JAMA | Review

# Gastroesophageal Reflux Disease
## A Review

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**IMPORTANCE** Gastroesophageal reflux disease (GERD) is defined by recurrent and troublesome heartburn and regurgitation or GERD-specific complications and affects approximately 20% of the adult population in high-income countries.

**OBSERVATIONS** GERD can influence patients' health-related quality of life and is associated with an increased risk of esophagitis, esophageal strictures, Barrett esophagus, and esophageal adenocarcinoma. Obesity, tobacco smoking, and genetic predisposition increase the risk of developing GERD. Typical GERD symptoms are often sufficient to determine the diagnosis, but less common symptoms and signs, such as dysphagia and chronic cough, may occur. Patients with typical GERD symptoms can be medicated empirically with a proton pump inhibitor (PPI). Among patients who do not respond to such treatment or if the diagnosis is unclear, endoscopy, esophageal manometry, and esophageal pH monitoring are recommended. Patients with GERD symptoms combined with warning symptoms of malignancy (eg, dysphagia, weight loss, bleeding) and those with other main risk factors for esophageal adenocarcinoma, such as older age, male sex, and obesity, should undergo endoscopy. Lifestyle changes, medication, and surgery are the main treatment options for GERD. Weight loss and smoking cessation are often useful. Medication with a PPI is the most common treatment, and after initial full-dose therapy, which usually is omeprazole 20 mg once daily, the aim is to use the lowest effective dose. Observational studies have suggested several adverse effects after long-term PPI, but these findings need to be confirmed before influencing clinical decision making. Surgery with laparoscopic fundoplication is an invasive treatment alternative in select patients after thorough and objective assessments, particularly if they are young and healthy. Endoscopic and less invasive surgical techniques are emerging, which may reduce the use of long-term PPI and fundoplication, but the long-term safety and efficacy remain to be scientifically established.

**CONCLUSIONS AND RELEVANCE** The clinical management of GERD influences the lives of many individuals and is responsible for substantial consumption of health care and societal resources. Treatments include lifestyle modification, PPI medication, and laparoscopic fundoplication. New endoscopic and less invasive surgical procedures are evolving. PPI use remains the dominant treatment, but long-term therapy requires follow-up and reevaluation for potential adverse effects.

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Gastroesophageal reflux disease (GERD) is defined by its cardinal symptoms (recurrent and troublesome heartburn and regurgitation) or by its specific complications (esophagitis, peptic strictures, and Barrett esophagus).[1] Barrett esophagus is a columnar metaplasia replacing parts of the native squamous cell epithelium that can progress to esophageal adenocarcinoma.[2] GERD can be a serious problem and should not be confused with less severe disease such as gastritis or the very common symptoms of dyspepsia or regurgitation that occur in almost all individuals without any underlying gastrointestinal pathology. GERD is caused by gastric contents' reaching the esophagus. Except for causing esophageal symptoms or complications, gastric juices can also reach more proximally (ie, into the pharynx, mouth, larynx, and airways) and cause or worsen various extraesophageal symptoms and conditions such as hoarseness, wheezing, cough, and asthma.[1] Established risk factors for developing GERD include increased body mass index, tobacco smoking, and genetic predisposition,[3] whereas infection with the gastric bacterium *Helicobacter pylori* can decrease this risk.[4] The prevalence of GERD is high and increasing, with greater rates in high-income countries (15%-25%) than in most low- and middle-income countries (<10%).[2,5] GERD can result in diminished health-related quality of life, and its prevalence and need for long-term treatment can consume substantial health care resources and result in high costs to society.[6,7] This review provides an update of the current evidence regarding GERD, with an emphasis on its clinical management in adults.

## Methods

A literature search was conducted with PubMed and Cochrane databases for English-language studies from January 1, 2015, until September 15, 2020. The search terms were *gastroesophageal reflux disease* and associated diseases and conditions, focusing on clinical management of GERD. The bibliographies of the retrieved articles were manually searched for additional relevant studies. Emphasis was given to the selection of randomized clinical trials (RCTs), systematic reviews, meta-analyses, clinical practice guidelines, and large cohort studies. In accordance with these search criteria, a total of 113 reports were included and form the basis of this review, including 9 RCTs, 23 systematic reviews and meta-analyses, and 7 clinical practice guidelines.

## Observations

### Pathophysiology

GERD involves dysfunction in the esophagogastric junction barrier, including loss of effective lower esophageal sphincter function, allowing increased regurgitation of acidic gastric contents into the esophagus.[8] Transient lower esophageal sphincter relaxation is a normal physiologic response to gastric distention that facilitates belching, but can contribute to GERD if the relaxations are frequent and prolonged.[9] A sliding hiatal hernia (ie, in which a portion of the proximal stomach has herniated through the diaphragm and is located in the thoracic cavity) is a common anatomic configuration that facilitates reflux by increasing the angulation between the gastroesophageal junction and the gastric fundus, reducing the valve function.[9]

### Occurrence

A recent meta-analysis of 79 studies from 36 countries found an overall prevalence of GERD in adults of 13.3% (95% CI, 12.0%-14.6%), with higher rates than average in South Asia (22.1%; 95% CI, 11.5%-35.0%), Central America (19.6%; 95% CI, 16.2%-23.4%), South America (17.6%; 95% CI, 11.0%-25.3%), Europe (17.1%; 95% CI, 15.1%-19.1%), and North America (15.4%; 95% CI, 10.7%-20.9%).[3,5] The prevalence of GERD is age dependent. Nearly 50% of newborn infants regurgitate or vomit daily, but this resolves spontaneously in 90% of children by aged 1 year.[10] After that, the prevalence of GERD again increases with age, and by adolescence, its prevalence approaches that of adults.[10] In adults, the prevalence further increases with older age, and a meta-analysis of 19 studies found a prevalence of 14.0% (95% CI, 9.9%-18.7%) among individuals younger than 50 years and 17.3% (95% CI, 13.3%-21.7%) among those aged 50 years or older, resulting in an odds ratio (OR) of 1.32 (95% CI, 1.12-1.54).[3] A pooled analysis of 70 studies from various global regions found that women had slightly higher rates of GERD than men, with a pooled prevalence of 16.7% among women (95% CI, 14.9%-18.6%) and 15.4% among men (95% CI, 13.5%-17.4%), corresponding to an OR of 1.13 (95% CI, 1.05-1.21); however, no such sex difference was found in pooled analyses when restricted to studies from North America, Europe, South Asia, or Australasia.[3]

