However, patients with infrequent heartburn can present with severe GERD complications, including Barrett's esophagus. Furthermore, Barrett's esophagus, an impor-

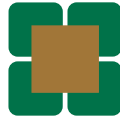
tant risk factor for esophageal adenocarcinoma, has no symptoms to differentiate it from uncomplicated GERD. These issues make diagnosis difficult, but not impossible. Ongoing research may enable investigators to draw stronger connections between GERD symptoms and GERD complications, and between one GERD complication and another. New studies may also make it easier to assess a patient's risk of developing serious GERD complications, such as Barrett's esophagus and esophageal adenocarcinoma. Until then, patients and physicians must learn to view heartburn as a symptom of a potentially serious condition and treat it accordingly.<sup>53</sup>

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# Profile and assessment of GERD pharmacotherapy

PAUL N. MATON, MD

## ■ ABSTRACT

The choice of a medical therapy to treat gastroesophageal reflux disease (GERD) centers around several factors, including the efficacy and safety of the agent and the severity of the patient's symptoms and complications. Although the efficacy of antacids and alginic acid has not been proven definitively in clinical trials, these agents are effective against mild GERD symptoms in clinical practice. Along with sucralfate, these agents are also useful in special populations, such as pregnant women, for whom acid-suppressive therapy may not be the best option. The withdrawal of cisapride from the US market has lessened the role of promotility agents for treating GERD, as their efficacy must be weighed against their side effects. Acid-suppressive agents have become the drugs of choice for GERD. Both proton pump inhibitors (PPIs) and histamine H<sub>2</sub>-receptor antagonists effectively and safely treat GERD. However, PPIs have been shown to provide the highest levels of GERD symptom relief and esophageal healing to the most patients, in the shortest time, and with the fewest side effects.

Pharmacotherapy is considered first-line treatment for patients with gastroesophageal reflux disease (GERD). Although some guidelines recommend instituting lifestyle changes at the same time as an initial trial of empiric medical therapy,<sup>1</sup> others note that these diet and lifestyle changes have little therapeutic benefit, and recommend medical therapy as initial treatment.<sup>2</sup> The following medical therapies are available for

the treatment of GERD:

- **Prokinetic agents**, which target the underlying motility dysfunction that causes GERD
- **Mucosal-protective agents**—ie, sucralfate, which binds with damaged mucosa to form a barrier against harmful acid reflux, and alginic acid, which forms a foamy barrier on top of the refluxate to protect the esophagus
- **Acid neutralizers (antacids)**, which work locally to raise the pH of the refluxate
- **Acid-suppressive agents**—ie, histamine H<sub>2</sub>-receptor antagonists (H<sub>2</sub>RAs) and proton pump inhibitors (PPIs), which inhibit acid production in the parietal cell.

Guidelines also differ on which medical therapy should be used as initial GERD treatment. Therapy for any disease must be effective and safe, and fit the needs of the patient. Other issues, such as concomitant conditions, recurrence of symptoms, and cost to treat, should also be considered when deciding on a course of therapy.

This article examines the safety and efficacy of the available medical therapies for GERD. End points for the efficacy of these agents include:

- Symptom relief, which is a measure of the reduction in symptoms (usually heartburn and regurgitation, but some studies assess noncardiac chest pain and other atypical or extraesophageal symptoms)
- Symptom resolution, which indicates the absence of symptoms
- Erosive esophagitis healing rates.

Maintenance studies have examined maintenance of erosive esophagitis healing and symptom recurrence. Safety considerations include adverse events and the effects of long-term treatment.

This article also presents data from placebo-controlled and comparative trials of the available H<sub>2</sub>RAs and the available PPIs, as well as trials comparing efficacy between H<sub>2</sub>RAs and PPIs. Much of the literature on GERD pharmacotherapy focuses on the safety and comparative efficacy of these acid-sup-

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pressive agents. PPIs have been recognized as the most effective medical therapy for GERD symptom relief, for healing all grades of erosive esophagitis, and for maintenance of healing. Although some patients experience symptom relief and healing of erosive esophagitis with H<sub>2</sub>RAs, PPIs produce more frequent and rapid symptom relief and esophageal healing for a greater percentage of patients.<sup>1</sup>

### ■ PROKINETIC AGENTS

Prokinetic agents that treat GERD increase lower esophageal sphincter pressure (LESP), accelerate gastric clearance, stimulate esophageal peristalsis, increase the amplitude of esophageal contractions, or perform a combination of two of these actions.

All prokinetic agents (bethanechol, metoclopramide, domperidone, and cisapride) are effective, to varying degrees, in improving GERD symptoms and healing esophagitis. However, efficacy data for these agents come from small, sometimes poorly designed studies, often without a placebo control. Also, the adverse-event profile of these agents must be weighed against any clinical benefit of GERD treatment. Although domperidone (available in Canada but not in the United States) is well tolerated, metoclopramide and bethanechol have been associated with significant adverse events (**Table 1**).<sup>3</sup> Cisapride, in particular, although the most effective of the prokinetic agents for treating GERD, was removed from the US market because of deaths associated with cardiac arrhythmia.

#### Bethanechol

Bethanechol is a direct-acting muscarinic receptor agent that acts by stimulating the parasympathetic nervous system to release acetylcholine. It has been shown to increase LES and improve esophageal peristaltic clearing.

**Clinical efficacy.** Some small, double-blind, placebo-controlled studies have investigated the efficacy of bethanechol in GERD treatment, with mixed results. One placebo-controlled study conducted in 20 patients found that a 2-month course of bethanechol 25 mg four times daily reduced heartburn and reduced antacid use.<sup>3</sup> However, in another study of 44 patients by Thanik and colleagues,<sup>4</sup> the improvement of GERD symptoms in patients receiving bethanechol plus antacids was not statistically significantly different from that in patients receiving antacids plus placebo.

Results also differ among studies examining the

efficacy of bethanechol in healing erosive esophagitis. In a comparative trial of bethanechol and cimetidine, the two agents had fairly similar healing rates (52% of patients receiving bethanechol and 68% of those receiving cimetidine experienced complete healing). Both agents were administered with high doses of antacids, which may have helped produce these high healing rates.<sup>3</sup> Interestingly, although Thanik and colleagues<sup>4</sup> found bethanechol to be no more effective than placebo in improving GERD symptoms, 45.5% of patients receiving bethanechol 25 mg four times daily experienced complete healing of erosive esophagitis, compared with 13.6% of patients receiving placebo plus antacids ( $P < 0.015$ ).

**Safety.** Unfortunately, at the dosage level necessary to treat GERD (25 mg four times daily), bethanechol can cause significant side effects, such as abdominal cramping, blurred vision, fatigue, and increased urinary frequency. Side effects occur in about 10% to 15% of patients, and are more common in the elderly. Bethanechol is also associated with a long list of contraindications (**Table 1**) that compromise its use as an anti-GERD agent.<sup>3</sup>

#### Metoclopramide

Metoclopramide is a dopamine antagonist. Although its precise mechanism of action is unclear, it seems to sensitize tissues to the action of acetylcholine. It has been shown to increase the amplitude of gastric and esophageal contractions, increase LES, and increase the speed of gastric emptying and intestinal transit.

**Clinical efficacy.** In two small, placebo-controlled studies in which 31 and 15 patients with GERD received metoclopramide 10 mg three times daily, symptom improvement did not differ significantly between the treatment and control groups. However, in studies conducted in 30 and 31 patients with GERD, a higher dosage of the agent, 10 mg four times daily, either alone or in combination with an antacid, was more effective than placebo at improving symptoms.<sup>5,6</sup>

Comparative studies have found that metoclopramide is as effective as H<sub>2</sub>RAs (cimetidine and ranitidine) in relieving heartburn and other GERD symptoms.<sup>7,8</sup> All of these comparative trials were conducted in small patient populations,<sup>3</sup> and all but one were conducted without a placebo control.<sup>8</sup> The largest one, conducted in 73 patients, found no difference in symptom relief between patients given cimetidine 400 mg four times daily alone and those

TABLE 1

Contraindications and adverse events associated with prokinetic agents<sup>3</sup>

Agent	Contraindications	Adverse events
Bethanechol	<ul style="list-style-type: none"> <li>Intravenous or intramuscular use may cause severe cholinergic reaction</li> <li>Hyperthyroidism, peptic ulcer, bronchial asthma, mechanical obstruction of gastrointestinal or lower urinary tract, peritonitis, parkinsonism, bradycardia, atrioventricular conduction defects, hypotension, and coronary artery disease</li> </ul>	<ul style="list-style-type: none"> <li>Abdominal cramping, blurred vision, fatigue, and increased urinary frequency in 10% to 15% of patients</li> </ul>
Metoclopramide	—	<ul style="list-style-type: none"> <li>Antidopaminergic side effects in up to 30% of patients, including drowsiness, lassitude, anxiety, agitation, and motor restlessness</li> <li>Dystonic reactions in 1% of patients</li> <li>Parkinson symptoms (tremor, rigidity, akinesia, tardive dyskinesia) rare except with high doses (30–80 mg)</li> <li>Gynecomastia, galactorrhea, and menstrual disorders</li> </ul>
Domperidone	—	<ul style="list-style-type: none"> <li>Hyperprolactinemia, resulting in breast enlargement, nipple tenderness, galactorrhea, and amenorrhea, in 10% to 15% of patients</li> <li>Otherwise well tolerated</li> </ul>
Cisapride	—	<ul style="list-style-type: none"> <li>Deaths associated with cardiac arrhythmia led to voluntary removal from US market</li> </ul>

given a combination of cimetidine with metoclopramide 10 mg three times daily.<sup>9</sup>

Although symptom improvement has been demonstrated with metoclopramide, this agent does not seem to be significantly more effective than placebo at promoting healing of erosive esophagitis.<sup>3</sup> In the one placebo-controlled study comparing it with cimetidine, metoclopramide improved the appearance of esophageal erosions in 82% of patients, but this was not significantly different from rate with either cimetidine or placebo (78% for each).<sup>8</sup> In another comparative study, both metoclopramide and ranitidine produced significant healing, but metoclopramide was effective in fewer patients (52% healing rate, vs 81% with ranitidine).<sup>10</sup> The recommended dosage of metoclopramide is 10 mg four times daily, whereas the recommended dosage of ranitidine is 75 mg twice daily.

