

World Gastroenterology Organisation Global Guidelines

GERD Global Perspective on Gastroesophageal Reflux Disease



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This is the second WGO guideline published to complement World Digestive Health Day themes. WGO guidelines are intended to highlight appropriate, context-sensitive and resource-sensitive management options for all geographical regions, regardless of whether they are considered to be “developing,” “semi-developed,” or “developed.”

- There is a concern that guidelines from developed countries, by emphasizing high-tech investigations and Barrett esophagus (BE) surveillance, for example, may divert research and clinical resources from more urgent problems in developing and semideveloped countries.
- However, one could argue that there are similar problems in developed countries and that an over-emphasis on complications or “proposed GERD associations” (as in the Montreal Consensus¹) is leading to inappropriate investigations and resource utilization even in developed regions.

- It is also important to emphasize to health care insurers and funding bodies that appropriate, effective therapy is both therapeutic and diagnostic and that conducting mandatory investigations [eg, esophagogastroduodenoscopy (EGD) to permit proton-pump inhibitor (PPI) therapy is not patient-centered and, more importantly, is likely not to be cost-effective.
- WGO Cascades are thus context-sensitive, and the context is not necessarily defined solely by resource availability.

Neither the epidemiology of the condition, nor the availability of resources for the diagnosis and management of gastroesophageal reflux disease (GERD), is sufficiently uniform throughout the world to support the provision of a single, gold-standard approach.

WGO Cascades: a hierarchical set of diagnostic, therapeutic, and management options for dealing with risk and disease, ranked by the resources available.

GERD is now widely prevalent around the world (Table 1), with clear evidence of increasing prevalence in many developing countries. Prevalence estimates show considerable geographic variation, but it is only in East Asia that they are currently consistently lower than 10%.² The high prevalence of GERD, and hence of troublesome symptoms, has significant societal consequences, impacting adversely on work productivity³ and many other quality-of-life aspects for individual patients.^{4,5}

Practice recommendations should be sensitive to context, with the goal of optimizing care in relation to local resources and the availability of health care support systems. The expression of the disease is considered to be

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TABLE 1. GERD Symptoms: Range of Incidence

Incidence	Region
High	North America Australia/Oceania
Medium	Northern Europe Western Asia Southern Asia South America
Low	Eastern Asia
Insufficient data	Southern Europe Africa

GERD indicates gastroesophageal reflux disease.

similar across regions, with heartburn and regurgitation as the main symptoms. For initial management, the patient may purchase over-the-counter (OTC) medication for heartburn relief or seek further advice from a pharmacist. When patients perceive that their symptoms are more troublesome, they may seek a doctor’s advice; depending on the patient’s circumstances and the structure of the local health care system, patients may seek advice at the primary care level or they may consult a gastroenterology specialist or surgeon, directly or by referral. The WGO Cascade approach aims to optimize the use of available health care resources for individual patients, based on their location and access to various health care providers.

CLINICAL FEATURES

Predisposing and Risk Factors

GERD is a sensorimotor disorder associated with impairment of the normal antireflux mechanisms (eg, lower esophageal sphincter function, phrenicoesophageal ligament), with changes in normal physiology (eg, impaired esophageal peristalsis, increased intragastric pressure, increased abdominothoracic pressure gradient) or, very rarely, excess gastric acid secretion (Zollinger-Ellison syndrome).

Eating and Lifestyle

- An increase in GERD symptoms occurs in individuals who gain weight.⁶
- A high body mass index (BMI) is associated with an increased risk of GERD.⁷
- High dietary fat intake is linked to a higher risk of GERD and erosive esophagitis (EE).⁸
- Carbonated drinks are a risk factor for heartburn during sleep in patients with GERD.⁹
- The role of coffee as a risk factor for GERD is unclear; coffee may increase heartburn in some GERD patients,¹⁰ but the mechanism is unknown and it may be due to caffeine, rather than coffee per se. Coffee is not a dominant risk factor.
- The role of alcohol consumption as a risk factor for GERD is unclear. Excessive, long-term use may be associated with progression to esophageal malignancy, but this may be independent of an effect of alcohol on GERD.^{11,12}
- The role of smoking as a risk factor for GERD is unclear, although like alcohol, it is associated with an increased risk of malignancy.^{13,14}

Medication—Certain Medications May Affect GERD

See the Patient history and physical examination section.

The treatment of comorbidities (eg, with calcium channel blockers, anticholinergics, and nonsteroidal anti-inflammatory drugs (NSAIDs)) may negatively affect GERD and its treatment.¹⁵ Some medications (eg, potassium supplements, tetracycline, bisphosphonates) may cause upper gastrointestinal (GI) tract injury and exacerbate reflux-like symptoms or reflux-induced injury.

Pregnancy

Heartburn during pregnancy usually does not differ from the classic presentation in the adult population, but it worsens as pregnancy advances. Regurgitation occurs with approximately the same frequency as heartburn, and GERD in the first trimester is associated with a number of altered physiological responses.^{16,17} Factors that increase the risk of heartburn¹⁸ are: heartburn before pregnancy, parity, and duration of pregnancy. Maternal age is inversely correlated with the occurrence of pregnancy-related heartburn.¹⁹

Symptomatology

GERD has a wide spectrum of clinical symptom-based and injury-based presentations, which may manifest either separately or in combination.