### Etiology

Increasing body mass index from normal to obese is associated with increased risk of developing GERD.[11] A recent meta-analysis of 22 studies found a prevalence of GERD of 22.1% (95% CI, 17.4%-27.2%) among obese individuals compared with 14.2% (95% CI, 10.8%-18.0%) among nonobese ones, corresponding to an OR of 1.73 (95% CI, 1.46-2.06).[3] Increased intra-abdominal pressure, a higher prevalence of hiatal hernia, higher gradient of abdominal to thoracic pressure, increased levels of estrogen, and increased production of bile and pancreatic enzymes may contribute to the association between obesity and GERD.[12] An association between tobacco smoking and GERD is also well documented. A meta-analysis of 30 studies comparing smokers and nonsmokers showed a pooled prevalence of 19.6% among smokers (95% CI, 14.9%-24.7%) and 15.9% in nonsmokers (95% CI, 13.1%-19.0%), corresponding to an OR of 1.26 (95% CI, 1.04-1.52).[3] Tobacco can prolong acid clearance time of the esophagus and reduce the pressure in the lower esophageal sphincter.[12] The third well-established risk factor is genetic predisposition. Two large studies of twins estimated that heritability accounts for 31% to 43% of the predisposition to develop GERD,[13,14] and some studies have indicated genetic risk factors for the development of GERD, although no single specific risk locus has yet been identified.[15,16] Infection with *H pylori* may prevent GERD by causing atrophy of the gastric mucosa, which can decrease the acid production of the parietal cells.[4] A meta-analysis of 27 studies showed that eradication of *H pylori* increased the risk of developing reflux esophagitis (relative risk, 1.46; 95% CI, 1.16-1.84).[17] Alcohol consumption and dietary factors might precipitate episodes of like symptoms in individuals with known GERD, but these exposures have not been associated with the development of GERD.[3]

Table 1. Differential Diagnoses to Be Considered in the Evaluation of a Patient With Suspected Gastroesophageal Reflux Disease

| Differential diagnosis | Main symptoms | Main diagnostic tool |
|---|---|---|
| Coronary heart disease | Chest pain, particularly when triggered by effort | ECG, blood tests such as for troponin level, exercise stress test with ECG |
| Gastrointestinal malignancy | Eating difficulties, weight loss, vomiting | Endoscopy |
| Peptic ulcer disease | Epigastric pain, nausea, vomiting | Endoscopy |
| Biliary tract disease | Abdominal pain, jaundice | Ultrasonography, blood tests |
| Eosinophilic esophagitis | Swallowing difficulties with hooking, reflux symptoms | Endoscopy |
| Achalasia or other upper gastrointestinal motility disorders | Swallowing difficulties, vomiting of undigested food | Esophageal manometry |

Abbreviation: ECG, electrocardiography.

### Clinical Presentation

The cardinal symptoms of GERD are heartburn and acid regurgitation, but chest pain is also common.[18] Less common symptoms, often denoted as atypical, include dysphagia, bleeding, chronic cough, asthma, chronic laryngitis, hoarseness, teeth erosions, belching, and bloating.[9,18,19] The differential diagnoses for these symptoms are presented in **Table 1**.[18,20] Patients with GERD symptoms combined with warning symptoms of malignancy such as progressive dysphagia, involuntary weight loss, or bleeding should undergo upper gastrointestinal endoscopy. Patients who do not respond to an empirical medical treatment trial with a proton pump

inhibitor (PPI) of standard dose once daily should also be considered for endoscopy. Endoscopy can reveal malignancy, complications of GERD (eg, erosive esophagitis, esophageal strictures, Barrett esophagus), and other explanations for the symptoms.[1,21,22] Patients with GERD often have reduced health-related quality of life, but this can be improved by effective treatment.[7,23,24] A systematic review including 9 studies of 14 774 patients showed improved health-related quality of life in patients who responded well to PPI treatment, but not in nonresponders.[7]

## Consequences of GERD

### Survival

A recent population-based cohort study found no increased overall all-cause or cancer-specific mortality among 4758 patients with severe GERD symptoms compared with 51 381 individuals without them.[25]

### Esophagitis

The most common complication of GERD is esophagitis, an inflammation of the mucosa of the distal esophagus that causes erosions and occurs in 18% to 25% of patients with GERD symptoms.[26,27] Erosive reflux esophagitis can be associated with typical symptoms of GERD, but may also be asymptomatic. Esophagitis is detected at endoscopy and graded according to the Los Angeles classification, which grades the extent of the mucosal erosive areas from A to D.[28,29] Grade A corresponds to greater than or equal to 1 erosion less than 5 mm, grade B represents greater than or equal to 1 erosion 5 mm or larger, grade C is greater than or equal to 1 erosion between the tops of 2 or more mucosal folds involving less than 75% of the circumference, and grade D is greater than or equal to 1 erosion involving 75% or more of the circumference.[29] Patients with esophagitis should be treated with long-term PPIs because discontinuation often leads to recurrence, but once clinically effective, the dose should be titrated to the lowest daily one tolerated.[22]

### Stricture

Peptic esophageal strictures can occur if the acidic exposure to the esophagus results in fibrotic scarring. The incidence of peptic strictures is 7% to 23% in untreated patients with erosive esophagitis.[30] Patients with esophageal stricture often present with dysphagia. The treatment includes continuous long-term PPI therapy combined with endoscopic balloon dilatation, which might need to be repeated and which successfully resolves esophageal strictures in more than 80% of patients.[31] Dilatation combined with injection with corticosteroids can be considered if the scarring reoccurs despite several dilatations; however, the studies supporting this approach are small, have limited follow-up, and are not definitive.[31]