**Safety.** To an even greater extent than with bethanechol, side effects are a significant drawback to GERD therapy with metoclopramide. Because it is a centrally acting dopamine antagonist that crosses the blood-brain barrier, antidopaminergic side effects are common, occurring in 20% to 30% of patients. Drowsiness and lassitude are most common, and anxiety, agitation, confusion, hallucina-

tions, and motor restlessness have also been reported.<sup>3,11</sup> The most serious effects are depression and tardive dyskinesia, which may be irreversible. Adverse events are most common at higher doses and in children, young adults, and the elderly. Other less common adverse events are listed in **Table 1**.

### Domperidone

Domperidone is another dopamine antagonist, although it is not available in the United States. It stimulates esophageal peristalsis, increases LES, and accelerates gastric emptying.

**Clinical efficacy.** As with bethanechol and metoclopramide, data on the efficacy of domperidone in GERD treatment come from small studies. The largest one, conducted in 45 patients, compared domperidone and ranitidine without a placebo control.

The efficacy of domperidone in GERD treatment has not been persuasively proven in well-controlled double-blind studies, and results with domperidone at dosages of 20 mg three or four times daily are inconsistent.<sup>3</sup> In one study, domperidone was no more effective than placebo in reducing the number of reflux episodes or improving GERD symptoms, although antacids were used less frequently at the

**TABLE 2**  
Results of comparative trials of sucralfate  
in the healing of erosive esophagitis

Investigators	N	Weeks	Patients with healed erosive esophagitis	
			Sucralfate	Comparator
Simon et al <sup>20</sup>	41	8	64%	68% (ranitidine)
Hameeteman et al <sup>21</sup>	42	8	31%	14% (cimetidine)
Laitinen et al <sup>22</sup>	68	6	53%	34% (alginate + antacid)

end of the trial compared with baseline in the domperidone group.<sup>12</sup> Other studies have shown domperidone to be effective in relieving symptoms but not in healing esophagitis.<sup>3</sup> In two non-placebo-controlled comparative trials of domperidone and H<sub>2</sub>RAs (ranitidine or famotidine), the two agents proved to be similarly effective in symptom relief and in promotion of esophageal healing. However, the combination of domperidone with an H<sub>2</sub>RA was not significantly better than each agent given alone.<sup>13,14</sup>

**Safety.** Although domperidone is a dopamine antagonist, it does not cross the blood-brain barrier (unlike metoclopramide) and was developed to act as a specific antagonist to the inhibitory effects of dopamine on the gastrointestinal tract. It is well tolerated, with few significant side effects. The adverse events that do occur are related to the stimulation of prolactin release (Table 1) and are seen in approximately 10% to 15% of patients. These events can be seen with metoclopramide use but are more common with domperidone because it is administered in higher doses. Domperidone rarely causes extrapyramidal side effects.<sup>3</sup>

### Cisapride

Any discussion of cisapride must be prefaced with a note on its profile and current market availability. High blood concentrations of cisapride can cause QT prolongation and cardiac arrhythmia, including ventricular arrhythmia, such as torsades de pointes. Coadministration of a number of drugs can reduce hepatic metabolism of cisapride and increase the likelihood of toxic concentrations.

Cisapride was removed from the US market in July 2000 after 341 cases of arrhythmia and 80 deaths were spontaneously reported to the FDA from July 1993 to May 1998. The agent is now available only on a restricted basis through a limited-access program for patients who have failed to respond to or cannot receive alternate therapies.<sup>15</sup>

Cisapride acts locally on the gastrointestinal tract and seems to facilitate release of acetylcholine from postganglionic neurons in the myenteric plexus. There is also evidence that it influences the activity of other chemical mediators of mucosal and muscular function in the gut, interacting with the serotonin 5-HT<sub>4</sub> receptor in the myenteric plexus. Cisapride increases smooth muscle contractility, increases LES pressure, and enhances esophageal peristaltic function.

**Clinical efficacy.** Before its removal from the US market, cisapride was indicated for supplemental treatment of nocturnal heartburn symptoms. It was the most effective pro-motility agent available for the treatment of GERD, in terms of both higher efficacy and fewer reported side effects. In clinical trials, cisapride was consistently better than placebo at improving the symptoms of GERD and promoting healing of erosive esophagitis. Optimal efficacy for relieving symptoms was achieved at a dosage of 10 mg three times daily, whereas 10 mg four times daily showed efficacy in healing esophagitis. One study found that 10 mg of cisapride given four times daily was as effective as 20 mg given four times daily in healing esophagitis.<sup>16</sup>

Comparative trials of cisapride and H<sub>2</sub>RAs yielded similar efficacy rates in healing esophagitis.<sup>3</sup> Gal-miche and colleagues<sup>17</sup> found that cimetidine 400 mg and cisapride 10 mg, each given four times daily, produced endoscopic healing rates of 57% and 56%, respectively, in patients with erosive esophagitis grades I to III (ie, mild to moderate esophagitis). (Here and except where noted otherwise, references to erosive esophagitis grades in this article are to the Savary-Miller classification system.)

## ■ MUCOSAL-PROTECTIVE AGENTS

### Sucralfate

Sucralfate is a mucosal-protective agent that binds to inflamed tissue, creating a protective barrier. It blocks diffusion of gastric acid and pepsin across the barrier and inhibits the erosive action of pepsin and bile.<sup>18</sup>

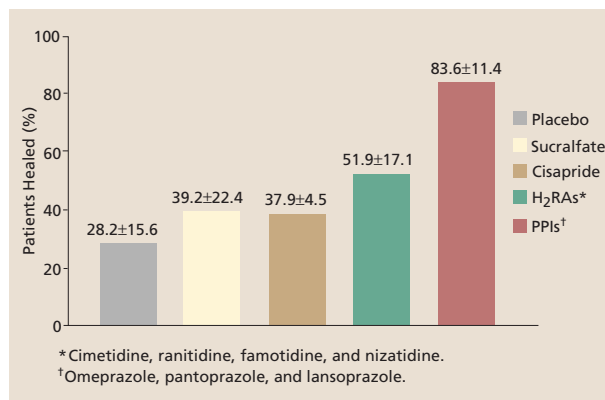
Sucralfate is available in the United States in

tablets and in suspension form. As suspension, sucralfate is administered in 1-g doses four times daily. Physicians rarely prescribe this agent to treat GERD, but it can be useful as an anti-GERD therapy in special populations, such as in women who are pregnant. Although sucralfate contains aluminum, which can be harmful to a fetus, little systemic absorption of the agent occurs. As a result, sucralfate is considered safe enough for the treatment of heartburn in pregnant women.<sup>19</sup>

**Clinical efficacy.** The findings of three comparative, non-placebo-controlled studies<sup>20–22</sup> examining the effects of sucralfate in patients with all grades of erosive esophagitis are summarized in **Table 2**. The trials compared sucralfate with H<sub>2</sub>RAs or with alginic acid plus antacids. Patients in all three studies had endoscopically confirmed reflux esophagitis, and the results of therapy were endoscopically confirmed as well. The degree of healing with sucralfate correlated with the degree of injury, with higher grades of erosive esophagitis responding less favorably to treatment. In all three trials, symptom improvement was rated as equally good for patients in all groups. Esophagitis healing rates among the sucralfate and H<sub>2</sub>RA recipients were not statistically significantly different in one trial<sup>20</sup> but did differ in another study,<sup>21</sup> with more patients showing healed or improved esophagitis in the sucralfate group. In the remaining study,<sup>22</sup> sucralfate generated complete healing more often than did alginic acid/antacid. However, these studies are significantly limited by their relatively small size (40 to 70 patients) and lack of a placebo control.

Other studies have been conducted in more specific patient populations and have included a placebo arm as a comparison. Chiba and colleagues<sup>23</sup> pooled data from several studies of the erosive esophagitis healing rates achieved with various agents, including sucralfate, in patients with grades II through IV esophagitis (**Figure 1**). Healing occurred in an average of 39% of patients who received sucralfate, but this healing rate was accompanied by a very large 95% confidence interval (3.6% to 74.8%), indicating that it was not statistically significantly different from the rate with placebo.

Sucralfate has also been studied in patients with GERD without erosive esophagitis. Simon and colleagues<sup>24</sup> tested the effects of sucralfate gel and placebo in 141 patients with moderate to severe GERD but with no esophageal erosions or ulcers. The overall response rate after 6 weeks of treatment was 71%



**FIGURE 1.** Overall pooled healing rates for placebo, sucralfate, cisapride, H<sub>2</sub>RAs, and PPIs in patients with Savary-Miller grades II to IV erosive esophagitis.<sup>23</sup>

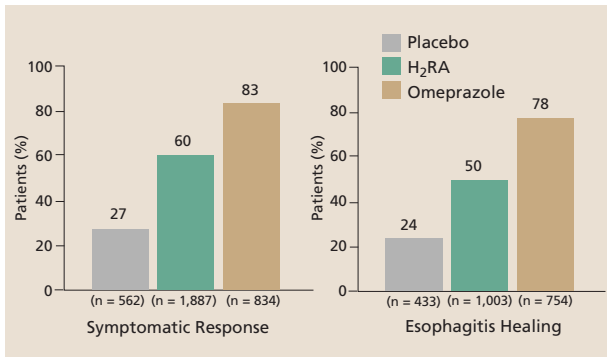
with sucralfate, compared with 29% with placebo ( $P < 0.0001$ ). Improvement in the maximum severity of daytime and nighttime heartburn occurred in 77% and 67%, respectively, of patients given sucralfate, compared with 48% and 51%, respectively, of patients given placebo.

