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# Gastroesophageal Reflux Disease: The Basics

*Thomas A. Gossel, R.Ph., Ph.D., Professor Emeritus, Ohio Northern University, Ada, Ohio and*
*J. Richard Wuest, R.Ph., PharmD, Professor Emeritus, University of Cincinnati, Cincinnati, Ohio*

*Dr. Thomas A. Gossel and Dr. J. Richard Wuest have no relevant financial relationships to disclose.*

**Goal.** The goal of this lesson is to review gastroesophageal reflux disease, non-pharmacologic measures to modify symptoms, and information to pass along to patients.

**Objectives.** At the completion of this activity, the participant will be able to:

1. demonstrate knowledge of gastroesophageal reflux disease, including its definition and causes, potential risk factors, epidemiology, prevalence, pathogenesis and clinical presentation;
2. select non-pharmacologic measures that are reported to modify symptoms of gastroesophageal reflux disease; and
3. exhibit knowledge of information relative to gastroesophageal reflux disease to convey to patients and/or their caregivers.

## Background

Gastroesophageal reflux disease (GERD; gastro-oesophageal reflux disease, GORD in the U.K.) is a complex, chronic, and relapsing condition that imposes a risk of morbidity and potential for resulting complications. It is the most common outpatient gastrointestinal diagnosis in the United States, with 4.6 million ambulatory office visits recorded and more than $10 billion in direct costs for drug therapy each year. The incidence appears to be increasing.

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A population-based study showed that 44 percent of U.S. adults experience the hallmark symptoms of heartburn and regurgitation at least once each month; 14 percent, weekly; and 7 percent, daily. Men and women experience GERD with equal frequency. Most patients with GERD do not seek medical attention immediately; rather, they will first self-medicate with OTC products. This may be problematic in that classic reflux symptoms are not consistently present in patients with GERD. Moreover, a significant number of patients with GERD present with atypical (extraesophageal) symptoms (Table 1).

## Definition

A degree of reflux into the lower esophagus without causing symptoms is regarded as physiological gastroesophageal reflux. When reflux of the gastric contents incite troublesome symptoms (i.e., at least two heartburn episodes a week) and/or complications, the condition is termed GERD. At present, several definitions are used to describe GERD (Table 2), although none has been validated prospectively. Any of the standard definitions can cause confusion because the threshold distinction between physiologic reflux and reflux disease is arbitrary. Symptoms are troublesome if they adversely affect an individual's well-being. Esophageal GERD syndromes are categorized as those that are symptom-based and those that are defined by tissue injury. Extra-esophageal syndromes are classified as being established by association with GERD. This acknowledges that while the evidence on hand is sufficient to link those syndromes to reflux, it is not sufficient to establish causation.

## Pathogenesis

The primary mechanism for GERD is believed to result from transient relaxation of the lower esophageal sphincter (LES). The LES is a 3- to 5-cm ring of smooth muscle fibers that circle the junction of the esophagus with the stomach. This sphincter normally remains constricted, except during swallowing, to prevent reflux of gastric contents into the esophagus. The LES is not a true anatomical sphincter since it is histologically indistinct from surrounding tissue. The entrance of the esophagus into the stomach is at an oblique angle, which aids the LES in preventing gastrointestinal reflux.

**Table 1**
**Symptoms and conditions associated with GERD**

**Esophageal**
- Heartburn
- Esophagitis
- Esophageal ulcers
- Peptic stricture
- Barrett's esophagus
- Adenocarcinoma
- Asthma
- Odynophagia±
- Nausea

**Extraesophageal***
- Cardiac sinus arrhythmia
- Chest pain (noncardiac)
- Chronic bronchitis
- Chronic cough
- Chronic hoarseness
- Chronic sinusitis
- Dental erosions
- Globus±
- Halitosis
- Laryngeal cancer
- Laryngeal nodules
- Laryngitis
- Nocturnal choking
- Pneumonitis
- Polyps
- Pulmonary fibrosis
- Sore or burning throat
- Throat clearing