### Barrett Esophagus

GERD can cause Barrett esophagus, the precursor lesion to esophageal adenocarcinoma. It has been estimated that 5.6% of adults in the United States have Barrett esophagus.[32,33] A meta-analysis of 42 studies and 26 521 individuals with GERD found a pooled prevalence of Barrett esophagus in 7.2% (95% CI, 5.4%-9.3%), including 13.9% with dysplasia (95% CI, 8.9%-19.8%), with more than 80% of patients having low-grade dysplasia.[34] The absolute risk of esophageal adenocarcinoma is low in nondysplastic Barrett esophagus, but considerably higher in the presence of dysplasia. A meta-analysis of 24 studies and 2694 patients found an annual incidence rate of esophageal adenocarcinoma of 0.54% (95% CI, 0.32%-0.76%) among patients with Barrett esophagus with low-grade dysplasia, which was 1.73% (95% CI, 0.99%-2.47%) when high-grade dysplasia was added as an outcome.[35] Another meta-analysis of 20 studies and 74 943 patients with Barrett esophagus found that the main risk factors for tumor progression were older age, male sex, tobacco smoking, longer segment of the Barrett mucosa, and central obesity.[36] Screening for Barrett esophagus of the general adult population is not recommended, but can be considered among high-risk individuals, such as men older than 60 years with GERD.[37] Current guidelines recommend surveillance of individuals with known Barrett esophagus because of earlier detection of esophageal adenocarcinoma, and surveillance endoscopies are recommended every 3 to 5 years in patients without dysplasia; and if low-grade dysplasia is present, repeated surveillance endoscopy should be conducted within 6 months.[38-40] Patients with Barrett esophagus should be treated with continuous PPI treatment.[38] For patients with high-grade dysplasia and in some cases low-grade dysplasia, endoscopic removal of Barrett mucosa is the recommended treatment.[40]

### Esophageal Adenocarcinoma

GERD is, through development of Barrett esophagus, associated with esophageal adenocarcinoma.[41] The incidence of esophageal adenocarcinoma has increased rapidly during the last 4 decades, particularly in Western countries, with a global incidence rate of 1.1 cases per 100 000 person-years among men and 0.3 per 100 000 person-years among women,[42] and less than 20% of patients survive for 5 years.[42-45] Yet, although the relative risk of esophageal adenocarcinoma is increased among patients with GERD, the absolute risk is low because of the rarity of this tumor in the population.[46] Whether treatment of GERD reduces the risk of esophageal adenocarcinoma is a matter of controversy. A meta-analysis of 9 observational studies and 5712 patients with Barrett esophagus did not find any statistically significant association between PPI treatment and risk of esophageal adenocarcinoma (OR, 0.43; 95% CI, 0.17-1.08).[47] An RCT (AspECT) that included 2557 patients with Barrett esophagus found that high-dose PPI (40 mg esomeprazole twice daily) with a median follow-up of 8.9 years did not decrease the risk of esophageal adenocarcinoma compared with low-dose PPI (20 mg esomeprazole once daily); 3.1% and 3.2% of patients developed esophageal adenocarcinoma, respectively, with a time ratio of an accelerated failure time model of 1.04 (95% CI, 0.67-1.61), although the statistical power was low.[48] A recent population-based study from all 5 Nordic countries of 942 071 patients with GERD who were followed up for up to 50 years found no decreased risk of esophageal adenocarcinoma after antireflux surgery (48 863 patients; median follow-up, 13.6 years; 0.3% developed esophageal adenocarcinoma) or PPI treatment (893 208 patients; median follow-up, 5.1 years; 0.5% developed esophageal adenocarcinoma) compared with that of the background population; the standardized incidence ratio among patients with more than 15 years of follow-up was 4.57 (95% CI, 3.44-5.95) after surgery and 3.07 (95% CI, 2.65-3.54) after medication.[49] In a meta-analysis of 10 studies,[50] there was no significant association between antireflux surgery or medication and reduced risk of esophageal adenocarcinoma. However, a recent cohort study from the United Kingdom, including 838 755

Table 2. Key Statements From the Major Current Clinical Guidelines Regarding the Diagnosis and Treatment of Gastroesophageal Reflux Disease[a]

| Guideline | American Gastroenterology Association[22] | Society of American Gastrointestinal and Endoscopic Surgeons[52] | National Institute for Clinical Excellence (no evidence grading available)[53] |
|---|---|---|---|
| Diagnosis | Montreal consensus, "a condition which develops when reflux of stomach contents causes troublesome symptoms and/or complications" (no grade) | ≥1 of the following conditions exists: a mucosal break observed on endoscopy in a patient with typical symptoms, Barrett esophagus on biopsy, a peptic stricture in the absence of malignancy, or positive pH measurement (grade A) | |
| Investigations | Endoscopy with biopsy for all patients with GERD and dysphagia (grade B)<br>Endoscopy for patients with GERD who have not responded to twice-daily PPI therapy (grade B)<br>Manometry for patients with GERD who have not responded to twice-daily PPI therapy and have normal endoscopy result (grade B)<br>Ambulatory impedance pH, catheter pH, or wireless pH monitoring for patients with GERD who have not responded to twice-daily PPI therapy and have normal endoscopy and manometry results (grade B) | No consensus on preoperative investigations | Patients presenting with dyspepsia together with significant acute gastrointestinal bleeding are to be referred immediately (same day) to a specialist |
| Lifestyle advice | Weight loss advised for overweight or obese patients with GERD (grade B)<br>Elevation of head of bed for select patients (grade B) | | Offer simple lifestyle advice, including advice on healthy eating, weight reduction, and smoking cessation<br>Recognize that psychological therapies, such as cognitive behavioral therapy and psychotherapy, may reduce dyspeptic symptoms in the short term |
| Medical treatment | PPIs are more effective than histamine$_2$ receptor antagonists, which are more effective than placebo (grade A)<br>Twice-daily PPI therapy for patients with inadequate response to once-daily therapy (grade B) | | Offer patients with GERD a full-dose PPI for 4 or 8 wk<br>Offer histamine$_2$ receptor antagonist therapy if there is an inadequate response to a PPI |
| Surgical intervention | When antireflux surgery and PPI therapy are judged to offer similar efficacy, PPI therapy should be recommended owing to better safety (grade A)<br>When a patient with GERD is responsive to but intolerant of acid-suppression therapy, antireflux surgery should be recommended (grade A) | Surgical therapy for GERD is an equally effective alternative to medical therapy and should be offered to appropriately selected patients by appropriately skilled surgeons (grade A)<br>Surgical therapy effectively addresses the mechanical issues associated with the disease and results in long-term patient satisfaction (grade A)<br>Laparoscopic fundoplication should be preferred over its open alternative because it is associated with superior early outcomes and no difference in late outcomes (grade A) | Consider laparoscopic fundoplication for patients who have a confirmed diagnosis of acid reflux and adequate symptom control with acid-suppression therapy, but who do not wish to continue with this therapy long term<br>a confirmed diagnosis of acid reflux and symptoms that are responding to a PPI, but who cannot tolerate acid-suppression therapy |