Symptom evaluation is key to the diagnosis of GERD, particularly in the evaluation of the effectiveness of therapy. Heartburn and regurgitation are the most common symptoms, but atypical symptoms of GERD may occur, with or without the common symptoms. Atypical symptoms may include epigastric pain²⁰ or chest pain,^{1,21} which may mimic ischemic cardiac pain, as well as cough and other respiratory symptoms that may mimic asthma or other respiratory or laryngeal disorders. Dysphagia may also occur. A minority of GERD patients have multiple unexplained symptoms, which may be associated with psychological distress²² (Table 2).

Natural History

- Most cases of GERD are mild and are not associated with a significant increase in morbidity or mortality in comparison with the general population.
- In most GERD patients, the severity of the condition remains stable or improves over a 5-year observation period during current routine clinical care.²⁶
- There is a relationship between GERD and obesity: a higher BMI or larger waist circumference and weight

TABLE 2. GERD Symptoms^{23,24}

Typical	Atypical
Heartburn (daytime or nighttime)	Nausea, eructation (belching)* Slow digestion, early satiety*
Regurgitation (daytime or nighttime)	Epigastric pain* Bloating*
Water brash (hypersalivation)	Vomiting Chest pain (precordial) Respiratory symptoms (cough, wheeze, chronic rhinosinusitis) ENT symptoms (hoarseness, pharyngeal pain, globus) Early awakening Nocturnal awakening, nightmares

*Can be considered to be associated with GERD if symptoms improve in response to PPI treatment.²⁵
ENT indicates ear, nose, and throat; GERD, gastroesophageal reflux disease; PPI, proton-pump inhibitor.

- gain are associated with the presence of symptoms and complications of GERD, including BE.²⁷
- Complicated GERD is characterized by stricture, BE, and esophageal adenocarcinoma. The Montreal consensus includes EE as a complication of GERD (recognizing that the definition of “mucosal breaks” used in the Los Angeles classification includes esophageal ulceration in the range of reflux esophagitis).²⁸
 - Nonerosive reflux disease (NERD) may progress to EE in approximately 10% of GERD patients,²⁹ and EE may therefore be considered as a manifestation of more severe reflux disease.
 - EE is associated with BE and is a major risk factor for BE. In comparison with patients who were free of GERD at follow-up, those with EE had a 5-fold increased risk of BE after 5 years, in a cohort of the general population in Sweden.³⁰
 - Globally, BE is rare in patients with GERD. It is more common in western populations.
 - It is not known when BE develops relative to the onset of GERD; however, it appears to be more prevalent in older individuals and is strongly associated with an increased risk of esophageal adenocarcinoma.³¹
 - There is a well-documented association between BMI and adenocarcinoma of the esophagus and gastric cardia, although the risk of malignancy in a given individual with GERD is very low.³²

Alarm Features

Most alarm features are not specific for GERD; many are associated with alternative diagnoses that are unrelated to GERD. In most countries, many of these features relate to gastric cancer, complicated ulcer disease, or other serious illnesses.

- Dysphagia.³³
- Odynophagia (painful swallowing).
- Recurrent bronchial symptoms, aspiration pneumonia.
- Dysphonia.
- Recurrent or persistent cough.
- GI tract bleeding.
- Frequent nausea and/or vomiting.
- Persistent pain.
- Iron-deficiency anemia.
- Progressive unintentional weight loss.
- Lymphadenopathy.
- Epigastric mass.
- New-onset atypical symptoms at age 45 to 55 years (a lower age threshold may be appropriate, depending on local recommendations).
- Family history of either esophageal or gastric adenocarcinoma.³⁴

The WGO Global Guideline on common GI symptoms may also be consulted: <http://www.worldgastroenterology.org/guidelines/global-guidelines/common-gi-symptoms> and http://journals.lww.com/jcge/Fulltext/2014/08000/Coping_With_Common_Gastrointestinal_Symptoms_in.4.aspx.

DIAGNOSIS

Diagnostic Considerations

The presence of heartburn and/or regurgitation symptoms 2 or more times a week is suggestive of GERD.³⁵ Clinical, endoscopic, and pH-metric criteria provide a comprehensive characterization of the disease, although investigations are usually not required to establish a diagnosis of

GERD—with the caveat that the pretest probability of GERD varies markedly between geographical regions.

The initial evaluation should document the presence, severity, and frequency of heartburn, regurgitation (acid or otherwise), and alarm features; atypical esophageal, pulmonary, otorhinolaryngological, and oral symptoms should also be sought. It may be helpful to evaluate precipitating factors such as eating, diet (fat), activity (stooping), and recumbence; and relieving factors (bicarbonate, antacids, milk, OTC medications).

At this point, it is important to rule out other GI diagnoses, particularly upper GI cancer and ulcer disease, especially in areas in which these are more prevalent. It is also important to consider other, non-GI diagnoses, especially ischemic heart disease.

Diagnostic questionnaire tools for GERD (reflux disease questionnaires, RDQs) have been developed for epidemiological studies. However, RDQs did not perform particularly well in the Diamond study.³⁶ In fact, diagnosis by a physician such as the family practitioner or GI specialist showed better sensitivity and specificity for the diagnosis of GERD than did the RDQ. Questionnaires are generally difficult to use in clinical practice. A careful history is the basis for symptomatic diagnosis, with EGD being reserved for identifying or excluding significant structural lesions in selected cases.

A region-based assessment of the local “pretest probability” may provide some guidance with regard to the choices and sequence of diagnostic tests needed, given the relatively poor predictive value of most symptoms.