*Association with GERD established but good evidence for causation only when accompanied by an esophageal syndrome.
±Odynophagia: Pain with swallowing; Globus: Subjective sensation as of a lump or mass

Genetic factors are believed to play an important role in its pathogenesis, suggesting that both genetic and environmental concerns must be considered. Among environmental influences, lifestyle factors such as overweight/obesity, inappropriate dietary habits, smoking, and lack of regular physical activity have often been suggested as possible risk factors for GERD. The exact role these factors contribute to GERD is still debatable. Likewise, the beneficial outcome of specific recommended alterations in lifestyle habits also remains highly controversial. Risk factors and lifestyle considerations will be discussed subsequently.

The traditional hypothesis to explain the pathogenesis of GERD is that reflux esophagitis develops when gastric acid refluxes from the stomach into the esophagus and inflicts a chemical burn on the esophageal mucosa. Refluxed hydrogen ions directly damage esophageal epithelium. The acidic environment, along with pepsin, attacks the tight junctions between cells that maintain the epithelial barrier. This permits the intercellular spaces to dilate, and allows acid and pepsin greater access to deeper epithelial layers. With continuous reflux injury, surface esophageal epithelium is necrosed, which in turn triggers both an inflammatory and a proliferative response.

## Symptoms and Complications

The primary reason for symptom appearance is reflux of the acidic gastric contents across the LES. The esophageal lining cannot tolerate the digestive juices, so when reflux occurs the regurgitated gastric contents irritate the esophageal lining. Symptoms appear whenever the acid-neutralizing capacity of the lower esophagus is exhausted.

The classic symptom of GERD is substernal pain that affected individuals usually describe as heartburn (pyrosis) or acid indigestion. Heartburn is typically described as an upward migration of the burning sensation. Sufferers may report feeling a "burning sensation" or pressure just above their stomach, or having a sour taste in their mouth. Although it can appear while the person is upright, it is more common when they are reclining or bending over. It is also relieved by swallowing. Symptoms are usually only mildly annoying. But they can also be intense and debilitating and radiate to the person's back.

GERD symptoms may be confused with angina pectoris or myocardial infarction, and these must be differentiated. The pain is probably not of cardiac origin if it follows a large meal, worsens when lying down, and is relieved by antacids. Pain of cardiac origin is often relieved by resting, is exacerbated with exercise and is unaffected by antacids. Pain that occurs when the stomach is empty, but is relieved by eating, suggests peptic ulcer disease. If symptoms also appear in other family members, the cause may be infectious (i.e., food poisoning), especially if the affected persons have eaten the same food.

Complications of GERD are always possible (Table 1). Barrett's esophagus is the replacing of normal squamous cell epithelium with columnar cell epithelium. It is an uncommon complication of long-standing reflux. The main implication to detecting it is the prognosis for malignancy. Barrett's esophagus is considered to be premalignant for adenocarcinoma which

**Table 2**
**GERD definitions**

**Geneva Workshop Report** (1999) – "Individuals exposed to the risk of physical complications from gastroesophageal reflux or those who experience clinically significant impairment of health-related well-being (quality of life) because of reflux-related symptoms, after adequate reassurance of the benign nature of their symptoms."

**Canadian Consensus Conference** (2004) – "The reflux of gastric contents into the esophagus causing symptoms sufficient to reduce quality of life or cause injury. Endoscopy negative reflux disease applies to individuals who have gastroesophageal reflux disease and normal endoscopy findings."

**American College of Gastroenterology** (2005) – "Symptoms of mucosal damage produced by the abnormal reflux of gastric contents into the esophagus."

**Montreal Definition** (2006) – "A condition that develops when reflux of gastric contents causes troublesome symptoms or complications."

**American Gastroenterological Association** (2008) – Montreal definition adopted.

may develop in up to 10 percent of patients.

Severe and prolonged reflux may stimulate scar tissue formation. This can interfere with swallowing, leading to difficult and/or painful swallowing.