Abbreviations: GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor.

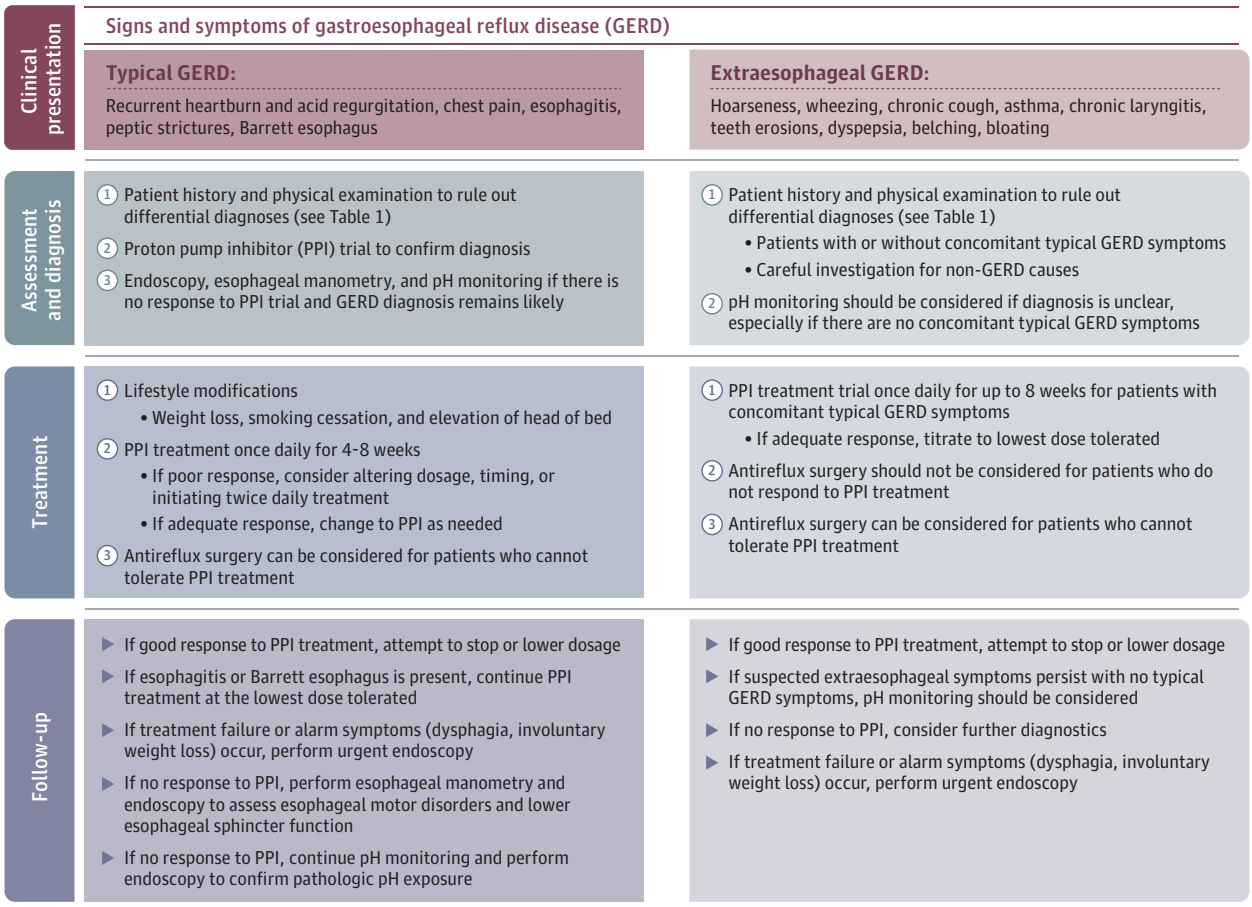
[a] Grade of evidence is provided when available.

patients with GERD, found a decreased risk of esophageal adenocarcinoma in the 22 321 who underwent antireflux surgery (hazard ratio, 0.64; 95% CI, 0.52-0.78).[51] Although current evidence is limited, it is reasonable to offer antireflux therapy to patients with Barrett esophagus irrespective of their symptoms, whereas the treatment of GERD in patients without it should be directed at controlling GERD symptoms either medically or surgically according to what a patient prefers.