### Alginic acid

Alginic acid is often given in combination with an antacid. The first component provides a floating barrier on the gastric pool to minimize contact between gastric contents and esophageal mucosa, while the antacid temporarily neutralizes stomach acid.<sup>25</sup> Like antacids alone, this combination therapy helps to control mild to moderate reflux symptoms in clinical practice.<sup>26</sup> Tytgat and Nio<sup>11</sup> noted that improvement in GERD symptoms occurred in three of four studies that compared alginate/antacid combination therapy with placebo. However, when compared with antacids alone, the alginate combination therapy was superior in only one of four studies. Convincing proof of esophageal healing has never been obtained in any study, and alginic acid therapy is probably no better than antacid therapy in treating moderate to severe GERD.<sup>26</sup>

### ANTACIDS

Antacids are the most widely used agents for treating GERD because patients with mild heartburn often self-medicate with these over-the-counter drugs and never seek treatment for their reflux symptoms. Available in liquid and tablet forms, antacids are used as needed. Some patients use antacids to supplement other anti-GERD therapies. In clinical



**FIGURE 2.** Symptom response rates and esophagitis healing rates in patients with GERD receiving H<sub>2</sub>RAs, omeprazole, or placebo. The H<sub>2</sub>RA dosages represented here are cimetidine 800 to 1,600 mg/day, ranitidine 300 to 600 mg/day, nizatidine 600 mg/day, and famotidine 40 mg/day, all given in divided doses either twice or four times daily. Omeprazole was given at a dosage of 20 mg to 60 mg once daily.<sup>1</sup>

practice, antacids help to control mild to moderate reflux symptoms in a large proportion of patients.<sup>26</sup> Because they act locally, antacids are considered first-line therapy for pregnant women who experience heartburn. However, magnesium-containing agents should be avoided in the latter part of pregnancy.<sup>19</sup>

**Clinical efficacy.** Despite widespread use of antacids, definitive evidence of their therapeutic benefit in the treatment of GERD is limited by the paucity of well-designed, large, placebo-controlled trials. For the placebo-controlled studies that are available, results are conflicting.

One placebo-controlled study comparing a high-dose antacid (10 mL seven times daily) with an H<sub>2</sub>RA in 37 patients with GERD found that symptom improvement was better in the antacid group than in the placebo group, but healing of erosive esophagitis was not. However, another study in 32 patients found that placebo actually performed slightly better than the high-dose antacid (15 mL seven times daily) in relieving GERD symptoms and in healing esophagitis.<sup>11</sup>

Many studies of the efficacy of antacids in combination with alginic acid have produced favorable results in terms of GERD symptom relief. However, data from these studies, including a non-placebo-controlled comparative trial in children, two open studies without placebo groups, a nonblinded study, and several comparative trials, are of limited use because of the lack of true placebo controls.<sup>25</sup>

Most studies testing the efficacy of antacids have found that, even at high doses, their effect on healing erosive esophagitis is no better than that of

placebo.<sup>11,26</sup> For example, in a 4-week, randomized, double-blind, placebo-controlled trial, Furman and colleagues<sup>27</sup> compared a high-dose liquid antacid (7 oz/day) given 15 minutes and 1 hour after meals with cimetidine 300 mg four times daily. Patients underwent endoscopy, biopsy, and acid perfusion testing at baseline and at the end of the study. They also were asked to complete symptom diary cards during the study. Only patients given cimetidine had a significant reduction in the frequency and severity of heartburn ( $P < 0.05$ ). The liquid antacid was similar to placebo in its reduction of heartburn severity. No treatment improved regurgitation. Furthermore, neither cimetidine nor the liquid antacid improved any objective measure of GERD severity (endoscopy, acid perfusion test results).

Often in clinical trials, a reduction in the use of antacids is a hallmark of efficacy for other agents (ie, H<sub>2</sub>RAs or PPIs).

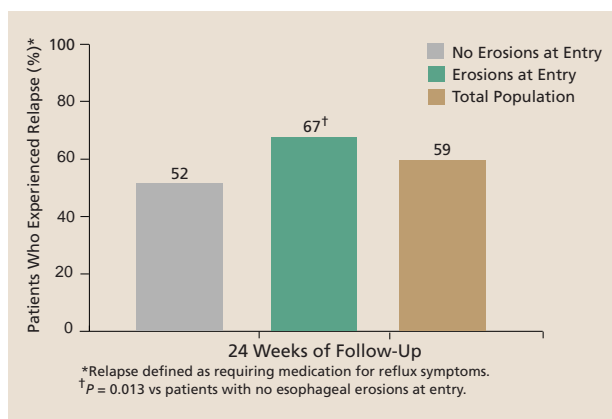
## ■ HISTAMINE H<sub>2</sub>-RECEPTOR ANTAGONISTS

Histamine H<sub>2</sub>-receptor antagonists are acid-suppressive agents that treat GERD by decreasing acid secretion and thus decreasing the causticity of the refluxate. The H<sub>2</sub>RAs approved for use in the United States are cimetidine, ranitidine, famotidine, and nizatidine. All are available by prescription and in over-the-counter formulations that are usually one half the standard prescription dose.

Although there are some variations in potency, duration, and onset of action, H<sub>2</sub>RAs have similar efficacy rates in symptom relief and healing of esophagitis.<sup>1</sup> Because they are all metabolized via the cytochrome P450 system in the liver, some drug interactions can occur. However, as a class, they are considered very safe, with few side effects.<sup>28</sup> In clinical trials, these agents consistently reduced GERD symptoms and promoted esophageal healing at a rate significantly better than placebo, especially in patients with milder grades of esophagitis.

### Pharmacokinetic/pharmacodynamic overview

Oral absorption of H<sub>2</sub>RAs is fairly rapid, with peak plasma concentrations attained within 1 to 3 hours after administration. A second peak after oral administration has been observed with all H<sub>2</sub>RAs except nizatidine. Mean oral bioavailability differs somewhat among the agents, ranging from a low of 40% with famotidine to a high of 80% with cimetidine.



**FIGURE 3.** GERD symptom relapse rates after discontinuation of a successful 4-week course of treatment with ranitidine 150 mg two or four times daily or placebo.<sup>30</sup>

Plasma concentrations of H<sub>2</sub>RAs and inhibition of gastric acid secretion are directly related, implying a rapid equilibration between drug concentration in plasma and at the site of action.<sup>29</sup>

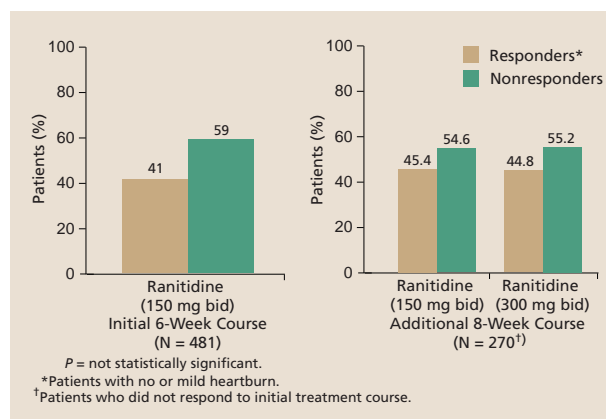
In general, the acid-suppressive abilities of H<sub>2</sub>RAs are more effective on nocturnal acid secretion. Duration of acid inhibition is longer when the drug is taken in the evening or before bedtime. Equipotent doses of H<sub>2</sub>RAs equally inhibit acid secretion.

### Efficacy: symptom improvement

Overall, H<sub>2</sub>RAs relieve symptoms in 60% of patients with GERD, whereas placebo relieves symptoms in 27% (Figure 2).<sup>1</sup> H<sub>2</sub>RAs are effective in the control of nocturnal acid reflux episodes as well.<sup>11</sup> In patients with no erosive esophagitis and with mild or intermittent GERD symptoms, symptomatic treatment response rates are 70% or higher.<sup>21</sup> Patients with esophagitis experience lower rates of symptom relief and are more likely to have symptom relapse once therapy is stopped.

**Relapse.** Hallerback and colleagues<sup>30</sup> examined symptom relapse in patients after a 4-week course of either ranitidine or placebo. The study included 423 patients with GERD symptoms, most of whom had mild reflux disease; 67.4% had either a normal-appearing esophagus or erythema only. Another 28.1% had grade I esophagitis, which consists of small, isolated lesions. Only 4.5% of this study population had esophagitis grades II through IV. Patients with more extensive injury were excluded.

Initially, patients were randomized to receive either ranitidine 150 mg twice daily or placebo for 2 weeks. After the initial trial, those who were satis-



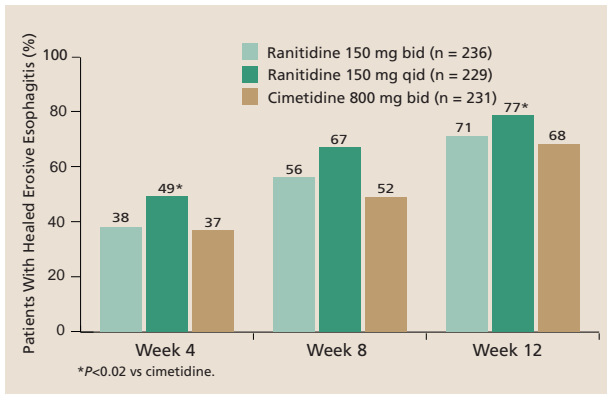
**FIGURE 4.** Rates of treatment response (heartburn relief) to an initial course of standard-dose ranitidine therapy (150 mg twice daily) and to an additional course of standard-dose or high-dose (300 mg twice daily) ranitidine therapy in patients with GERD.<sup>31</sup>

fied with their treatment (ie, responded to therapy with either improved or complete relief) continued with that therapy. Patients who were not satisfied with their treatment were then re-randomized to receive ranitidine 150 mg two or four times daily for another 2 weeks. Patients whose symptoms did not respond after 4 weeks of therapy were removed from follow-up. After 4 weeks of therapy, all responders were taken off therapy and followed for an additional 24 weeks.<sup>30</sup>