PPI Treatment as an Aid to Diagnosis

- “PPI trial.” It is no longer recommended to administer an empirical short-term (1 to 2 week) course of high-dose PPI treatment to determine whether or not the patient’s symptoms are acid related,³⁶ since this is neither sensitive nor specific. Nonetheless, this is commonly done in practice.
- A formal course of PPI therapy, of adequate duration (usually 8 weeks) is required to assess the treatment response in GERD patients.
- Weakly acidic reflux episodes may be a substantial proportion of all reflux episodes. If this is the case, such patients may not respond well to PPI therapy (20% to 40% of GERD patients may not respond to PPI treatment).²⁰ In addition, genuinely alkaline reflux may comprise up to 5% of all reflux episodes.
- In a subset of PPI nonresponders, reflux-like symptoms may be due to functional heartburn, rather than GERD.²⁰ Alternative diagnoses, including peptic ulcer disease, upper GI malignancy, functional dyspepsia, eosinophilic esophagitis, achalasia of the cardia, and cardiovascular disease should also be considered.
- In patients with cases that are refractory to PPI treatment, ambulatory 24-hour esophageal pH/impedance monitoring, with the patient off PPI therapy, may be considered to help characterize symptoms.³⁷
 - If there has been complete failure to respond to PPI treatment, the PPI should be stopped at least 1 week before 24-hour pH monitoring is performed (rescue antacid may be allowed when necessary), to assess for acid reflux.
 - If the refractory reflux symptoms have responded partially, 24-hour pH monitoring (with or without

esophageal impedance monitoring) should be performed with PPI administration being continued, to assess for acid reflux that is persistent despite treatment.

- Occasionally, 24-hour pH monitoring with esophageal impedance monitoring may be required, with the patient both on and off PPI therapy.³⁸

***Helicobacter pylori* Infection³⁹**

In many countries with a high prevalence of *H. pylori* infection, peptic ulcer and gastric cancer continue to be more common than GERD and cause much higher morbidity and mortality.⁴⁰

- In this setting, any approach to the diagnosis and management of upper gut symptoms must include an assessment of the risks of infection with *H. pylori* and an awareness of the overlap among, and difficulty of discriminating between, symptoms of GERD, peptic ulcer disease, and functional symptoms—with a decision regarding the relative merits of a test-and-treat approach in comparison with EGD to test for *H. pylori* and related diseases before empirical antireflux therapy.
- Although epidemiological studies show a negative association between the prevalence of *H. pylori* infection and the presence and severity of GERD, this is not proof of causation. *H. pylori* infection should be sought and eradication therapy given when indicated in accordance with international, national, or local guidelines.⁴¹
- Although there may be an inverse correlation between *H. pylori* infection and GERD prevalence and severity, this may well reflect differing effects of a separate, distinct factor or factors on the 2 conditions, rather than a causal relationship between *H. pylori* and GERD.
- Physiological studies using pH monitoring have shown that abnormal esophageal acid exposure, which is the hallmark of esophageal reflux, is not influenced by the presence or absence of *H. pylori* infection.
- In most patients, *H. pylori* status has no effect on symptom severity, symptom recurrence, or treatment efficacy in GERD. *H. pylori* eradication does not exacerbate preexisting GERD or affect treatment efficacy.⁴² Indeed, in patients with *H. pylori*-positive uninvestigated dyspepsia, eradication therapy is associated with a lower prevalence of reflux-like symptoms (36%) than control therapy (49%).⁴³
- A subgroup of patients infected with more proinflammatory strains of *H. pylori* (virulence factors *vacA* and *cagA*) may be less likely to have severe esophagitis or BE. This may be because infection in these patients more often causes severe corpus gastritis with atrophy, resulting in reduced acid output. However, these patients are at much greater risk of developing gastric cancer. Eradication therapy in these patients has the potential to reduce the risk of gastric malignancy.⁴¹

PPIs and *H. pylori*

PPIs are associated with a worsening of the histologic grade of gastritis in *H. pylori*-infected patients, accompanied by an increased prevalence of gastric mucosal atrophy and intestinal metaplasia⁴⁴ that occurs earlier, as well as more frequently, than in *H. pylori*-infected patients who do not take PPIs. As gastric mucosal atrophy and intestinal metaplasia are known to be the major risk factors for the development of gastric adenocarcinoma, most expert guidelines recommend testing and treating for *H.*

pylori before long-term PPI therapy, particularly in younger patients.

Endoscopy

EGD is usually performed for new-onset upper GI symptoms, almost irrespective of age, in regions where it is available and affordable and where both the frequency of ulcer disease and the concern about malignancy are high, as in most of Asia.⁴⁵ The Cascades given below address the limited availability of endoscopy in less well-resourced areas by suggesting the use of empiric *H. pylori* eradication therapy as a first-line strategy.

- If EGD is performed in regions where the prevalence of GERD is low, the majority of GERD patients will have NERD; in these circumstances, the sensitivity of EGD for the diagnosis of GERD will be low and the main outcome will therefore be the exclusion of other upper GI diagnoses.
- Endoscopy is particularly recommended for patients with alarm features suggestive of GERD with complications or of other significant upper GI disease such as dysphagia, bleeding, odynophagia, or weight loss.
- Patients with dysphagia should undergo investigation for a potential complication or for an underlying motility disorder, achalasia, stricture, ring, eosinophilic esophagitis, or malignancy.²⁵
- In several Asian countries, the preference for EGD is driven by the risk of malignancy at an early age and by the availability of “affordable, direct-access” endoscopy—an “endoscopy first” approach.