## Assessment and Diagnosis

**Table 2** summarizes major guidelines regarding the diagnosis and treatment of GERD, and a proposed clinical management algorithm for patients with suspected GERD is shown in the **Figure**. A thorough medical history can help determine the differential diagnoses for patients presenting with GERD-like symptoms (Table 1). Symptoms resembling GERD are common and are not always caused by it.[1,18,54] In patients with a history of chest pain, especially if it is of sudden onset or is related to physical activity, cardiac pathology should be suspected and evaluated with electrocardiography, laboratory tests including troponin level, and exercise stress test with electrocardiography. In patients with typical heartburn and acid regurgitation, a presumptive diagnosis of GERD can be made and a trial treatment with a PPI initiated. Endoscopy, esophageal manometry, and esophageal pH monitoring are indicated if the patient does not respond to empirical PPI treatment and the diagnosis of GERD remains likely but needs to be further investigated to rule out other possible causes for the symptoms (Table 1).[18,55] An international consensus evaluated diagnostic tests for GERD and concluded that esophagitis grade C or D according to the Los Angeles classification system of erosive esophagitis (≥1 erosion between the tops of 2 or more mucosal folds engaging <75% of the circumference or 1 or more erosions involving ≥75% of the circumference), Barrett esophagus, or peptic strictures on endoscopy establish a diagnosis of GERD, as does acid exposure time of more than 6% during pH monitoring, whereas acid exposure time of less than 4% or fewer than 40 reflux episodes observed during 24-hour pH monitoring suggest that

Figure. Proposed Assessment and Management of Patients With Signs and Symptoms Indicating Gastroesophageal Reflux Disease




Adapted from Katz et al[18] and Spechler.[54]

Table 3. Potency Between Different Proton Pump Inhibitors According to Omeprazole Equivalents

| Drug at lowest available dosage, mg | Omeprazole equivalent, mg |
|---|---|
| Pantoprazole, 20 | 4.5 |
| Lansoprazole, 15 | 13.5 |
| Omeprazole, 20 | 20 |
| Esomeprazole, 20 | 32 |
| Rabeprazole, 20 | 36 |

Based on data from Graham and Tansel.[65]

GERD is not present and other diagnoses should be considered (Table 1).[56] There is no need for blood tests in the primary evaluation of GERD.

## Treatment

### Lifestyle Changes

Lifestyle changes can reduce GERD symptoms, primarily weight loss in obese patients and tobacco smoking cessation in smokers.[18,22,57,58] In the presence of nocturnal GERD, particularly regurgitation, elevation of the head of the bed and avoiding late meals are recommended.[18,22] Exclusion of food items that patients report trigger symptoms of GERD (eg, alcohol, spicy food, chocolate) is recommended, whereas alkaline water and a Mediterranean diet can be beneficial.[18,22,59]

### Medication

PPI use is the most effective pharmacologic treatment of GERD symptoms and healing of erosive esophagitis.[18,22] PPIs irreversibly inhibit hydrogen-potassium ATPase in the parietal cells of the stomach, reducing the acidity of the gastric contents, and usually alleviate GERD symptoms. PPI is one of the most commonly prescribed medications, used by an estimated 7% to 9% of all adults worldwide and by more than 20% of those aged 65 years or older.[60-64] A meta-analysis found no differences in effectiveness of acid suppression when comparing equivalent doses of different types of PPIs (**Table 3**), indicating that these can be used interchangeably if the dose is adjusted accordingly.[65] Current clinical guidelines support an initial trial treatment period of once-daily PPI of standard dose for 4 weeks in patients with typical GERD symptoms[18,22] and a treatment period of 8 weeks for healing of endoscopy-verified erosive esophagitis.[18] If this treatment is successful, the patient should receive PPI of the lowest effective maintenance dose, provided that continued medication is considered necessary for a longer period.[18,22] Patients with typical GERD symptoms can often begin receiving on-demand or intermittent PPI treatment, whereas those with known esophagitis or Barrett

esophagus should continue once-daily PPI even in the absence of symptoms because of the risk of recurrence of esophagitis or tumor progression, respectively.[22] A large portion of patients use PPIs for considerably longer periods than recommended by current guidelines.[60,66,67] The American Gastroenterological Association recommends that patients with uncomplicated GERD receive PPI for 4 to 8 weeks and thereafter attempt to stop or reduce the dose; if this is not possible because of recurrence of symptoms, pH and impedance monitoring is recommended to distinguish GERD from a functional syndrome.[68] PPI treatment is considered safe for pregnant patients, with pantoprazole, lansoprazole, rabeprazole, and dexlansoprazole graded B (no evidence for risk in humans), but omeprazole and esomeprazole graded C (risk cannot be ruled out).[18,69,70]

Patients with GERD-like symptoms who do not have adequate relief after a 4- to 8-week trial of PPI treatment should be evaluated for adherence to medical therapy that might explain their lack of response or undergo further testing to establish a diagnosis of GERD. A GERD evaluation might include a more detailed and objective evaluation of the upper gastrointestinal tract with endoscopy, manometry, and pH measurement.[18] If these examinations yield diagnoses of GERD and the symptoms persist, twice-daily PPI dosing can be initiated. This increases the time that the gastric pH is greater than 4 and may thus more effectively reduce GERD symptoms.[22,65] Patients with extraesophageal symptoms such as cough or hoarseness combined with typical symptoms of GERD should be given an initial trial of PPI as described earlier. If the cough or hoarseness is not associated with typical GERD symptoms yet GERD is suspected as causing them, pH monitoring should be obtained to establish a diagnosis of GERD. Ambulatory esophageal pH monitoring can be used to assess the proportion of time with esophageal pH less than 4, and to correlate objective measures of reflux and the experience of symptoms. According to the results, GERD can be confirmed or other diagnoses such as functional heartburn revealed. Functional heartburn is diagnosed when a patient has GERD-like symptoms but objective assessments of GERD do not establish its presence.[71] Manometry evaluates esophageal motor function and is used for patients with persistent symptoms despite adequate treatment or for preoperative surgical planning.[55]