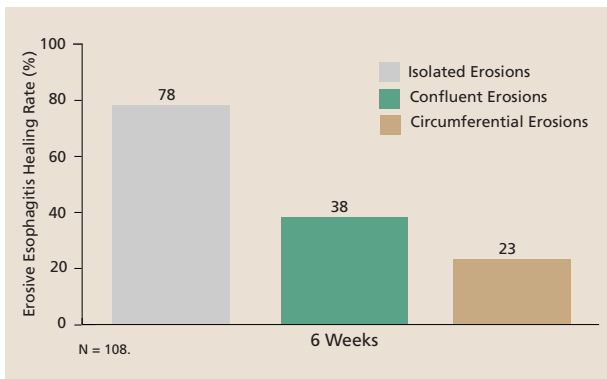
Figure 3 shows the symptomatic relapse rates in the total population and in patients with and without erosive esophagitis. At 24 weeks of follow-up, symptom relapse had occurred in 52% of patients with GERD who did not have erosive esophagitis compared with 67% of those who did have erosive esophagitis ( $P = 0.013$ ).<sup>30</sup>

**Dosage level.** In the Hallerback study,<sup>30</sup> the percentage of patients who experienced symptom improvement or complete relief at week 4 was similar in all groups that received ranitidine, regardless of dosage level. This finding was confirmed in a similarly designed study of longer duration. In this study, Kahrilas and colleagues<sup>31</sup> compared high-dose and standard-dose ranitidine therapy in patients who remained unresponsive after 6 weeks of ranitidine 150 mg twice daily. Of the 481 patients with GERD symptoms who initially received a 6-week course of 150 mg twice daily, 285 (59%) remained symptomatic. Of this group, 270 were re-randomized to receive either 150 mg or 300 mg of ranitidine twice daily. After an additional 8 weeks of therapy, only 44.8% of patients receiving the higher dose of ranitidine and 45.4% of those receiving the lower





**FIGURE 5.** Comparison of erosive esophagitis healing rates with ranitidine 150 mg two or four times daily and cimetidine 800 mg twice daily.<sup>32</sup>



**FIGURE 6.** Healing of erosive esophagitis with ranitidine 150 mg or 300 mg twice daily, by severity of disease.<sup>33</sup>

dose achieved treatment response (mild or no heartburn) (Figure 4).

### Efficacy: healing of erosive esophagitis

In general, the results of treatment with H<sub>2</sub>RAs are not as good in patients with severe erosive esophagitis. However, healing of erosions occurs in 50% of patients with erosive esophagitis who are treated with H<sub>2</sub>RAs.<sup>26,28</sup>

Placebo-controlled studies demonstrate that H<sub>2</sub>RAs provide better symptomatic relief of GERD and mucosal healing of erosive esophagitis than does placebo. Although many trials do not contain a placebo arm, Tougas and Armstrong<sup>28</sup> cited a placebo healing rate of 16.5% at 12 weeks for patients with grade II to grade IV esophagitis in a review of the efficacy of H<sub>2</sub>RAs for treatment of GERD. That compared with a mucosal healing rate of 39.7% ( $P < 0.0005$ ) for H<sub>2</sub>RAs in the same review. Placebo was associated with a 13% rate of overall symptom relief,

**TABLE 3**  
H<sub>2</sub>RAs indicated for the treatment of GERD and their recommended nonprescription dosages<sup>35</sup>

H <sub>2</sub> RAs	Dosage (over-the-counter)
Nizatidine	75 mg twice daily, as needed
Famotidine	10 mg twice daily, as needed
Cimetidine	200 mg twice daily, as needed
Ranitidine	75 mg twice daily, as needed

compared with a 44% rate of overall relief with H<sub>2</sub>RAs ( $P < 0.001$ ). All four H<sub>2</sub>RAs, when used at the usual recommended dose, were equally safe and effective, although their efficacy was limited in more severe forms of GERD, such as erosive esophagitis (endoscopic healing rates of 40% to 50%, symptom improvement rates of 40% to 60%).<sup>28</sup>

Some non-placebo-controlled comparative studies involving H<sub>2</sub>RAs have produced 12-week healing rates as high as 70%.<sup>25</sup> For example, a comparative study of ranitidine (150 mg two or four times daily) and cimetidine (800 mg twice daily) for the healing of erosive esophagitis demonstrated 12-week healing rates ranging from 68% to 77% (Figure 5).<sup>32</sup> Another study of esophagitis healing found that the 6-week healing rate with ranitidine was 78% for isolated erosions but dropped to 38% for confluent erosions and to only 23% for circumferential erosions (Figure 6).<sup>33</sup>

### Tolerance

The suppression of intragastric acidity diminishes with repeated administration of H<sub>2</sub>RAs.<sup>34</sup> A single dose of an H<sub>2</sub>RA (Table 3)<sup>35</sup> inhibits acid secretion for approximately 4 to 8 hours and decreases stimulated acid secretion by approximately 70% in patients with esophagitis. However, H<sub>2</sub>RA treatment has several disadvantages, including a relatively short duration of action (compared with PPIs), incomplete inhibition of acid secretion in response to a meal, and the development of tolerance. It is therefore not easy for H<sub>2</sub>RAs to effectively heal the more severe forms of erosive esophagitis, even when very high doses are used. When severe erosive esophagitis is not present, relief of reflux symptoms has been obtained after 4 weeks using a twice-daily regimen. In grades I or II

esophagitis, healing can be achieved with any of the H<sub>2</sub>RAs in 40% to 60% of cases in 8 weeks. This success rate can be increased to 50% to 70% by a substantial increase in dose, but this entails cost and compliance considerations.<sup>36</sup>

It is possible that tolerance may develop as a result of the down-regulation of H<sub>2</sub>-receptors. Another possibility is that there are adaptive changes in acid secretion that are stimulated by acetylcholine, gastrin, or both.

A number of clinical studies have shown that tolerance to standard H<sub>2</sub>RAs probably develops within the first 2 weeks of therapy.<sup>36</sup> More recently, however, tolerance has been shown to develop within 72 hours when intravenous administration of ranitidine is used to control bleeding in the upper gastrointestinal tract. To avoid such tolerance, more frequent dosing of ranitidine, more careful monitoring of intragastric pH, and repeated dose adjustments would be needed.<sup>37</sup>

## ■ PROTON PUMP INHIBITORS

Proton pump inhibitors are the most effective medical treatment for GERD. They profoundly suppress acid secretion through inhibition of H<sup>+</sup>,K<sup>+</sup> adenosine triphosphatase (ATPase), the proton pump of the parietal cell responsible for acid production. Unlike H<sub>2</sub>RAs, they block acid production regardless of the method of stimulation, providing a greater degree of acid suppression for a longer duration of time. All PPIs are prodrugs, so-called substituted benzimidazoles, which must be activated by acid to inhibit the proton pump. This translates into higher efficacy rates in terms of GERD symptom relief and healing of erosive esophagitis.<sup>26</sup> A once-daily, morning dose of a PPI will relieve symptoms in 83% of patients with GERD and heal erosive esophagitis in 78%.<sup>1</sup> Furthermore, these rates are achieved after only 4 to 8 weeks of therapy. As with H<sub>2</sub>RAs, healing of esophagitis with PPIs correlates with the severity of esophagitis.

Excellent healing rates have been reported in even the most severe grades of esophagitis after PPI therapy.<sup>26</sup> There is a wealth of study data on the safety and efficacy of omeprazole, the first PPI approved for treatment of GERD. Other available PPIs include lansoprazole, rabeprazole, and pantoprazole. Clinical efficacy in GERD and the safety profiles among this first generation of PPIs are very similar. The newest PPI, esomeprazole, the S-isomer

**TABLE 4**  
Possible drug interactions with PPIs resulting from metabolism via the cytochrome P450 system<sup>40-43</sup>

PPI	Interactions
Omeprazole	<ul style="list-style-type: none"> <li>• Inhibits metabolism of phenytoin, diazepam, antipyrine, aminopyrine, and the R-isomer of warfarin</li> <li>• Does not inhibit metabolism of propranolol, theophylline, or the S-isomer of warfarin</li> </ul>
Lansoprazole	<ul style="list-style-type: none"> <li>• No clinically significant interactions with most drugs metabolized through the cytochrome P450 system</li> <li>• Increases metabolism rate of theophylline by 10%</li> </ul>
Pantoprazole	<ul style="list-style-type: none"> <li>• No clinically significant interactions with drugs metabolized through the cytochrome P450 system</li> <li>• No interactions with oral contraceptives</li> </ul>
Rabeprazole	<ul style="list-style-type: none"> <li>• No clinically significant interactions with drugs metabolized through the cytochrome P450 system</li> </ul>
Esomeprazole	<ul style="list-style-type: none"> <li>• No clinically significant interactions with drugs metabolized through the cytochrome P450 system</li> </ul>

of omeprazole, has demonstrated more complete symptom relief in patients with GERD and esophageal healing for a greater proportion of patients and in a shorter time period compared with omeprazole.<sup>38,39</sup>

### Pharmacokinetics and pharmacodynamics

All PPIs are metabolized in the liver via the cytochrome P450 system, specifically by the CYP2C19 and CYP3A4 enzymes.<sup>40</sup> There are subtle differences, however, in how each PPI is metabolized within this system. An agent's preference for one enzyme over another influences the metabolic pathway and leads to differences among the PPIs in interactions with other drugs (Table 4).

Because PPIs reduce gastric acidity, they may alter the absorption of other orally administered drugs. Elevated gastric pH has the potential to affect the stability of agents that are acid-labile or alkaline-labile, as well as the absorption of agents that have pH-dependent formulations. Whether these interactions are clinically significant is more difficult to determine. However, PPIs reduce the area

under the curve (AUC) and the peak plasma levels of ketoconazole to such an extent that patients starting therapy with ketoconazole may need to discontinue PPI therapy.<sup>40</sup>

Individual PPIs differ in clinical pharmacology. The following sections identify selected features of the clinical pharmacology of the five available PPIs.