Additional investigations other than EGD are rarely needed; furthermore, they have variable accuracy and are often unavailable.

Patient History and Physical Examination

The goals of patient evaluation include the assessment of symptoms and risk factors for the diagnosis of GERD and the prediction of long-term sequelae. In this regard, it is important to consider the regional epidemiology of upper GI disease and the pretest probability of GERD relative to other conditions. In Asia, for instance, BE is uncommon and it is not therefore an important risk for esophageal adenocarcinoma, which is itself uncommon. The prevalence of peptic ulcer and gastric cancer are the greater drivers of endoscopy in Asia where, unlike in the west, esophageal adenocarcinoma is less common.

Personal and Family History Features

The following features may be helpful in making a diagnosis and assessing the severity of GERD:

- Predisposing factors and risk factors, including family history.
- Duration of symptoms.
- Daytime symptoms, including time of day and relationship to meals.
- Nocturnal symptoms, including impact on sleep and the effects of a recumbent position and large, late evening meals.
- Treatments and remedies tried, including symptomatic response to therapy; symptom improvement with acid-lowering medications including antacids supports a diagnosis of GERD.
- Periodic dysphagia or food bolus impaction may suggest reflux-related esophageal injury, stricture or malignancy, as well as eosinophilic esophagitis or esophageal dysmotility.⁴⁶

Drug History

The patient should be asked about any medications that may contribute to upper gut symptoms (not necessarily GERD):

- Aspirin/NSAIDs, iron, potassium, quinidine, tetracycline, bisphosphonates.
- Zidovudine, anticholinergic agents, α -adrenergic antagonists, barbiturates.
- β_2 -adrenergic agonists, calcium channel blockers, benzodiazepines, dopamine.
- Estrogens, narcotic analgesics, nitrates, progesterone, prostaglandins, theophylline.
- Tricyclic antidepressants, chemotherapy.

Dietary History

- In some patients, bloating or constipation may be associated with an increased risk of GERD or gastroesophageal reflux symptoms (GERS).⁴⁷
- Several studies suggest that stopping smoking and some physical measures, as well as modification of meal size and timing, can be beneficial, but there is limited evidence for the avoidance of alcohol and certain dietary ingredients including carbonated drinks, caffeine, fat, spicy foods, chocolate, and mint.⁴⁸
- In those who are overweight, weight loss may be associated with improvement in GERD or GERS.⁴⁹
- Fermentable carbohydrates may increase the propensity for reflux.⁵⁰

Physical Evaluation

There are usually no physical signs of GERD.

- Waist circumference, weight, and BMI are relevant to risk.
- Peripheral stigmata of scleroderma may, rarely, be present.
- Evaluation and inspection to exclude other medical problems such as asthma, cardiac disease, and cancer.

Diagnostic Tests for GERD

A presumptive diagnosis of GERD can be established in the setting of typical symptoms: heartburn and regurgitation. In pregnancy, GERD can be reliably diagnosed on the basis of symptoms alone.

If the dominant or most troublesome symptoms are atypical for GERD, other diagnoses should be considered, including *H. pylori*-related diseases and NSAID-related disease. In regions with a high prevalence of *H. pylori* infection, an initial *H. pylori* test-and-treat strategy, or endoscopy if available, should be considered.

Radiologic examinations are seldom required. Esophageal pH or pH-impedance monitoring and esophageal manometry can be performed safely, but are seldom required except to assess structural disorders (eg, hiatal hernia) in patients with dysphagia symptoms. Intractable reflux symptoms or GERD complications can be evaluated safely using EGD^{16,17} (Table 3).

TABLE 3. Diagnostic Options for GERD

Diagnostic test	Indication	Recommendation
Empirical PPI therapy (“PPI trial”)	Classic symptoms, no alarm features. For extraesophageal GERD	A negative trial does not rule out GERD
Urea breath test or <i>Helicobacter pylori</i> stool antigen test	For uninvestigated dyspepsia, in populations in which the <i>H. pylori</i> prevalence is high (> 20%): “test-and-treat” strategy	This approach is subject to local cost-benefit considerations It should be based on a noninvasive test of active infection ³⁹ (UBT, monoclonal stool antigen test)
Endoscopy	For alarm symptoms, screening of high-risk patients, chest pain Differentiates EE from NERD Diagnoses other causes or upper gut symptoms	Consider early for elderly, those at risk for BE, noncardiac chest pain, patients unresponsive to PPI Prompt endoscopy is recommended in areas with high incidence of upper GI cancer ⁵¹
Esophageal biopsy	To exclude non-GERD causes for symptoms—for example EoE. For suspected BE (ESEM)	Not indicated for diagnosis of GERD
Gastric biopsy	For unknown <i>H. pylori</i> status in patients undergoing EGD for upper GI symptoms	Indicated for the diagnosis of unexplained, previously uninvestigated upper GI symptoms (dyspepsia) and to detect <i>H. pylori</i> infection before long-term PPI therapy. Eradicate infection if detected
Esophageal manometry	To diagnose motility disorders in endoscopy-negative patients unresponsive to PPI therapy Preoperative evaluation for surgery Location of pH probe	Not recommended for GERD diagnosis When achalasia/scleroderma is being considered Preoperative
pH or impedance pH monitoring	For atypical symptoms For PPI-refractory GERD symptoms Preoperatively, for nonerosive disease	Correlate symptoms with reflux, document abnormal acid exposure or reflux frequency
Barium swallow	For evaluation of dysphagia and occasionally for characterization of hiatal hernia	Not useful for GERD diagnosis Do not use unless evaluating for complications (stricture, ring, dysmotility)

On the basis of Katz et al.⁵²

Note: The definition of NERD is based on investigations, and it is probably not relevant to the diagnosis and management of GERD by family practitioners and other community-based health care providers, such as pharmacists.