Emerging research suggests that long-term PPI treatment might be associated with adverse events or complications, including kidney diseases, certain infections, osteoporosis, and gastric cancer (**Table 4**). Among proposed adverse events are chronic kidney disease and acute kidney injury, and the evidence to date supports that patients with kidney disease who require long-term PPI treatment should have their kidney function monitored.[73,74] Studies have also indicated an increased risk of *Clostridium difficile* infection and community-acquired pneumonia after long-term PPI treatment.[72,75,76] In accordance with the data available, the Food and Drug Administration issued a safety announcement regarding *C difficile* infection, urging patients to seek health care if they experience continual diarrhea during PPI therapy, whereas the evidence regarding the risk for developing community-acquired pneumonia is insufficient for clinical recommendations.[83] Recent studies have identified long-term PPI treatment as a potential risk factor for osteoporosis,[77] and the Food and Drug Administration has posted a drug safety communication urging health care professionals to consider this risk before starting high-dose and long-term PPI treatment.[84] Recent research also suggests that long-term PPI-treatment increases the risk of gastric cancer, with a proposed mechanism of hypergastrinemia leading to hyperproliferation of the gastric mucosa, but the absolute risk is still low because of low population incidence of gastric cancer.[78-81] Most of the evidence regarding PPI and adverse events is based on observational studies in which residual confounding cannot be excluded. An RCT that included 17 598 patients did not show any statistically significantly increased risks of adverse events, but the follow-up was short (median, 3.1 years) and the statistical power low. Taken together, the long-term consequences of PPI treatment remain uncertain.

Long-term PPI treatment may cause rebound acid hypersecretion when the treatment is discontinued, which may be related to

**Questions for Clinicians**

**How does gastroesophageal reflux disease (GERD) present?**
Patients with GERD typically present with a burning retrosternal pain or regurgitation of gastric contents, but can also present with extraesophageal symptoms such as chronic cough, wheezing, asthma, or chronic laryngitis. Other atypical symptoms are dyspepsia, nausea, bloating, and belching.

**What does the typical evaluation of a patient with suspected GERD include?**
The evaluation begins with a thorough patient history. It is important to identify any chest pain caused by cardiac disease. Patients who present with dysphagia and weight loss solely or in combination with GERD symptoms should be investigated for upper gastrointestinal malignancies. If a diagnosis of GERD is probable, empirical treatment with a PPI can be tried to determine whether the symptoms resolve. If uncertainties remain about the GERD diagnosis, patients should be evaluated with endoscopy, pH monitoring, and esophageal manometry.

**What are the main treatment options?**
Most patients are successfully treated with a PPI, starting with a 4-week period of once-daily dosing. If esophagitis is present, an initial treatment duration of 8 weeks is recommended. After the initial treatment period, the medication is reduced or stopped. If known esophagitis or Barrett esophagitis is present, continuous medication with a PPI in the lowest dose tolerated to control symptoms is recommended. Surgery with laparoscopic fundoplication may be considered in select cases.

**Are there adverse events associated with long-term treatment using PPI?**
Some evidence has suggested a risk of adverse events after long-term PPI treatment, including kidney disease and injury, *Clostridium difficile* infection, community-acquired pneumonia, fractures owing to osteoporosis, and gastric cancer. But current evidence about the complications of long-term PPI use is not definitive enough to recommend stopping an ongoing necessary treatment or avoid initiating treatment if clinically indicated.

**What are the long-term consequences of GERD?**
Long-term GERD can lead to esophagitis and strictures of the esophagus because of acidic exposure. GERD increases the risk of developing a metaplasia of the epithelium of the esophagus, known as Barrett esophagus, which in turn is associated with an increased risk of esophageal adenocarcinoma. Yet a very low number of patients with GERD develop esophageal adenocarcinoma during their lifetime.

Table 4. Studies Assessing the Risk of Adverse Events After Treatment With Proton Pump Inhibitors

| Source | Study design | No. of participants | Risk estimate, OR (95% CI) | Comments | Evidence level[a] |
|---|---|---|---|---|---|
| Chronic kidney disease | | | | | |
| Moayyedi et al,[72] 2019 | RCT | 17 598 | 1.17 (0.94-1.45) | | 1B |
| Nochaiwong et al,[73] 2018 | Meta-analysis | 689 953 | RR, 1.36 (1.07-1.72) | Based on 4 cohort studies, high degree of heterogeneity | 2A |
| Hart et al,[74] 2019 | Population-based cohort study | 84 600 | 1.20 (1.12-1.28) | | 2B |
| Acute kidney injury | | | | | |
| Nochaiwong et al,[73] 2018 | Meta-analysis | 2 140 913 | RR, 1.44 (1.08-1.91) | Based on 5 cohort studies, high degree of heterogeneity | 2A |
| Hart et al,[74] 2019 | Population-based cohort study | 93 335 | 4.35 (3.14-6.04) | | 2B |
| Acute interstitial nephritis | | | | | |
| Nochaiwong et al,[73] 2018 | Meta-analysis | 585 296 | 3.61 (2.37-5.51) | Based on 2 case-control studies and 1 cohort study, low degree of heterogeneity | 3A |
| *Clostridium difficile* infection | | | | | |
| Moayyedi et al,[72] 2019 | RCT | 17 598 | 2.26 (0.70-7.34) | Few cases among both exposed and unexposed patients | 1B |
| Cao et al,[75] 2018 | Meta-analysis | 342 532 | 1.26 (1.12-1.39) | Based on 36 case-control studies and 14 cohort studies, high degree of heterogeneity | 3A |
| Community-acquired pneumonia | | | | | |
| Moayyedi et al,[72] 2019 | RCT | 17 598 | 1.02 (0.87-1.19) | | 1B |
| Nguyen et al,[76] 2020 | Meta-analysis | 967 279 | 1.86 (1.30-2.66) | Based on 7 case-control studies, high degree of heterogeneity | 3A |
| Fractures | | | | | |
| Moayyedi et al,[72] 2019 | RCT | 17 598 | 0.96 (0.79-1.17) | | 1B |
| Mortensen et al,[77] 2020 | Meta-analysis | 352 008 | 1.41 (1.16-1.71) | Based on 3 case-control studies, 1 cohort study, and 1 cross-sectional study; high degree of heterogeneity | 3A |
| Gastric cancer | | | | | |
| Brusselaers et al,[78] 2019 | Population-based cohort study | 796 425 | SIR, 1.31 (1.12-1.53) | | 2B |
| Cheung et al, 2018[79] | Cohort study | 63 397 | HR, 2.44 (1.42-4.20) | | 2B |
| Liu et al,[80] 2020 | Case-control study | 6513 | 1.13 (0.91-1.40) | | 3B |
| Liu et al,[80] 2020 | Cohort study | 472 029 | HR, 1.15 (0.73-1.82) | | 2B |
| Lee et al,[81] 2020 | Case-control study | 6491 | 1.07 (0.81-1.42) | | 3B |

Abbreviations: HR, hazard ratio; OR, odds ratio; RCT, randomized clinical trial; RR, risk ratio; SIR, standardized incidence ratio.