**Omeprazole** is inactivated when it is exposed to gastric acid, so it has been formulated in granules that release the drug only when the pH is greater than 6.0, resulting in a bioavailability of approximately 50%. Peak plasma concentrations occur 2 to 4 hours after oral administration and increase during the first days of therapy. The plasma half-life of omeprazole is approximately 1 hour. Food intake has no effect on the drug's pharmacokinetics.<sup>40</sup>

Omeprazole differs from other PPIs in that its bioavailability increases with repeat dosing. A single dose of omeprazole has a bioavailability of approximately 35%, which increases with repeat dosing to around 60%. Mean AUC and peak plasma concentrations also increase disproportionately between days 1 and 5 of treatment.<sup>40</sup>

One 20-mg dose of omeprazole inhibits acid secretion by 65% after 4 to 6 hours, dropping to 25% after 24 hours. Inhibition increases after subsequent doses and plateaus after four to six doses. Steady-state inhibition varies widely among patients, ranging from 35% to 65% based on acid secretion measurements taken 24 hours after drug inhibition, and from 30% to 100% based on measurements of 24-hour gastric acidity based on intragastric pH.<sup>41</sup> In one study, 20-mg and 40-mg doses resulted in a mean intragastric pH greater than 4.0 for approximately 42% and 62%, respectively, of a 24-hour period after 5 days of administration.<sup>42</sup> In general, when larger doses of omeprazole are given, variation of acid inhibition in patients is reduced, and acid inhibition is increased.<sup>41</sup>

**Lansoprazole.** Like other PPIs, lansoprazole is acid-labile. The drug is rapidly absorbed, with peak plasma concentration reached only 1.7 hours after administration. Food intake with lansoprazole delays the drug's absorption.<sup>40</sup> Multiple dosing does not alter its pharmacokinetics. Lansoprazole's bioavailability is approximately 80%, and its elimination half-life is less than 2 hours.<sup>43</sup>

Some, but not all, studies have shown that lansoprazole's ability to suppress acid secretion is dose-dependent and increases with repeated administration. In clinical trials, a 30-mg dose resulted in an

intragastric pH greater than 4.0 for 41% of a 24-hour period on the first day of administration, rising to 66% on the fifth day. A 15-mg dose yielded an intragastric pH greater than 4.0 for 22% of a 24-hour period on the first day of administration and for 49% of a 24-hour period by the fifth day. The onset of antisecretory activity also differs between doses, with the 30-mg dose causing an increase in intragastric pH in 1 to 2 hours after administration and the 15-mg dose causing an increase in 2 to 3 hours. This time decreased with repeated dosing for both dosage strengths.<sup>43</sup>

**Pantoprazole.** All PPIs are rapidly degraded by acidic conditions, but pantoprazole is slightly more stable than omeprazole and lansoprazole under neutral conditions or conditions that are mildly acidic (pH  $\approx$ 3.5 to pH  $\approx$ 7.4). Pantoprazole is therefore easier to produce in intravenous form.<sup>42</sup> A 40-mg dose of pantoprazole reaches peak plasma concentrations 2 to 4 hours after administration. The estimated bioavailability of 77% reflects a low first-pass hepatic extraction. Food intake delays absorption of pantoprazole. The drug's mean plasma terminal elimination half-life is 0.9 to 1.9 hours. Repeated dosing does not alter the pharmacokinetics of pantoprazole.<sup>42</sup> In this way, pantoprazole is similar to lansoprazole but unlike omeprazole.

Steady-state acid inhibition by a repeated once-daily dose of pantoprazole is dose-related over the range of 20 mg to 60 mg. However, minimal additional inhibition occurs with higher doses. After 5 days of oral administration of 40 mg or 60 mg, significant reductions in basal, nocturnal, and 24-hour intragastric pH occurred. The 40-mg dose achieved an intragastric pH greater than 4.0 for approximately 41% of a 24-hour cycle after 5 days of administration.<sup>42</sup>

**Rabeprazole** is degraded by acid in a manner similar to lansoprazole and omeprazole and is less stable at a neutral pH than other PPIs. Maximum plasma concentrations occur 3 to 4 hours after a single dose, regardless of the dosage strength. The bioavailability of rabeprazole following a 20-mg single dose is approximately 52%. Peak plasma concentrations and the AUC increase with rising dosages, but the pharmacokinetics are not altered by multiple doses. Rabeprazole's plasma half-life is similar to that of omeprazole at approximately 1 hour. The time to achieve maximum plasma concentration is significantly prolonged by food intake. This is of no clinical significance, however, as the AUC is not altered

to a significant extent. It has been suggested that the effect of food on the time to maximum plasma concentration is secondary to the effect of food in prolonging the gastric emptying time of the enteric-coated tablets.<sup>40</sup>

The acid-suppressive effects of rabeprazole do not increase to a significant extent with increasing doses. For instance, patients with GERD achieved an intragastric pH of 4.0 or greater for approximately 16 hours after 5 days of administration of 20 mg of rabeprazole, compared with approximately 18 hours after 5 days of administration of 40 mg.<sup>44</sup>

**Esomeprazole.** Discussion of esomeprazole requires brief mention of stereoisomers, which are molecules with one or more “chiral” centers that allow the possibility of forms with the same chemical formula but differing spatial arrangements. These differences can translate into clinical differences in terms of a compound’s efficacy and toxicity.

Esomeprazole is the S-enantiomer of racemic S,R-omeprazole. It has been shown to be stable, with more than 40% of each dose showing conversion to the R-isomer.<sup>45</sup>

Esomeprazole reaches maximum plasma concentration approximately 2 hours after administration of a single dose. As with omeprazole, the bioavailability of esomeprazole is altered by repeat dosing. In clinical studies, a 20-mg dose of esomeprazole was 50% bioavailable on day 1 of administration, increasing to 68% on day 5. The total AUC increased by 90% over 5 days. With a 40-mg dose of esomeprazole, bioavailability increased from 64% on day 1 to 89% on day 5, with an AUC increase of 159%.<sup>46</sup> The plasma clearance rate of esomeprazole decreases from 22 L/hour to 16 L/hour over a 5-day period, and its plasma elimination half-life increases from 0.8 hours to 1.2 hours with repeat dosing.

The pharmacokinetic and pharmacodynamic profile of esomeprazole differs from that of omeprazole. Esomeprazole given daily for 5 days had a 70% higher AUC than the same dosage of omeprazole given over the same period.<sup>47</sup> Furthermore, although there is variability in omeprazole’s acid inhibition among individual patients, this effect is substantially reduced with esomeprazole.

### **Efficacy: symptom improvement**

Symptom relief is the primary goal of medical therapy for GERD and is highly predictive of endoscopic healing if esophagitis is present.<sup>48</sup> Interestingly, the severity of a patient’s heartburn is not necessarily

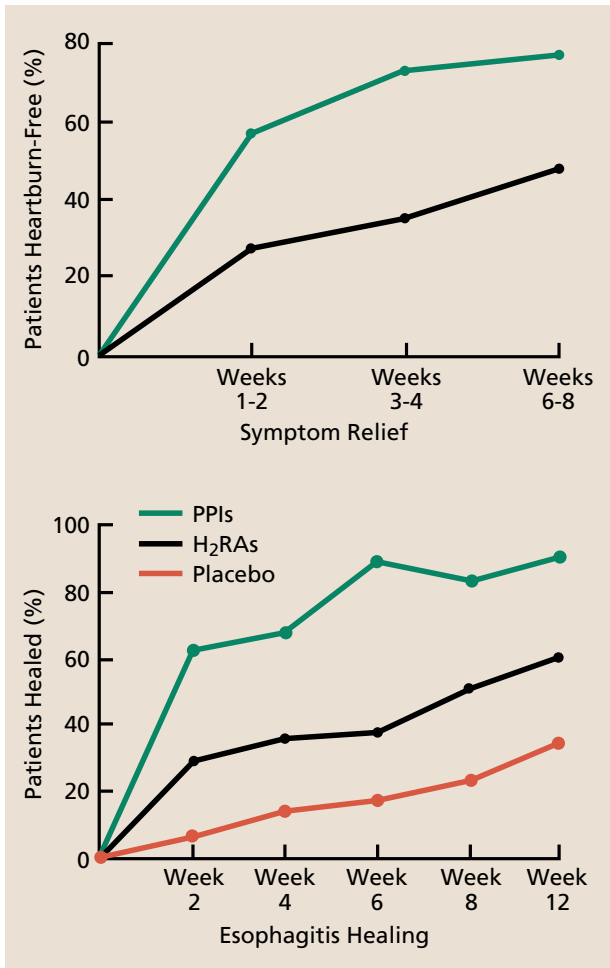
predictive of the severity of erosive esophagitis that he or she experiences. This was clearly shown in a clinical trial by Venables and colleagues,<sup>49</sup> who found that chronic GERD symptoms were unreliable in predicting the presence of underlying esophagitis in patients at trial entry. Although patients with severe heartburn may have normal endoscopy findings, many will have undetected erosive esophagitis. This study compared the efficacy of omeprazole 10 mg or 20 mg daily with that of ranitidine 150 mg twice daily for relief of heartburn. The 20-mg omeprazole dose was the most effective initial therapy for relief of GERD symptoms.<sup>49</sup>

Many studies have compared the effects of H<sub>2</sub>RAs and PPIs on symptom improvement. In general, PPIs are more effective than H<sub>2</sub>RAs and work at a faster rate. Additionally, omeprazole has been compared with other PPIs for symptom improvement in several trials. Overall, there is not a significant difference in efficacy among the PPIs; however, there is some variability in different clinical trials.

In their meta-analysis of the efficacy of GERD therapies for treating grades II through IV erosive esophagitis, Chiba and colleagues<sup>23</sup> showed that PPIs provide complete heartburn relief in a higher percentage of patients and at a faster rate compared with H<sub>2</sub>RAs. They found that more patients became heartburn-free by the second week of treatment with PPIs (58.0% ± 16.9%) than by 8 weeks of therapy with H<sub>2</sub>RAs (48.8% ± 16.2%). The speed of heartburn relief was faster with PPIs than with H<sub>2</sub>RAs: at week 2, patients treated with PPIs became heartburn-free at a rate of 31.8% (±7.9%) per week, compared with a rate of 17.9% (±5.8%) per week for patients treated with H<sub>2</sub>RAs (**Figure 7**).