Aspiration of the reflux is a complication that requires immediate attention. At the first onset of symptoms, a physician must be contacted at once. The pulmonary system has no defense against the gastric juice and can be irreparably damaged. In one cohort of patients with idiopathic pulmonary fibrosis, 67 percent were later diagnosed as having concurrent GERD.

## Diagnosis

When symptoms of GERD are typical and the patient responds positively to acid suppression therapy such as histamine-2 receptor antagonists ($H_2$RAs) or proton pump inhibitors (PPIs), no further specific diagnostic tests are necessary. When heartburn and regurgitation occur together, a physician can diagnose GERD with greater than 90 percent accuracy. The usual reasons prompting diagnostic testing are to identify any complications (including esophageal stricture, Barrett's metaplasia or adenocarcinoma), and evaluate treatment failures.

## Potential Risk Factors

The metabolic syndrome is a risk factor for GERD and its progression. Subjects with enlarged waist circumference, hypercholesterolemia, hyperuricemia, hypertension, low HDL-cholesterol level, hypertriglyceridemia, and a diagnosis of metabolic syndrome were more likely to progress from nonerosive esophagitis to erosive disease, and less likely to regress from erosive to nonerosive states.

***Overweight/Obesity.*** An increase in the frequency of overweight and obesity with GERD in the Western world has strongly suggested a pathogenic link between these two conditions. However, conflicting results have been obtained clinically.

A meta-analysis of epidemiological studies that suggested an association between overweight/obesity and GERD demonstrated that being overweight (BMI [body mass index], 25 to 30 kg/m$^2$) or obese (BMI, >30 kg/m$^2$) correlated positively with GERD symptoms, erosive esophagitis and esophageal adenocarcinoma. A cross-sectional analysis of 206 consecutive patients who were not on acid-suppressing medications and underwent 24-hour pH measurement confirmed that there was a significant association between a BMI >30 kg/m$^2$, a large waist circumference and acid reflux episodes. Another meta-analysis of clinical trials that pointed to a relationship between overweight/obesity and reflux symptoms, esophagitis, or GERD-related hospitalization documented a positive association between the two conditions in studies carried out in the United States, but such results are not homogeneous in European trials.

The precise mechanism responsible for an association/relationship between overweight/obesity and GERD has not been fully identified, but some hypotheses have been suggested. For example, it has long been thought that visceral adiposity, described as increased abdominal waist circumference, could increase intra-abdominal pressure that would, in turn, promote GERD. Visceral fat is metabolically active and is associated with low serum levels of protective cytokines (proteins that act as intercellular mediators) such as adiponectin (a protein hormone produced and secreted exclusively by adipocytes that regulates metabolism of lipids and glucose), and high serum levels of inflammatory cytokines, such as tumor necrosis factor alpha (TNFα), interleukin (IL)-1ß and IL-6. An increase in these inflammatory cytokines in patients with erosive esophagitis and Barrett's esophagus has been observed.

Another potential mechanism associates overweight/obesity with separation of the LES from the extrinsic crural diaphragm (fibroelastic bands that arise from the lumbar vertebrae and insert into the central tendon of the diaphragm), a disruption that could predispose overweight/obese subjects to hiatal hernia (protrusion of a segment of the stomach wall through the diaphragm to form an intra-thoracic pouch). The result is a degree of functional incompetence at this barrier. This has been demonstrated in hiatal hernia patients with GERD. On the other hand, while many patients with GERD have a hiatal hernia, a contemporary theory holds that a hiatal hernia can actually serve as a reservoir for acid refluxed into the esophagus.

Still another possible mechanism is represented by slower refluxed esophageal acid clearance. Subjects with GERD show altered esophageal motility and overweight/obese patients also have impaired esophageal acid clearance.

The most important reflux mechanism in overweight or obese subjects seems to be transient lower esophageal sphincter relaxation (TLESR). The main stimulus for generating TLESR episodes is gastric distension that promotes stimulation of both stretch and tension mechanoreceptors in the proximal stomach. In one study, three groups of subjects without GERD (28 obese, 28 overweight, 28 normal weight) underwent upper endoscopy, manometry and pH recordings during both fasting and postprandial periods. During the two-hour postprandial period, overweight/obese individuals showed a significantly higher rate of TLESR episodes and a higher number of TLESR episodes accompanied by acid reflux and total acid exposure than normal weight subjects. Therefore, it seems that overweight and obesity promote a higher postprandial intragastric pressure, which provokes more postprandial TLESR episodes.