[a] Evidence level according to the Oxford Centre for Evidence-based Medicine.[82] Evidence level 1A: systematic review of RCTs. Evidence level 1B: individual RCT. Evidence level 1C: all or none, met when all patients died before the prescription became available but some now survive while receiving it, or when some patients died before the prescription became available but none now die while receiving it. Evidence level 2A: systematic review of cohort studies. Evidence level 2B: individual cohort study. Evidence level 2C: "outcomes" research or ecologic studies. Evidence level 3A: systematic review of case-control studies. Evidence level 3B: individual case-control study. Evidence level 4: case series (and poor-quality cohort and case-control studies). Evidence level 5: expert opinion without explicit critical appraisal, or based on physiology, bench research, or "first principles."

the high levels of gastrin after the treatment, which stimulates gastric acid production.[85] This problem can be avoided or reduced by gradually tapering the PPI-dose before stopping it.[85,86]

An alternative to PPI as maintenance therapy for GERD is histamine$_2$ receptor antagonists, the GERD medication of choice before the introduction of PPIs.[18,22] Histamine$_2$ receptor antagonists block the histamine receptors in the parietal cells of the stomach, thereby reducing the production of acid and often offering reasonable symptom control.[87] Recent analyses, however, found high levels of the probable human carcinogen *N*-nitrosodimethylamine in the histamine$_2$ receptor antagonist ranitidine, and the levels of this impurity increased during storage.[88,89] Therefore, the Food and Drug Administration and the European Medicines Agency have withdrawn all formulations of ranitidine from the US and European markets, respectively.[88,89] Nevertheless, other types of histamine$_2$ receptor antagonists (eg, famotidine, nizatidine) are still available.[88,89] Another medical treatment option is antacids (eg, magnesium hydroxide), which neutralize stomach acid. Because of limited efficacy compared with PPIs and histamine$_2$ receptor antagonists, these are not included in current clinical guidelines, but can be used if

patients experience good symptom relief. Recent studies have also investigated alginate as a treatment option for GERD. A meta-analysis of 14 studies (2095 patients) found that alginate relieves GERD symptoms better than antacids or placebo (OR, 4.42; 95% CI, 2.45-7.97) and has approximately the same effect as PPIs or histamine$_2$ receptor antagonists (OR, 0.58; 95% CI, 0.27-1.22).[90] However, more research is needed. In addition, an RCT of 280 patients found that adding a bile acid sequestrant to PPI treatment may reduce heartburn severity by another 12%.[91]

### Surgery

The most commonly performed surgical procedure for GERD is laparoscopic fundoplication, which enhances the esophagogastric junction's ability to prevent reflux into the esophagus.[92,93] An RCT of 456 patients found a similar effect of partial and total fundoplication for controlling GERD 3 years after surgery, with a median time with esophageal pH below 4 of 1.8% (interquartile range, 0.7%-4.4%) after partial fundoplication and 2.5% (interquartile range, 0.8%-6.8%) after total fundoplication. Partial fundoplication resulted in less dysphagia 2 years after surgery, with a mean dysphagia score of 1.3 (SD, 0.9) compared with 1.7 (SD, 1.2) for total fundoplication.[94] Before surgery is performed to treat GERD, a thorough evaluation should be performed to exclude other diagnoses that may present like GERD (Table 1). Fundoplication may be considered in select patients with low surgical risks and objectively confirmed GERD.[18,95] The preoperative evaluation should include endoscopy to rule out other mucosal pathologies such as malignancy, esophageal manometry to exclude motility disorders such as achalasia, and pH monitoring to confirm that GERD-like symptoms are indeed caused by acid reflux. A 5-year follow-up of 372 patients included in an RCT comparing the PPI esomeprazole with laparoscopic fundoplication found similar remission rates in the medication group (92%; 95% CI, 89%-96%) and surgery group (85%; 95% CI, 81%-90%), but worse symptoms of acid regurgitation in the medication group (13%) compared with the surgery group (2%).[96] A Cochrane Review of 4 RCTs and 1160 patients showed better short-term GERD-specific quality of life (0.58 SDs higher [95% CI, 0.46-0.70]), less heartburn (4.2% compared with 22.2%; risk ratio, 0.19 [95% CI, 0.1-0.34]), and fewer reflux symptoms (2.1% compared with 13.9%; risk ratio, 0.15 [95% CI, 0.06-0.35]) within 1 to 5 years after fundoplication compared with medication, whereas surgery had a higher risk of severe adverse events than medication (18.1% compared with 12.4%; risk ratio, 1.46 [95% CI, 1.01-2.11]).[93]

The risk of short-term mortality after laparoscopic fundoplication is low (0.1%-0.2%),[97] but complications can occur. In a population-based study of 2655 operated patients, 4.1% had a predefined complication within 30 days of surgery, mainly infection (1.1%), bleeding (0.9%), and iatrogenic esophageal perforation (0.9%), and the GERD recurrence rate was 17.7%.[98] In a Danish study of 2465 patients followed up to 9 years, 4.6% required reoperation after primary fundoplication, and a study from the United States of 13 050 patients found a 6.9% reoperation rate within 10 years of primary fundoplication.[99,100] A trial of 372 patients randomized to laparoscopic antireflux surgery or esomeprazole who were followed for 5 years found similar rates of GERD remission after surgery and medication. The surgery group had more dysphagia (11% compared with 5%), bloating (40% compared with 28%), and flatulence (57% compared with 40%).[96]