In the same analysis, PPIs also provided the greatest overall symptom relief, as 77.4% (±10.4%) of PPI-treated patients became heartburn-free, compared with 47.6% (±15.5%) of patients treated with H<sub>2</sub>RAs.<sup>23</sup>

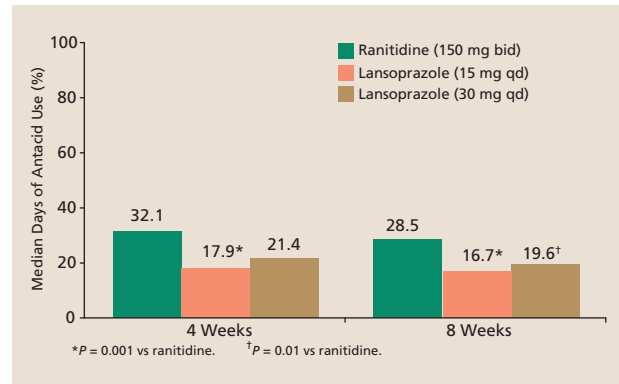
In a pair of randomized, double-blind, multicenter trials, Richter and colleagues<sup>50</sup> compared lansoprazole with ranitidine in 901 patients with symptomatic reflux disease confirmed by endoscopy to be nonerosive GERD. The frequency of antacid use served as an end point for evaluating these agents’ efficacy in relieving heartburn symptoms. Compared with patients who received either of two dosages of lansoprazole, patients treated with ranitidine reported ingesting antacids on a significantly higher per-



**FIGURE 7.** Time curves for rates of heartburn symptom relief (top) and esophagitis healing (bottom) with PPI and H<sub>2</sub>RA therapy in a meta-analysis of efficacy trials among patients with GERD.<sup>23</sup> By evaluation week 2, PPIs relieved heartburn and healed esophagitis in more patients than H<sub>2</sub>RAs did by weeks 8 or 12. Reprinted from reference 23 with permission from the American Gastroenterological Association.

centage of days (**Figure 8**) and ingesting a significantly higher number of antacid tablets per day. Across all treatment groups, the frequency of antacid use was associated with the frequency of days or nights with heartburn.

**Variations among PPIs.** Although all PPIs provide a comparably high level of symptom improvement, there are some variations in PPI performance in comparative clinical trials. Castell and colleagues<sup>51</sup> evaluated two doses of lansoprazole (15 mg and 30 mg once daily) in comparison with omeprazole (20 mg once daily) and placebo in 1,284 patients with endoscopically confirmed erosive esophagitis.

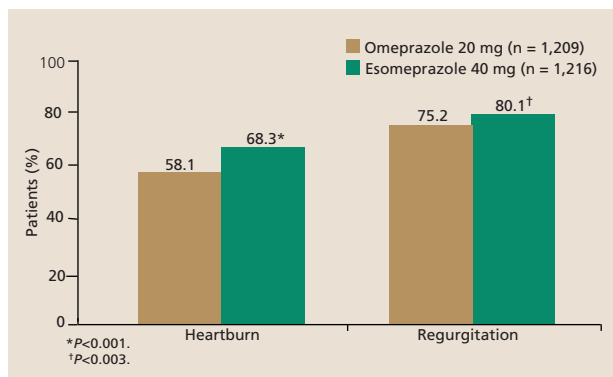


**FIGURE 8.** Four-week and 8-week comparisons of the median percentage of days antacids were used by patients with nonerosive GERD while receiving either ranitidine or one of two dosages of lansoprazole for relief of heartburn symptoms.<sup>50</sup>

All PPI-treated groups experienced relief of daytime and nighttime heartburn, regurgitation, and belching to a significantly greater degree than did the placebo group, as judged by investigators and patients. Omeprazole and the 30-mg dose of lansoprazole were more effective than placebo in relieving investigator-assessed painful swallowing, whereas the 15-mg lansoprazole dose was not significantly more effective than placebo. There were no differences between the omeprazole and lansoprazole 30-mg treatment groups in investigator-assessed symptom relief, but there were differences in patient-assessed relief. After 8 weeks of therapy, patients who received omeprazole reported experiencing heartburn on 11.8% of days and 8.9% of nights during the trial, whereas those receiving 30 mg of lansoprazole reported experiencing heartburn on 8.6% of days and 6.5% of nights ( $P < 0.05$  vs omeprazole). Patients receiving placebo reported experiencing heartburn on 60% of days and 45% of nights.

Mössner and colleagues<sup>52</sup> investigated symptom relief in 286 patients with grades II or III erosive esophagitis randomized to receive 40 mg of pantoprazole or 20 mg of omeprazole daily for 8 weeks. Investigator-assessed symptom relief was recorded after 2 weeks and 4 weeks of therapy. Differences between the treatment groups in relieving heartburn, regurgitation, and painful swallowing were not statistically significant at 2 weeks or 4 weeks. At 2 weeks, 59% of patients receiving pantoprazole and 69% of those receiving omeprazole were symptom-free; at 4 weeks, these percentages rose to 83% and 86%, respectively (not statistically significant).

Dekkers and colleagues<sup>53</sup> compared the efficacy of



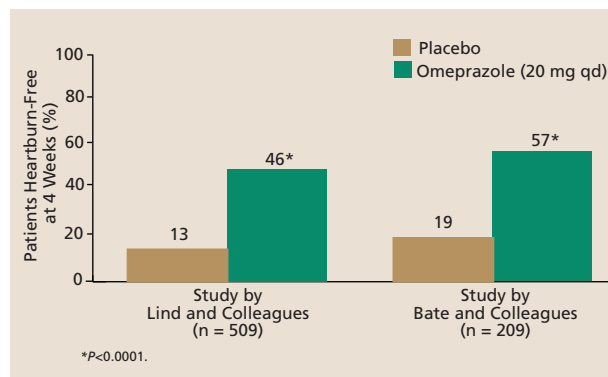
**FIGURE 9.** Percentages of patients with investigator-assessed resolution of GERD symptoms after 4 weeks of omeprazole or esomeprazole therapy.<sup>39,54</sup>

omeprazole 20 mg daily and rabeprazole 20 mg daily in an 8-week trial in 202 patients with erosive or ulcerative reflux disease. Similar improvements in heartburn frequency rates and in daytime and nighttime heartburn severity were seen in the two treatment arms. At 8 weeks, 73% of patients receiving rabeprazole and 76% of those receiving omeprazole reported a lessening of heartburn frequency. In terms of heartburn severity, 68% of patients receiving rabeprazole reported resolution of daytime heartburn and 64% reported resolution of nighttime heartburn, which were comparable to the rates in the omeprazole group (66% and 67%, respectively).

Kahrilas and colleagues<sup>38</sup> compared symptom relief with omeprazole 20 mg daily and esomeprazole 20 mg or 40 mg daily in 1,960 patients with erosive esophagitis. After 4 weeks of therapy, esomeprazole 40 mg daily provided more effective relief of symptoms: patients who received this regimen reported experiencing no heartburn on 72.7% of days and 84.7% of nights during the trial, whereas those receiving omeprazole reported experiencing no heartburn on 67.1% of days and 80.1% of nights ( $P < 0.05$ ). Onset of symptom relief was also faster with esomeprazole 40 mg daily, as 46.6% of patients receiving this regimen reported no heartburn on the first day of treatment, compared with 37.0% of patients receiving omeprazole.

Finally, a study by Richter and colleagues of 2,425 patients with GERD demonstrated better resolution of investigator-assessed heartburn and regurgitation after 4 weeks of treatment with esomeprazole 40 mg daily than with omeprazole 20 mg daily (**Figure 9**).<sup>39,54</sup>

**Symptom relief in nonerosive GERD.** PPIs have also been tested in patients who have GERD symp-



**FIGURE 10.** Percentages of patients with GERD but without erosive esophagitis who experienced complete relief of heartburn after 4 weeks of PPI therapy or placebo treatment.<sup>55,56</sup>

toms but do not have erosive esophagitis. Lind and colleagues<sup>55</sup> compared omeprazole 10 mg or 20 mg daily with placebo in 509 patients with GERD but without erosive esophagitis. After 4 weeks of therapy, 46% of patients receiving omeprazole 20 mg reported complete absence of heartburn, compared with 31% of patients receiving omeprazole 10 mg and 13% of placebo recipients (**Figure 10**). A study by Bate and colleagues<sup>56</sup> of 209 patients with GERD symptoms but no esophagitis yielded similar results. This study tested only the 20-mg dose of omeprazole against placebo. After 4 weeks of therapy, 57% of patients in the omeprazole group were free of heartburn (vs 19% in the placebo group [**Figure 10**]), 75% experienced no regurgitation (vs 47% with placebo), and 43% were completely asymptomatic (vs 14% with placebo).

While PPIs are significantly more effective than placebo in relieving heartburn in patients with erosive esophagitis, they are not as effective in patients with nonerosive reflux disease. Carlsson and colleagues<sup>57</sup> conducted a 4-week comparison of two dosages of omeprazole in 277 patients with erosive esophagitis and 261 patients with GERD symptoms without erosive esophagitis. Omeprazole 10 mg daily achieved complete symptom relief in 37% of patients with erosive esophagitis, compared with 31% of patients without erosive esophagitis. Similarly, omeprazole 20 mg daily achieved complete symptom relief in 48% of patients with erosive esophagitis vs 29% of those without erosive esophagitis.

**Dosage level.** Dosage is an important consideration in PPI therapy. In the absence of esophagitis, when symptoms are mild or intermittent, a standard-dose PPI has been found to be effective.<sup>57-59</sup> If symptoms are particularly troublesome or there is moder-

ate or severe erosive esophagitis, a twice-daily dosage may be necessary for a period of time. (However, no prospective data exist to support this recommendation.<sup>60</sup>) Following this, dose reduction should be attempted and a plan formulated for long-term therapy. Dosage level is significant to controlling symptoms and maximizing the success of PPI therapy.<sup>60</sup>

**Nocturnal acid breakthrough.** Several studies have assessed various therapeutic regimens for controlling the persistent problem of nocturnal acid breakthrough, including double-dose PPI therapy and single- or double-dose PPI therapy combined with an H<sub>2</sub>RA. Khoury and colleagues<sup>61</sup> found that combination therapy with 20 mg of omeprazole in the morning and 150 mg of ranitidine at night is not as effective in controlling intragastric pH as omeprazole 20 mg twice daily (one dose in the morning and one at night). In 20 healthy volunteers, the median percentage of time that intragastric pH was less than 4 when participants were upright was 29.7% in the ranitidine group and 18.9% in the double-dose omeprazole group ( $P = 0.003$ ). The median percentages of time that intragastric pH was less than 4 when participants were recumbent were 44.75% and 23.45%, respectively ( $P = 0.02$ ). In this study, ranitidine administered at bedtime did not eliminate the need for a second dose of omeprazole.