BE indicates Barrett esophagus; EE, erosive esophagitis; EGD, esophagogastroduodenoscopy; EoE, eosinophilic esophagitis; ESEM, endoscopic suspicion of esophageal metaplasia; GERD, gastroesophageal reflux disease; GI, gastrointestinal; NERD, nonerosive reflux disease; PPI, proton-pump inhibitors; UBT, urea breath test.

Differential Diagnosis

- Peptic ulcer disease.
- Upper gut malignancy.
- Functional heartburn—differentiate NERD and functional heartburn on the basis of a clinical response to therapeutic acid suppression, pH monitoring, or impedance pH monitoring.
- Schatzki ring, stricture—esophageal web.
- Achalasia of the cardia.
- Esophageal body motility disorders—scleroderma; diffuse esophageal spasm.
- Eosinophilic esophagitis.
- Infection—*Candida*, herpes simplex, etc.
- “Pill esophagitis.”
- Cardiac disease—ischemic heart disease, pericardial disease.
- Esophageal diverticulum.
- Other chest pathology.

Cascades for the Diagnosis of GERD

- For EGD, perform esophageal biopsy in abundantly resourced regions or biopsy for selected patients in regions with “medium resources” if features suggest eosinophilic esophagitis.
- For screening EGD, consider this only if there is a high prevalence of BE in the local population and if there are abundant resources.
- For most purposes, EGD will not alter the management, in the absence of alarm features or access to antireflux surgery.
- There is no role for upper GI series in the investigation of routine upper GI symptoms (uninvestigated dyspepsia) (Table 4).

MANAGEMENT

Management Principles

General Principles

Although the severity and frequency of symptoms vary greatly between GERD patients, occasional reflux symptoms (GERS) do not meet the criteria for a diagnosis of GERD and are managed with low-level intermittent treatments and lifestyle adjustments, as required. More frequent or severe symptoms interfere significantly with patients’ quality of life and warrant therapy sufficient to normalize their quality of life.

Generally, the management of GERD follows a stepwise approach, both with respect to the treatments and to the health care professionals who guide or provide therapy.

Core Principles

The core principles of GERD management are lifestyle interventions and reduction of esophageal luminal acid either by local acid neutralization or by suppression of gastric acid secretion using medical treatment; or, rarely, antireflux surgery. The primary goals of treatment are to relieve symptoms, improve the patient’s health-related quality of life, heal esophagitis, prevent symptom recurrence, and prevent or treat GERD-associated complications in the most cost-effective manner.

Stepwise Therapy

Infrequent heartburn occurring less than twice per week will probably respond to self-care with an antacid or alginate-antacid, taken once a week or less often. These

TABLE 4. Cascades for the Diagnosis of GERD

Resource Level	Diagnostic Recommendations*	
	Low <i>Helicobacter pylori</i> Prevalence†	High <i>H. pylori</i> Prevalence‡
Limited resources	<ol style="list-style-type: none"> 1. Empirical antacid therapy +/- alginate 2. Empirical H₂RA therapy 3. PPI therapy (od) if no response 4. Consider <i>H. pylori</i> testing 	<ol style="list-style-type: none"> 1. <i>H. pylori</i> “test-and-treat” eradication therapy until confirmed cure 2. Empirical acid suppression therapy 3. PPI therapy (od) if no response
Medium resources	<ol style="list-style-type: none"> 1. Empirical PPI therapy (od) (consider <i>H. pylori</i> testing) 2. PPI therapy (bid) if no response 3. EGD if no response to ≥ 16 wk of PPI therapy (od, bid) 4. Screening EGD for BE if white, male patient > 50 y 	<ol style="list-style-type: none"> 1. <i>H. pylori</i> “test-and-treat” eradication therapy until confirmed cure 2. PPI therapy (od) if no response 3. PPI therapy (bid) if no response 4. EGD if no response to ≥ 16 wk of PPI therapy (od, bid) 5. Screening EGD for BE if white, male patient > 50 y
High resources	<ol style="list-style-type: none"> 1. Empirical PPI therapy (od) (consider <i>H. pylori</i> testing) 2. PPI therapy (bid) if no response 3. EGD if no response to ≥ 16 wk PPI therapy (od, bid) 4. Esophageal manometry if EGD is normal 5. pH monitoring/impedance if persistent symptoms (or antireflux surgery is possible) 6. Screening EGD for BE if patient > 50 y 	<ol style="list-style-type: none"> 1. <i>H. pylori</i> “test and treat” eradication therapy until confirmed cure 2. PPI therapy (od) if no response 3. PPI therapy (bid) if no response 4. EGD if no response to > 16 wk PPI therapy (od, bid) 5. Esophageal manometry if EGD is normal 6. pH monitoring/impedance if persistent symptoms (or antireflux surgery is possible) 7. Screening EGD for BE if patient > 50 y

*Alarm features warrant EGD in all regions.