If GERD recurs after surgery, endoscopy and pH monitoring should be pursued to determine its etiology. Recurrent GERD-like symptoms after GERD surgery can be caused by the patient's not having a proper indication for the initial antireflux surgery, an incomplete preoperative evaluation, or inadequate surgical technique.[101]

### Emerging Treatments

New techniques in the treatment of GERD have been proposed as alternatives to long-term and high-dose PPI treatment or fundoplication. These techniques aim to be less invasive and reduce postoperative problems related to fundoplication. The long-term safety and efficacy of these techniques have not yet been established, and these procedures are not recommended.[18,22]

**Ablative Endoscopic Techniques** | The Stretta procedure involves application of radiofrequency energy delivered to several levels above and below the lower esophageal sphincter.[102] This results in thickening of the sphincter, decreased transient relaxation rate, and reduced esophageal acid exposure.[103] A meta-analysis of 28 studies (23 cohort studies, 4 RCTs, and 1 cohort study) including 2468 patients followed up for a mean of 25.4 months showed that Stretta improved average health-related quality of life (by 14.8 mean points) and heartburn (by 1.5 mean points), 51% of patients stopped PPI therapy, and the incidence of erosive esophagitis was reduced by 24%; however, most studies lacked a simultaneous control group and the included RCTs were small and not definitive.[104] To our knowledge, the risk of long-term adverse effects, specifically dysphagia rates, has yet to be reported in the literature.

**Transoral Incisionless Fundoplication** | Transoral incisionless fundoplication involves endoscopically suturing serosa-to-serosa plications including the muscle layers and constructs valves 3 to 5 cm long, taking up to 270° of the gastroesophageal circumference and deploying multiple nonabsorbable fasteners through the 2 layers in a circumferential pattern around the gastroesophageal junction.[105,106] In a cohort study of 49 patients, followed for up to 10 years, 8 (16%) were lost to follow-up and 7 (14%) remained unresponsive to transoral incisionless fundoplication and underwent fundoplication, but the majority of the remaining patients (92%) had stopped or reduced the use of PPI therapy.[107] An RCT of 63 patients comparing transoral incisionless fundoplication with PPI showed some short-term results favoring transoral incisionless fundoplication because at the 6-month follow-up, troublesome regurgitation was eliminated in 97% of transoral incisionless fundoplication patients vs 50% of PPI patients (risk ratio, 1.9; 95% CI, 1.2-3.1).[108] The 5-year follow-up of this trial suggested efficacy of transoral incisionless fundoplication, with only 34% of patients receiving daily PPI therapy, and showed improved mean scores for GERD-specific health-related quality of life, from 22 at baseline to 7 at 5 years.[109] However, another RCT of 60 patients showed at 12 months that, although GERD-specific health-related quality of life improved after transoral incisionless fundoplication, normalization of esophageal pH measurement was accomplished in only 29% of patients and resumption of PPI therapy occurred in 61%.[110] The discrepancy in findings between these trials may be a reflection of technical difficulty in performing transoral incisionless fundoplication or reflect a potential lack of clinical efficacy of the device. Thus,

clinical use of this device cannot be recommended outside of enrollment in well-designed RCTs.

**Magnetic Sphincter Augmentation** | A magnetic sphincter augmentation device was introduced in 2007 as an alternative surgical procedure less invasive than laparoscopic fundoplication.[111,112] The LINX (Torax Medical Inc) type of such a device is placed around the distal esophagus and comprises titanium beads with magnets in the center that augment lower esophageal tone and thus prevent reflux.[113,114] The device is commonly placed laparoscopically and requires less dissection than laparoscopic fundoplication.[115] An RCT of 152 patients that compared magnetic sphincter augmentation (n = 50) with twice-daily PPI (n = 102) in patients with moderate to severe regurgitation despite 8 weeks of once-daily PPI therapy showed improvements in the augmentation group: 84% of the patients with augmentation reported relief of regurgitation compared with 10% in the PPI group, and 81% the of augmentation group vs 8% of PPI group had greater than 50% improvement in GERD-specific health-related quality-of-life scores after 6 months.[116] A meta-analysis of 19 observational studies and 12 697 patients showed that compared with fundoplication, magnetic sphincter augmentation conferred control equivalent to that of fundoplication, as measured by requirement for postoperative PPI therapy and GERD-specific health-related quality of life.[117] Augmentation was associated with fewer gas bloating problems (OR, 0.34; 95% CI, 0.16-0.71) and greater ability to belch (OR, 12.34; 95% CI, 6.43-23.70).[117] This systematic review also suggested acceptable long-term safety of the device, with reoperation required in only 3.3% of patients. There are 2 main limitations to dissemination of this technique. First, to our knowledge no RCT has directly compared magnetic sphincter augmentation with laparoscopic fundoplication. Second, there are limited long-term data concerning the safety of augmentation and the incidence of device-related erosions.

## Discussion

GERD is one of the most common chronic diseases globally and is associated with reduced health-related quality of life and a risk of serious complications. The clinical management of GERD strongly influences the lives of many patients and has substantial implications for health care and society. Typical GERD symptoms relieved by PPI treatment are often sufficient to determine the diagnosis. Except for lifestyle recommendations, the primary treatment option is PPI medication. Fundoplication may be considered in select cases but conducted only after objective investigations confirm GERD. New endoscopic and minimally invasive techniques are emerging, but these have not yet demonstrated long-term safety and efficacy.

### Limitations

This review has several limitations. First, the broad scope of GERD, as well as the broad clinical and pathologic perspectives, makes a comprehensive review challenging. Therefore, the review is focused on aspects of relevance for clinicians, such as clinical management. Second, because of the quantity of literature published on GERD, the current review has maintained its focus on key references only.

## Conclusions

The clinical management of GERD influences the lives of many individuals and is responsible for substantial consumption of health care and societal resources. Treatments include lifestyle modification, PPI-medication, and laparoscopic fundoplication. New endoscopic and less invasive surgical procedures are evolving. PPI use remains the dominant treatment, but long-term therapy requires follow-up and reevaluation for potential adverse effects.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