Peghini and colleagues<sup>62</sup> compared three different regimens for controlling nocturnal acid breakthrough in 12 healthy volunteers. All participants received omeprazole 20 mg twice daily. They also received either an additional dose of omeprazole, 150 or 300 mg of ranitidine, or placebo at bedtime. Participants who received placebo at bedtime experienced an intragastric pH of less than 4 for 48% of the night. A third dose of omeprazole reduced this percentage to 31% ( $P < 0.005$ ), but ranitidine was the most effective therapy: participants who received 150 or 300 mg of ranitidine at bedtime experienced an intragastric pH of less than 4 for only 5% and 6% of the night, respectively ( $P < 0.01$  vs omeprazole 20 mg three times daily). These data suggest that double-dose PPI therapy daily plus an H<sub>2</sub>RA at bedtime may be an effective regimen for control of nocturnal acid breakthrough.

#### **Efficacy: healing of erosive esophagitis**

In their above-mentioned meta-analysis (Figure 1), Chiba and colleagues<sup>23</sup> noted that PPIs were more effective than H<sub>2</sub>RAs in treating patients with grades II through IV erosive esophagitis. PPIs pro-

vided more complete relief of symptoms and faster healing of esophagitis (Figure 7). At week 2, the healing rate per week was 31.7% ( $\pm 3.3\%$ ) for PPIs, compared with 15.0% for H<sub>2</sub>RAs. The healing rate per week slowed for both agents at each subsequent 2-week interval. However, PPIs maintained a therapeutic advantage because more patients were healed earlier in the course of PPI therapy, leaving fewer patients who were available to heal in later weeks. Overall, PPIs produced healing at a rate of 11.7% ( $\pm 0.5\%$ ) per week, which was twice as fast as the healing rate per week with H<sub>2</sub>RAs (5.9%  $\pm 0.2\%$ ) and four times as fast as that with placebo (2.9%  $\pm 0.2\%$ ). A mean of 83.6% ( $\pm 11.4\%$ ) of patients with erosive esophagitis were healed with PPI therapy, compared with 51.9% ( $\pm 17.1\%$ ) with H<sub>2</sub>RA therapy. These numbers compare with a healing rate of 28.2% ( $\pm 15.6\%$ ) with placebo.

A meta-analysis by Caro and colleagues<sup>63</sup> also found that PPIs were significantly more effective than H<sub>2</sub>RAs. The investigators analyzed 53 randomized controlled trials, 38 of which involved acute therapy, although 12 of these were subsequently excluded and 15 involved maintenance treatment. Of the 26 acute therapy trials, 18 compared a PPI with an H<sub>2</sub>RA. Of the 15 maintenance therapy trials, 5 compared a PPI with an H<sub>2</sub>RA. No study of pantoprazole met the inclusion criteria for maintenance therapy. Combined efficacy rates from both acute and maintenance studies yielded a risk ratio that was highly favorable to PPIs.

**Variations among PPIs.** In the same analysis, Caro and colleagues<sup>63</sup> compared the efficacy of lansoprazole, pantoprazole, and rabeprazole with that of omeprazole and found no differences in those head-to-head comparisons. Similar results were obtained by other investigators, including teams led by Castell,<sup>51</sup> Mössner,<sup>52</sup> and Dekkers.<sup>53</sup>

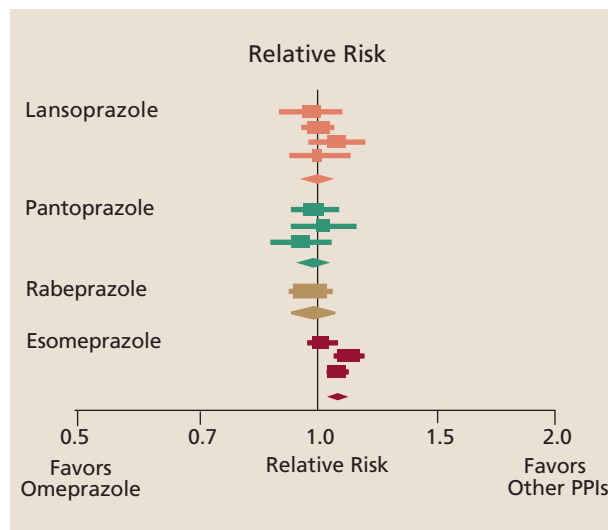
Although the study by Castell and colleagues<sup>51</sup> found differences in patient-assessed symptom relief between groups receiving omeprazole 20 mg daily or lansoprazole 30 mg daily, esophageal healing rates were not statistically different between the groups. Eight-week courses of each regimen healed esophagitis in approximately 91% of patients. In the study by Mössner and colleagues,<sup>52</sup> patients with esophagitis received an 8-week course of either pantoprazole 40 mg daily or omeprazole 20 mg daily. The healing rate with pantoprazole (94%) was not statistically different from that with omeprazole (90%). Finally, Dekkers and colleagues<sup>53</sup> found that an 8-week course

of rabeprazole 20 mg daily healed 92% of patients with erosive esophagitis, compared with 94% for an 8-week course of omeprazole 20 mg daily.

In the Castell study,<sup>51</sup> lansoprazole 15 mg daily healed 79% of patients, a significantly lower percentage than those achieved with lansoprazole 30 mg daily and omeprazole 20 mg daily ( $P < 0.05$ ). A similar dose-dependent pattern occurred in a study by Lundell and colleagues<sup>64</sup> between 10-mg and 20-mg doses of omeprazole. These researchers analyzed the efficacy of omeprazole in the healing of Los Angeles (LA) classification grades A through C erosive esophagitis by grade (mild through moderate-to-severe injury). With omeprazole 10 mg daily, healing efficacy was directly correlated to the grade of esophagitis: 77% of patients with grade A were healed, 50% of patients with grade B, and 20% of patients with grade C. However, this gradation in healing did not occur with omeprazole 20 mg daily, which healed roughly the same percentage (approximately 80%) of patients with grades A and B esophagitis. The 20-mg dose of omeprazole healed fewer patients with grade C esophagitis (approximately 40%) than with other grades, although it also healed more patients with this severity grade than did the 10-mg dose. A dose-related increase in healing efficacy with omeprazole was not observed, however, above the 20-mg dose.

Sontag and colleagues<sup>65</sup> compared 20-mg and 40-mg daily doses of omeprazole with placebo in 230 patients with GERD symptoms and erosive esophagitis. Whereas both doses of omeprazole were superior to placebo in all measures, symptom relief and esophagitis healing rates were similar in the two omeprazole groups. By the eighth week, 73.5% of patients receiving omeprazole 20 mg had complete esophageal healing, compared with 74.7% of patients receiving omeprazole 40 mg and 14.0% of placebo recipients. Omeprazole 20 mg achieved complete relief of daytime heartburn in 79.5% of patients and complete relief of nighttime heartburn in 79.5% of patients, compared with 81.6% and 85.1%, respectively, for omeprazole 40 mg, and 37.2% and 34.9%, respectively, for placebo. Although the higher dose of omeprazole resulted in faster relief of symptoms, differences between the treatment arms were not statistically significant.

A recent meta-analysis by Edwards and colleagues<sup>66</sup> found that esomeprazole 40 mg daily produced higher healing rates than omeprazole 20 mg daily at 4 and 8 weeks after treatment (**Figure 11**).



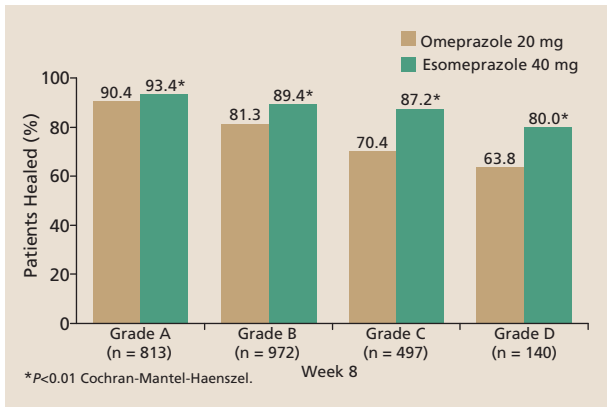
**FIGURE 11.** Relative risk of endoscopic healing at 8 weeks for all standard-dose PPIs compared with omeprazole 20 mg. Rectangles denote relative risk values from individual comparative trials with omeprazole; horizontal lines running through rectangles denote 95% confidence intervals. Diamonds indicate fixed effects from all comparative trials of the given PPI. Reprinted from reference 66 with permission from Blackwell Publishing.

In their analysis of 12 randomized controlled trials, these investigators found no significant differences among omeprazole and lansoprazole, pantoprazole, or rabeprazole at 4 and 8 weeks. They postulated that the superiority of esomeprazole to omeprazole may be related to its more effective suppression of intragastric acid. Recent acid-suppression studies<sup>67</sup> show that esomeprazole maintains intragastric pH above 4 significantly longer than lansoprazole, pantoprazole, or rabeprazole do, which may account for the differences in healing among the agents observed in this meta-analysis.

One of the studies included in the meta-analysis, conducted by Kahrilas and colleagues<sup>38</sup> (described in “Efficacy: symptom improvement” above), compared healing rates among omeprazole 20 mg daily and esomeprazole 20 mg and 40 mg daily. After 8 weeks of therapy, esomeprazole 40 mg healed esophagitis in 94.1% of patients, whereas omeprazole did so in 86.9% of patients ( $P < 0.05$ ).