†*H. pylori* prevalence: low: <30% nationally, low-risk population, confirmed eradication. High: ≥ 30% nationally, older patients, high-risk region (eg, First Nations in North America), high-risk ethnic groups (immigrants from eastern Europe, South America, Africa, Indian subcontinent, Asia).

BE, Barrett esophagus; bid, bis in die (twice a day); EGD, esophagogastroduodenoscopy; GERD, gastroesophageal reflux disease; H₂RA, histamine H₂-receptor antagonists; od, omni die (daily); PPI, proton-pump inhibitor.

medications are very unlikely to have any deleterious effects. Alginate-antacid combinations are useful and are superior to antacids alone.⁵³ Particularly in this group of patients, avoidance of foods or events that trigger symptoms and avoidance of large meals eaten late at night may be helpful. Weight reduction in those who are overweight may also reduce the frequency of symptoms.

Patients who have more frequent symptoms should be assessed for longer-term therapy. A diagnosis of GERD—that is, troublesome symptoms 2 or more times per week—warrants empirical therapy with an acid inhibitor [PPI or, if unavailable, histamine H₂-receptor antagonists (H₂RA)]. Antacids/alginate may also be used if PPIs or H₂RAs are unavailable, or for prompt symptom relief in patients taking a PPI.

If OTC or lifestyle measures fail, patients will often present initially to a pharmacist or primary care physician. The definition of treatment failure depends to a large extent on the treatment being tried. In contrast, treatment may fail because the patient does not actually have GERD; in contrast, it may be that the treatment is inadequate to address the severity of the GERD. In the latter case, there may be a partial response to treatment, and subsequent management will be guided by the availability and optimization of more potent therapies. These latter steps may require referral to secondary care if initial management fails.⁵⁴ Approaches to reflux should focus on best clinical practice, with treatment of the symptoms being the priority.

- It is wise to choose the lowest effective dose of prescription drugs.
- For patients with mild symptoms, and some patients with NERD, self-directed, intermittent PPI therapy (“on-demand therapy”) is a useful management strategy in many cases.
- At the primary care level, PPIs or a combination of alginate-antacid and acid-suppressive therapy can be prescribed at the physician’s discretion for combination therapy, which may be more beneficial than acid-suppressive therapy alone.⁵⁴
- For better symptom control, patients should be informed about how to use PPI treatment properly; optimal therapy may be defined as taking the PPI 30 to 60 minutes before breakfast, and in the case of twice-daily dosing, 30 to 60 minutes before the last meal of the day as well.⁵⁵
- Patients in whom full-dose PPI treatment fails, with or without adjuvant therapies, may benefit from a trial of step-up therapy to a twice-daily PPI.
- Twice-daily PPI therapy may not work for a proportion of patients, either because the symptoms are not due to acid reflux—when an alternative diagnosis should be considered—or because the degree of acid suppression achieved is insufficient to control the symptoms. Referral to secondary care should be considered for “PPI-refractory” patients.
- OTC antacids show disappointing results in patients with EE.

Self-care

- Controlled weight reduction in the overweight and obese is an important part of the long-term management of GERD and should not be ignored as a therapeutic intervention, as it may reduce the frequency and intensity of symptoms and lessen the grade of EE, if present.
- Lifestyle—small meals, avoidance of late meals, avoidance of precipitating factors, use of a sleep positioning device (pillow).⁵⁶

- OTC medicines (antacids or alginate-antacids) offer the most rapid, but usually transient, symptom relief and can be taken as required.
- Alarm features (see the Alarm features section).

Options for Pharmacist-assisted Self-medication

- Reinforce lifestyle advice.
- Guide patients in the selection of medical OTC treatment by confirming the diagnosis, referring patients with alarm symptoms to physicians, and educating patients on the proper use of their OTC medication—which in some jurisdictions may include PPIs.⁵⁷ N.B.: the availability of treatment choices varies between countries.
- Antacids—recommended for short-term or intermittent relief:
 - Simple antacids neutralize gastric acid—that is, sodium, calcium, magnesium, and aluminum salts.
 - Alginate-containing agents: these include alginic acid with small doses of antacids: minimal buffering effects.
- H₂RAs—recommended for short-term to medium-term use.
 - Widely available OTC.
 - Cimetidine, ranitidine, famotidine, nizatidine.
 - More prolonged action than antacids.
 - Tachyphylaxis.
- OTC PPIs:
 - Patients seeking pharmacy advice for frequent reflux symptoms may benefit from OTC PPI treatment.
 - Esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole, which have different OTC availability in individual countries—see the Association of the European Self-Medication Industry Web site (<http://www.aesgp.eu/facts-figures/otc-ingredients/>).
 - Other OTC PPIs may be available in other jurisdictions.
- Alarm features (see the Alarm features section).

Self-treatment without investigation should be avoided in the presence of the following conditions^{58–61}:

- Heartburn or regurgitation symptoms when:
 - Duration >3 months with severe or nocturnal heartburn.
 - Continuing after 2 weeks of treatment with an OTC H₂RA or PPI.
 - Occurring when taking a prescription H₂RA or PPI.
- New-onset heartburn or regurgitation at age 45 to 55 years—lower age in several Asian regions.
- Dysphagia or odynophagia.
- Symptoms or signs of GI bleeding: hematemesis and melena, iron-deficiency anemia.
- Symptoms or signs of laryngitis: hoarseness, wheezing, coughing, or choking.
- Unexplained weight loss.
- Continuous nausea, vomiting, and/or diarrhea.
- Symptoms suggestive of cardiac-type chest pain: radiating to shoulder, arm, neck or jaw, shortness of breath, sweating.
- In pregnant women or nursing mothers.
- Children below 12 years of age for antacids/H₂RA, or below 18 years for PPIs.