While conflicting and non-definitive results exist, it is likely that GERD and overweight/obesity are in some way linked; in particular, abdominal obesity seems to play a key role in determining

**Table 3**
**Examples of foods and beverages reported to worsen reflux symptoms**

| |
|---|
| Carbonated beverages |
| Chocolate |
| Citrus fruits and drinks |
| Drinks with caffeine or alcohol |
| Fatty and fried foods |
| Garlic and onions |
| Mint flavorings |
| Spicy foods |
| Tomato-based foods |

GERD symptoms and complications through mechanical and metabolic effects. It is, therefore, possible to hypothesize that GERD may be a curable condition through control of body weight and, in particular, by reducing abdominal obesity.

It has also been observed that esophageal acid exposure was reduced significantly during weight loss induced by an intragastric balloon. GERD symptoms were also attenuated following weight loss induced by bariatric (gastric bypass) surgery. Such surgery may be successful at reducing GERD symptoms by diverting bile away from the esophagus, eliminating gastric acid production, and reducing the volume of acid refluxate. This hypothesis is supported by observation of rapid symptom improvement following the surgical procedure. Long-term symptom improvement is likely to result from sustained weight loss.

***Dietary Factors.*** Some foods are reported to induce or worsen GERD symptoms (Table 3). Healthcare professionals often advise patients to avoid foods that may worsen reflux symptoms. The literature provides conflicting results for identifying the most refluxogenic items, although fried foods, spicy foods and alcohol are reported to be the most common precipitating factors of heartburn.

A study used a dietary questionnaire to estimate the average food consumption over the previous year, along with a GERD questionnaire and an upper endoscopy for assessing GERD severity. There was a positive association between high fat intake and GERD symptoms and erosive esophagitis. A high-fiber diet seemed to reduce reflux symptoms. The effect of fat on GERD symptoms and erosive esophagitis was dependent on BMI since this is statistically significant only in overweight/obese individuals. Furthermore, a higher daily intake of fat was observed in participants with erosive esophagitis. The role of dietary fat in symptom generation has been confirmed by some, but not by all, clinical trials.

***Alcohol/Coffee.*** Considering the recommended advice of controlling alcohol intake and reducing or eliminating ingestion of coffee to prevent GERD symptoms, a number of studies have investigated the role of these beverages on GERD. While some authors have suggested that alcohol is an independent risk factor for GERD-related symptoms, others have failed to show such a relationship.

***Smoking.*** Population-based and epidemiologic trials have demonstrated that tobacco smoking may be a risk factor for GERD and is significantly associated with GERD-related symptoms. A monozygotic co-twin study provided compelling evidence that tobacco smoking increases the risk for occurrence of frequent GERD symptoms. Another case-control study on 3,153 patients with severe GERD-related symptoms reported that the duration of smoking was associated with increasing reflux symptoms in subjects who had smoked for >20 years.

Various mechanisms have been suggested to solidify the correlation between smoking and GERD. Cigarette smoking can reduce the LES pressure. It can decrease salivary bicarbonate secretion, thus reducing the physiological neutralizing effect of saliva on intraesophageal acid, and prolonging acid clearance. Added to these responses is that abrupt increases in intra-abdominal pressure common in smokers during coughing or deep inspiration have been associated with reflux symptoms. At the same time, however, other studies that have examined acid perfusion have noted that smokers, compared to non-smokers, do not show increased esophageal acid exposure time, despite having more reflux episodes. Two case-control studies that evaluated the effect of smoking cessation on GERD outcomes were unable to document improvement in GERD symptoms following cessation of tobacco use.