The study by Richter and colleagues<sup>39</sup> in 2,425 patients with erosive esophagitis confirmed these findings. After 8 weeks of therapy, erosive esophagitis was healed in 93.7% of patients receiving esomeprazole, compared with 84.2% of patients receiving omeprazole (by intention-to-treat analysis). Esomeprazole was more effective than omeprazole in healing





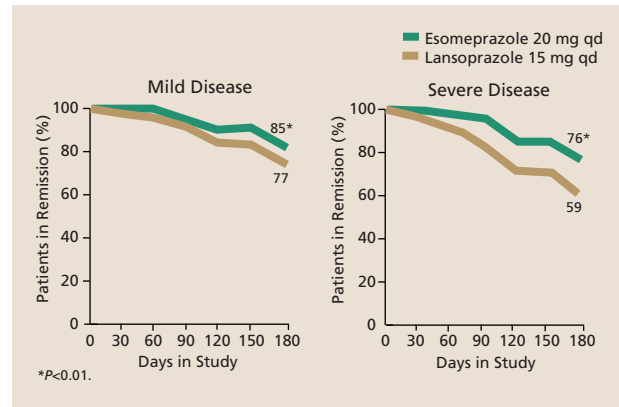
**FIGURE 12.** Grade-specific erosive esophagitis healing rates with omeprazole and esomeprazole therapy. Grades A and B in the Los Angeles (LA) classification represent mild to moderate esophagitis; grades C and D represent moderate to severe esophagitis.<sup>39</sup>

all grades of esophagitis, as shown in **Figure 12**. Among patients with LA grades C and D esophagitis, esomeprazole healed 85.8% of patients after 8 weeks of therapy, whereas omeprazole healed 68.1%.

More recently, a study by Castell and colleagues<sup>68</sup> showed that esomeprazole demonstrated a slightly but significantly higher healing rate (92.6%) than lansoprazole (88.8%) at week 8. The difference in healing rates between esomeprazole and lansoprazole increased as the baseline severity of erosive esophagitis increased.

**Maintenance of healing.** Lauristen and colleagues<sup>69</sup> demonstrated that esomeprazole was more effective than lansoprazole in maintaining the healing of all grades of esophagitis (**Figure 13**). They compared esomeprazole 20 mg once daily with lansoprazole 15 mg once daily in the maintenance treatment of 1,231 patients with healed reflux esophagitis. Analysis of remission rates based on the LA classification system showed that esomeprazole maintained patients in remission more consistently across all grades of reflux esophagitis, whereas the efficacy of lansoprazole decreased to a greater extent with increasing severity of disease.

Other studies have demonstrated the low relapse rate with esomeprazole therapy over a 6-month period. In a study conducted by Johnson and colleagues<sup>70</sup> of 318 patients with erosive esophagitis, 40-mg and 20-mg doses of esomeprazole once daily were highly effective at maintaining healing of erosive esophagitis over 6 months. Rates of erosive esophagitis recurrence were 6% and 7% with esomeprazole 40 mg and 20 mg, respectively, compared



**FIGURE 13.** Comparison of the maintenance of erosive esophagitis healing with esomeprazole and lansoprazole therapy in patients with mild and severe disease. Reprinted from reference 69 with permission from Blackwell Publishing.

with 71% with placebo. Also, more than 70% of patients remained symptom-free at 6 months.

**Table 5** presents the common dosing regimens and the efficacy rates of the available PPIs for the maintenance of erosive esophagitis healing.<sup>70–75</sup>

### Intravenous PPI therapy

Intravenous pantoprazole is the only PPI currently indicated in the United States for short-term treatment (7 to 10 days) of GERD in patients with a history of erosive esophagitis who are unable to take the oral formulation. In a double-blind placebo-controlled study, IV and oral pantoprazole were shown to be similar in their ability to suppress maximum and basal acid output. The study involved 65 patients with erosive esophagitis who were given 20 mg or 40 mg of oral pantoprazole for 10 days and then randomized to receive either IV pantoprazole or placebo for 7 days. Acid output was determined 24 hours after the last day of oral medication and on the first and last days of IV administration. Among patients receiving IV pantoprazole, acid suppression was comparable to that seen with oral pantoprazole and was significantly better than that achieved by patients receiving IV placebo. The recommended adult dosage of IV pantoprazole is 40 mg daily for 7 to 10 days.<sup>76</sup>

Omeprazole has been used in injectable form in some studies around the world in an effort to prevent rebleeding following treatment for bleeding ulcers. A study in Hong Kong by Lau and colleagues<sup>37</sup> demonstrated the efficacy of omeprazole (given as an 80-mg bolus injection followed by a

continuous infusion of 8 mg/hour for 72 hours) in preventing recurrent bleeding after endoscopic treatment of bleeding peptic ulcers. This study showed that a high-dose infusion of omeprazole reduced the rate of recurrent bleeding, decreased the need for endoscopic treatment and blood transfusions, and shortened the length of hospitalization.

### Failure of therapy

Treatment of GERD with PPIs provides fast and complete relief to a larger percentage of patients than any other medical therapy. As well as PPIs work, however, they do not cure GERD and may not relieve symptoms or heal esophagitis in all patients.

Treatment with a PPI may fail in some patients because their symptoms are not caused by GERD. PPI therapy may also fail in a patient who does have GERD if the PPI dosage or the duration of therapy is insufficient to control symptoms or heal esophagitis. Therapy may also be unsuccessful if the PPI fails to control gastric acidity, although such cases are rare.<sup>77,78</sup> Several reasons have been postulated for why a PPI may fail to control gastric acidity. These include oral bioavailability differences, meal timing that influences ATPase activation, increased metabolism of the PPI by the cytochrome P450 system, and hypersecretion of acid (including Zollinger-Ellison syndrome).

Patients with higher grades of esophagitis and more severe disease are less likely to experience complete healing with PPIs. A study conducted by Holloway and colleagues<sup>79</sup> in 61 patients with grades III or IV erosive esophagitis found that 30% of patients were not healed after 8 weeks of therapy with omeprazole 20 mg daily. These patients had greater total 24-hour esophageal acid exposure before treatment than those whose esophagitis was healed. Of those patients in whom the original course of therapy failed, 47% did not heal after 8 more weeks of therapy with a 40-mg daily dose of omeprazole. This final group of patients in whom both courses of therapy failed had levels of acid exposure before treatment that were similar to those of patients who were healed, but they had greater acid exposure during therapy, particularly at night while sleeping.

Several studies have been conducted with omeprazole to investigate the incidence of failure of PPI therapy. Leite and colleagues<sup>80</sup> studied 88 patients with refractory GERD symptoms who received 20 mg of omeprazole twice daily—twice the usual dose. Twenty-four-hour pH monitoring

**TABLE 5**  
Profile of PPIs in the maintenance of erosive esophagitis healing

PPI	FDA approval date	Prescribed dose (mg/d)	Efficacy (%) <sup>*</sup>
Omeprazole <sup>71</sup>	1989	10	58
		20	77
Lansoprazole <sup>72</sup>	1995	15	67–79
		30	55–90
Rabeprazole <sup>73</sup>	1999	10	75
		20	87
Pantoprazole <sup>74</sup>	2000	20	70–72
		40	83–86
Esomeprazole <sup>70,75</sup>	2001	20	93
		40	94

\* In controlled clinical trials for maintenance of healing.

was used to assess results. Of the 88 patients, 17 had an intragastric pH less than 4 for more than 50% of a 24-hour period (considered failure of therapy). These 17 were then compared with 19 of the original 88 patients with GERD and with 19 healthy volunteers who received either omeprazole 20 mg twice daily or placebo. The mean intragastric pH was found to be similar between the patients with persistent symptoms who were receiving omeprazole 20 mg twice daily and the healthy subjects receiving placebo. Gastric pH monitoring in 7 patients given 80 mg of omeprazole daily, however, demonstrated a significant reduction in the mean percentage of time that the pH was less than 4, indicating that response is often a dose-dependent phenomenon.

Up to 70% of healthy subjects given twice-daily PPI therapy experience an intragastric pH less than 4 for more than 1 hour overnight (between 10:00 PM and 6:00 AM). Katz and colleagues<sup>81</sup> noted that nocturnal acid breakthrough in patients who take omeprazole 20 mg twice daily is often accompanied by esophageal reflux and, therefore, esophageal acid exposure. Of 61 patients with GERD, 70% experienced nocturnal acid breakthrough and 33% experienced nighttime esophageal acid exposure. Of 15 patients with Barrett's esophagus, 80% experienced nocturnal acid breakthrough and 50% experienced esophageal acid exposure. In the control group (patients without GERD), these percentages were 67% (not significantly different) and 8% ( $P < 0.03$ ), respectively. Nocturnal acid breakthrough accom-

panied by esophageal reflux in patients on twice-daily PPI therapy has important implications for medical therapy in patients with severe GERD or Barrett's esophagus.

As previously discussed, Peghini and colleagues<sup>62</sup> found that the combination of an H<sub>2</sub>RA and a PPI may be effective in managing nocturnal acid breakthrough. A recent study by Fackler and colleagues<sup>82</sup> yielded differing results. The Fackler study showed that, because tolerance developed to 300 mg of ranitidine in patients with nocturnal acid breakthrough, there was no difference in acid suppression between omeprazole 20 mg twice daily and omeprazole 20 mg twice daily plus ranitidine after 1 week of combination therapy.

### Safety

In general, PPIs are a remarkably safe and well-tolerated class of drugs. Headache and diarrhea are the

most frequently reported side effects, and they develop at rates that do not differ significantly from those in placebo-treated patients.<sup>83</sup> Serious side effects resulting from PPI treatment are rare. Moreover, few clinically relevant drug interactions have been reported. The PPIs' benign safety profile has contributed to their widespread prescription and use.

The long-term safety of PPIs has been a topic of some debate because most randomized controlled trials of their effects have not extended beyond 1 year. Thjodleifsson and colleagues<sup>84</sup> addressed this concern in a 5-year controlled trial comparing efficacy and safety between rabeprazole and omeprazole. They concluded from their results that both PPIs were safe and well tolerated during the 5-year study period, contributing to a growing body of evidence confirming the long-term safety of PPIs in acid suppression.

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