Follow-up Action

- The goals of self-treatment are that the patient should become symptom-free and return to an optimal quality of life, with the most cost-effective therapy.
- If satisfactory and complete symptom relief is not achieved, patients should be recommended to visit a health care professional for diagnostic evaluation.
- PPI overuse—people who need sustained gastric acid suppression should have an appropriate indication for long-term PPI use; the long-term need for PPIs should be reassessed regularly. We advocate responsible PPI prescription, which should be based on good investigation and diagnosis and if the treatment does not work, medication should be stopped. Proper documentation is advocated.

Options for Family Physicians

- Reinforce lifestyle modifications.
- Endorse OTC medications (antacids and alginates, H₂RAs) as appropriate.
- Prescription H₂RAs.
- Currently available PPIs—daily standard doses from studies of healing in EE (not all PPIs may be available in all countries, and the standard dose of PPIs may differ in some countries):
 - Omeprazole (20 mg).
 - Rabeprazole (20 mg).
 - Lansoprazole (30 mg).
 - Pantoprazole (40 mg).
 - Esomeprazole (40 mg).
 - Dexlansoprazole (60 mg).
- Prokinetic drugs:
 - May decrease gastroesophageal reflux, but few prokinetics are available for clinical use and their efficacy in clinical trials has been modest at best. Not recommended.
 - Metoclopramide should be avoided, because of adverse effects.
 - Domperidone shows little benefit and is not recommended, because of safety concerns around prolongation of the QTc interval on electrocardiography.
 - Mosapride: limited availability and efficacy.
- Alarm features (see the Alarm features section).
 - Check medication interactions.
 - Rule out/treat other contributing conditions (constipation, exacerbating medications).

Options for Specialists (Secondary Care: Gastroenterologist, Surgeon)

To address patients’ needs, the full range of symptoms should be taken into account. Symptoms in addition to or other than heartburn may respond differently to treatment.

- Regurgitation may not respond to treatment as well as heartburn.
- Interrupting PPI treatment may lead to short-term symptom rebound in a minority of patients.^{62,63}
- PPI treatment failure^{64,65} may be related to:
 - Incorrect diagnosis: common with functional heartburn.
 - Noncompliance: patients with GERD may show poor adherence to the prescribed PPI, and this may play an important role in treatment failure.⁶⁶

- Incorrect dosing time: most PPIs are more effective if taken 30 to 60 minutes before a meal.
- Inadequate dosing.
- Low drug bioavailability (rapid metabolizers).
- Duodenogastroesophageal reflux, nocturnal reflux, weakly acidic reflux, residual acid reflux.
- Delayed/prolonged gastric emptying, gastric outlet obstruction.
- Esophageal hypersensitivity.
- Eosinophilic esophagitis.
- Psychological comorbidity.
- H₂RAs are effective for suppressing acid in short-term or intermittent use, but tachyphylaxis limits long-term benefits.
- There is little evidence to support the use of prokinetics (cisapride, domperidone, tegaserod, mosapride) alone or in combination with acid suppression. Serious adverse effects have led to withdrawal in many jurisdictions, and tachyphylaxis occurs. They cannot be recommended.
- Putative consequences or adverse effects of acid suppression⁶⁷: most of these are based on retrospective analyses of heterogeneous populations and therefore show associations that may not be causal.
 - Headache and diarrhea occur at a rate little different from that with placebo.
 - GI infections⁶⁸: a modestly increased risk of bacterial gastroenteritis and an association with increased risk of *Clostridium difficile* infection with PPI use.
 - Respiratory tract infections: reports describing a modestly increased risk of community-acquired pneumonia with PPI use acknowledge the heterogeneity of the study outcomes, the absence of a clear pathophysiological basis, and the potential for unmeasured confounders.
 - Low serum vitamin B₁₂: not clinically significant.
 - Hypomagnesemia—very rare, but documented with rechallenge studies.
 - Cancer—no evidence of increased risk associated with PPI use per se.
 - Osteoporosis, fractures—not likely or probable.
- Alarm features (see the Alarm features section):
 - Check medication interactions.
 - Rule out/treat other contributing conditions (constipation, exacerbating medications).
 - Decide on the place of further investigations, “off-label” medications, and surgery.

GERD Treatment in Pregnancy (Table 5)

Surgical Interventions

Surgical intervention (usually fundoplication) in GERD patients is rarely indicated, but may be considered if there is a large hiatal hernia causing volume-related reflux symptoms and if there is evidence of aspiration or cardia dysfunction. Other indications may include noncompliance with medical treatment, side effects associated with medical therapy, esophagitis refractory to medical therapy, or persistent symptoms documented as being caused by refractory GERD.⁵²

The response to acid suppression (or neutralization) in patients with functional heartburn is by definition absent or minimal at best, and patients are at risk of being referred for surgical treatment for GERD. Hence, all patients with

TABLE 5. Treatment Options for GERD in Pregnancy

Treatment option	Details
Dietary and lifestyle modifications	Frequent (every 3 h), small meals Last oral intake 3 h before bedtime Elevate head of bed
↓	
Antacids or sucralfate	Avoid long-term use or high doses of magnesium trisilicate Avoid sodium bicarbonate
↓	
H ₂ -receptor antagonists	Use ranitidine: FDA category B Limited data are available for other H ₂ -receptor antagonists, but they are probably also safe
↓	
PPIs	Use omeprazole: FDA category B Limited data are available for other PPIs, but they are probably also safe

FDA indicates Food and Drug Administration (United States); GERD, gastroesophageal reflux disease; PPI, proton-pump inhibitor.