***Physical Activity.*** Since previous investigations have demonstrated that strenuous exercise may induce GERD and that GERD symptoms are common among athletes, it has been suggested that physical activity represents another risk factor for GERD. Available evidence supports the contention that a positive association between exercise and GERD is present during vigorous, but not moderate, exercise. Running and resistance exercises are more refluxogenic than cycling. It seems there is a hierarchy of exercises for inducing reflux symptoms, although there is no general agreement with respect to the mechanism by which vigorous exercise induces reflux.

Exercise may alter esophageal motility and worsen symptoms of the upper gastrointestinal tract. The anatomical compromise of the LES resulting from frequent abdominal straining associated with strenuous exercise may predispose to exercise-induced reflux. Other suggestions are that GERD may be increased in athletes because of decreased gastrointestinal blood flow, alterations of hormone secretion, changes in motor function of the esophagus, and constrained body positioning during exercise.

While numerous studies suggest that specific physical activities play a possible pathogenic role in inducing GERD symptoms, these study results should not be extended to normal physical activity, which has been demonstrated to have a protective effect on GERD. Thus, the relationship between exercise and GERD remains con-

**Table 4**
**Drugs that may cause or exacerbate GERD**

| |
|---|
| Alpha-adrenergic antagonists |
| Anticholinergic agents |
| Calcium channel blockers |
| Nitrates |
| Prostaglandins |
| Sedatives |
| Theophylline |

troversial. It may be a consequence of differences in the populations studied (e.g., age, race), evaluation of exercise (e.g., short-term or long-term), method for assessment of physical activity (e.g., using different questionnaires) and means for diagnosis of the disease (e.g., a symptom scale or pH measurements). Mild routine physical activity, in association with diet modification, i.e., a diet rich in fiber and poor in fat, seems to be advisable to prevent reflux symptoms.

***Infection.*** There is controversy over the role of *Helicobacter pylori* infection in GERD. Concomitant *H. pylori* gastric infection may reduce symptoms of GERD by inducing gastric atrophy and decreasing gastric acid production; thus, eradication of *H. pylori* may worsen GERD by increasing gastric acid production. Furthermore, ammonia produced by *H. pylori* could buffer gastric fluid refluxing into the esophagus, an effect that would be lost after *H. pylori* eradication. Conversely, one prospective study demonstrated that eradication of *H. pylori* actually improved the endoscopic appearance of reflux esophagitis in patients with duodenal ulcer.

***Medications.*** Certain medications (Table 4) may initiate or exacerbate GERD by diminishing the LES pressure or decreasing esophageal acid clearance. Patients with GERD-related strictures may also need to avoid drug dosage forms that could lodge proximal to esophageal strictures and result in esophagitis, ulcers, and recurrent or refractory strictures. Nonsteroidal anti-inflammatory drugs, alendronate, potassium preparations, quinidine, iron supplements, and multiple antibiotics have been implicated in "pill-induced" esophagitis.

## Specific Patient Populations

***Infants.*** Transient relaxation of the LES may permit stomach contents to pass into the esophagus. This usually causes regurgitation or vomiting and is common in infants. It is mild, self-limiting, and requires no specific treatment. GERD in infants describes reflux of gastric contents that cause troublesome symptoms or complications. Transient regurgitation is sometimes diagnosed incorrectly as GERD in healthy infants who experience troublesome but harmless symptoms, and may lead to potentially inappropriate use of acid-reducing drugs.

Some reflux occurs in most infants, particularly in those who are preterm. It is more marked in those with slow gastric emptying or disorders of upper gastrointestinal motility due to severe neurodevelopmental impairment such as cerebral palsy, or cows' milk hypersensitivity. Reflux is classified as GERD when it causes troublesome symptoms such as poor weight gain, unexplained crying, distressed behavior, or complications such as esophagitis or respiratory pathology. Esophagitis may occur with irritability, clinical features mimicking colic (crying, drawing the legs up toward the abdomen), features of pain after feeding, and, possibly, hematemesis (vomiting blood). Esophageal motility may reduce sphincter tone further, making reflux even more likely. Possible correlation may exist between GERD and asthma, pneumonia, bronchiectasis (chronic dilatation of the bronchi or bronchioles marked by fetid breath and paroxysmal coughing, with expectoration of mucopurulent matter) and other life-threatening events in infants, but causality has not been established. In preterm infants, reflux is associated with episodic apnea (transient cessation of breathing) resistant to standard treatment and with exacerbation of bronchopulmonary dysplasia (abnormal development or growth).

***Older Adults.*** The care of older adults with GERD may present challenges not found in younger populations. Concurrent comorbidities, medication interactions and other normal physiological events associated with aging can conspire to alter the occurrence and natural history of the disease in older patients.

In the elderly, consistent with the general population, more than 40 percent experience occasional symptoms of GERD and 20 percent have weekly symptomatic GERD. As patients age, however, the intensity of heartburn lessens, while its complications become more frequent. A study of 12,000 patients aged 18 to 75 with endoscopically documented erosive esophagitis revealed that severe heartburn was seen in 30 percent of patients aged more than 70 years with erosive esophagus, compared with 47 percent of patients aged 31 to 40 years. Severe esophagitis was seen in 35 percent of elderly patients vs. 25 percent of patients aged 31 to 40 years among those with severe heartburn. Thus, while elderly patients may experience heartburn, severe esophagitis may be present without the hallmark symptom. This observation is likely due to several factors, including decreased perception of mucosal damage. Older adults who do not have the typical symptom of heartburn may, instead, complain of more atypical symptoms, including respiratory distress and vomiting.

## Non-pharmacologic Therapy

Patients with GERD can decrease the number and severity of symptoms by following suggestions directed toward avoidance of the known aggravating factors (Table 5). These involve changes in lifestyle, especially of the factors discussed herein.

Avoidance of tobacco, caffeine,

**Table 5**
**Patient advice for first-line management of GERD symptoms**

- Stop smoking.
- Lose weight if overweight or obese, or if onset of symptoms was concurrent with weight gain within the normal range (BMI 18.5 to 24.9).
- Reduce or avoid foods, beverages, or behaviors associated with GERD.
- *Nighttime symptoms*:
  - Avoid eating within 3 hours before bedtime.
  - Elevate head of bed 6 to 8 inches with wood blocks under bedposts. Foam wedges are not recommended because they may force the individual to bend slightly at the waist.
  - Sleep on your left lateral side.
- Unless instructed otherwise by your doctor, eat 4 to 6 small meals each day, instead of 2 or 3 larger ones.
- Avoid lying down after meals.
- Chewing gum or sucking on sugarless candy will stimulate saliva flow and help reduce symptoms.
- *Abdominal obesity*:
  - Avoid tight-fitting garments (suspenders may be preferred over belts), girdles and corsets.
- Your pharmacist can provide specific guidelines on foods to avoid and other actions to take to prevent or treat symptoms.

alcohol, chocolate, and citrus juice is typically recommended. While published data provide evidence that such measures lead to decreased LES pressures, there is much disagreement regarding whether their avoidance can result in actual clinical improvement in GERD. A review of the literature included 2,039 studies on lifestyle factors, including weight loss, timing of meals, elevation of the head during sleep, and avoidance of alcohol, smoking, coffee, citrus, and chocolate. Of the 100 relevant studies, no evidence was identified to support the efficacy of certain dietary measures, or avoiding smoking or alcohol in improving symptomatology, LES pressure, or esophageal pH profiles. The only efficacious factors were elevation of the head of the bed and lifestyle interventions that led to weight loss (mean loss of 12.4 kg in 13 weeks).

The Geneva Workshop Report, a consensus group of 35 gastroenterologists representing 16 countries, agreed that most reflux is postprandial; thus, avoidance of any foods and beverages that provoke reflux can be therapeutic. This group also agreed that, contrary to some published reports, nocturnal reflux is a problem only in a small subgroup of patients, that only these individuals benefit from elevating the head of the bed, and that it is not effective as a first-line treatment in most patients.

A primary premise is that affected individuals will have a life-long encounter with GERD because symptoms are correlated to lifestyle. Simple changes can provide symptomatic relief in a large number of, but not all, patients. The problem is that there are simply too many recommendations and each is too narrowly applicable to enforce the whole set on every patient. Some people perceive GERD to be little more than an annoyance and will not readily change their habits, many of which have developed over decades. And since they know that antacids, $H_2$RAs and PPIs are effective OTC therapies to prevent or treat their symptoms, these products inappropriately become their first-line intervention.

## Conclusions

GERD is associated with incompetence of the LES. Lifestyle modifications are currently recommended as first-line therapy for subjects with GERD. Even so, the pathogenic role of lifestyle factors and, consequently, the efficacy of their alteration remains controversial.

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This lesson is a knowledge-based CE activity and is targeted to pharmacists in all practice settings.

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# continuing education quiz

## Gastrointestinal Reflux Disease: The Basics

1. All of the following terms appropriately define GERD EXCEPT:
   a. chronic.
   b. complex.
   c. rare.
   d. relapsing.

2. The primary mechanism for GERD is believed to result from transient:
   a. constriction of the lower esophageal sphincter.
   b. relaxation of the lower esophageal sphincter.

3. Which of the following is classified as an extraesophageal symptom associated with GERD:
   a. adenocarcinoma.
   b. heartburn.
   c. peptic stricture.
   d. throat clearing.

4. The traditional hypothesis to explain pathogenesis of GERD is that reflux esophagitis develops from:
   a. chemical burn.
   b. nerve necrosis.
   c. pepsinogen activation.
   d. serotonin inhibition.

5. The pain of GERD can be differentiated from the pain of cardiac origin when it is relieved by:
   a. ingesting antacids.
   b. ingesting a large meal.
   c. lying down.

6. A GERD complication that requires immediate attention is:
   a. Barrett's esophagus.
   b. aspiration of the reflux.
   c. difficulty swallowing.
   d. painful swallowing.

7. Which of the following is LEAST likely to be a risk factor for GERD and its progression?
   a. Hypertension
   b. Hyperuricemia
   c. High HDL-cholesterol
   d. Metabolic syndrome

Completely fill in the lettered box corresponding to your answer.

| | | |
|---|---|---|
| 1. [a] [b] [c] [d] | 6. [a] [b] [c] [d] | 11. [a] [b] |
| 2. [a] [b] | 7. [a] [b] [c] [d] | 12. [a] [b] [c] [d] |
| 3. [a] [b] [c] [d] | 8. [a] [b] [c] [d] | 13. [a] [b] |
| 4. [a] [b] [c] [d] | 9. [a] [b] [c] [d] | 14. [a] [b] |
| 5. [a] [b] [c] | 10. [a] [b] [c] [d] | 15. [a] [b] [c] [d] |

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8. Visceral fat is associated with low serum levels of proteins that act on intercellular mediators called:
   a. interleukins.
   b. prostaglandins.
   c. inflammatory cytokines.
   d. protective cytokines.

9. Examples of foods and beverages reported to worsen reflux symptoms include all of the following EXCEPT:
   a. citrus fruits.
   b. legume-based foods.
   c. carbonated beverages.
   d. mint flavorings.

10. All of the following are considered to be potential risk factors for GERD EXCEPT:
   a. smoking.
   b. alcohol.
   c. chewing gum.
   d. coffee.

11. Available evidence supports the contention that a positive association between exercise and GERD is present during vigorous, but not moderate, exercise.
   a. True
   b. False

12. All of the following represent drugs that may cause or exacerbate GERD EXCEPT:
   a. calcium channel blockers.
   b. anticholinergic agents.
   c. alpha-adrenergic antagonists.
   d. ACE inhibitors.

13. Bronchiectasis is characterized by expectoration of mucopurulent matter.
   a. True
   b. False

14. As patients age, the intensity of heartburn:
   a. increases.
   b. decreases.

15. Appropriate patient advice for patients with GERD includes all of the following statements EXCEPT:
   a. lose weight if obese.
   b. eat four to six small meals a day.
   c. lie down after a heavy meal.
   d. avoid tight-fitting garments.

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