TABLE 6. Recommendations for Complications in GERD

Complication	Recommendation
EE	Use the Los Angeles (LA) classification system (see the Appendix) to describe the endoscopic appearance of EE Patients with LA Grade A esophagitis should undergo further testing to confirm the presence of GERD Repeat endoscopy should be performed in patients with severe EE after a course of antisecretory therapy, to exclude underlying BE and assess healing
Strictures and Schatzki ring	Continuous PPI therapy is recommended following dilation of peptic stricture, to improve dysphagia and reduce the need for repeated dilations Injection of intralesional corticosteroids can be used in refractory, complex strictures due to GERD Treatment with a PPI is suggested following dilation in patients who have a lower esophageal (Schatzki) ring
BE	Use the Prague criteria to describe the extent of BE ^{71,72} Consider screening for BE in patients with GERD who are at high risk on the basis of their epidemiologic profile (in regions in which the prevalence of BE is high) Symptoms in patients with BE can be treated similarly to patients with GERD who do not have BE Patients in whom BE is found at endoscopy should undergo periodic surveillance in accordance with guideline recommendations

These recommendations are based on the 2013 American College of Gastroenterology (ACG) Guidelines for managing complications of GERD.⁵² The ACG guideline should be consulted for information about strength of evidence, evidence levels, and references. The Los Angeles classification is outlined in Table A1 in the Appendix (see the Los Angeles Classification of Erosive Esophagitis section).

BE indicates Barrett esophagus; EE, erosive esophagitis; GERD, gastroesophageal reflux disease; PPI, proton-pump inhibitor(s).

TABLE 7. Cascades: Options in the Management of GERD

Level of Resources	Management Strategies
Limited resources	Lifestyle modifications (diet, weight loss) to minimize symptoms Locally available symptomatic remedies if they are safe, effective, and less costly than prescription medications Most effective available acid-suppression therapy Step-up therapy—AA, H ₂ RA, PPI od, PPI bid—as available Stop therapy after 8 wk to assess response Resume therapy, as needed, at lowest effective dose Intermittent On demand Continuous therapy for patients with (a) frequent symptoms, (b) stricture, (c) BE (to control symptoms) Consider <i>Helicobacter pylori</i> “test-and-treat” for patients on continuous PPI therapy
Medium resources	PPI od for 8-12 wk, then reassess PPI bid for 8-12 wk for persistent symptoms Switch PPIs to a modified-release PPI (effect lasting > 14 h/d, MR-PPI) if available (od or bid) Stop therapy on symptom resolution to assess response Resume therapy, as needed, at lowest effective dose Intermittent On demand Lifestyle modifications (diet, weight loss) to minimize symptoms Continuous therapy for patients with (a) frequent symptoms, (b) stricture, (c) BE (to control symptoms) Consider <i>H. pylori</i> “test-and-treat” for patients on continuous PPI therapy Laparoscopic antireflux surgery for structural disease (hiatus hernia) or volume reflux causing regurgitation, aspiration, stricture, or persistent nocturnal symptoms despite PPI bid
High resources	MR-PPI od for 8 to 12 wk, then reassess MR-PPI bid for 8 to 12 wk for persistent symptoms More frequent PPI therapy if incomplete response symptomatically and on pH monitoring Stop therapy on symptom resolution to assess response Resume therapy, as needed, at lowest effective dose Intermittent On demand Lifestyle modifications (diet, weight loss) to minimize symptoms Continuous therapy for patients with (a) frequent symptoms, (b) stricture, (c) BE (to control symptoms) Consider <i>H. pylori</i> “test-and-treat” for patients on continuous PPI therapy Laparoscopic antireflux surgery for structural disease (hiatus hernia) or volume reflux causing regurgitation, aspiration, stricture, or persistent nocturnal symptoms despite PPI bid

AA indicates alginate-antacid; BE, Barrett esophagus; bid, bis in die (twice a day); GERD, gastroesophageal reflux disease; H₂RA, histamine H₂-receptor antagonist; MR-PPI, modified-release proton-pump inhibitor; od, omni die (daily); PPI, proton-pump inhibitor.

symptoms of GERD who are referred for surgery should undergo 24-hour pH monitoring to rule out functional heartburn.⁶⁹ They should also undergo esophageal manometry, a barium swallow, and EGD to rule out other possible diagnoses.

Many surgical endoscopic antireflux techniques have been developed, but few have survived, due to limited success.⁷⁰ There is still a lack of long-term outcome data for some procedures and new techniques, and these options should only be offered in the context of clinical trials.

Managing Complications of GERD

Although the prognosis for patients with GERD is good, with up to 90% achieving good symptom control with optimum treatment, complications may occur—including bleeding, BE, strictures, ulceration, and malignancy (Table 6).

Cascades for the Management of GERD

A thorough diagnostic evaluation of the patient's history and a physical examination (see the Diagnostic considerations and Patient history and physical examination sections), including when symptoms occur (during the day or night, and in relation to meals) and the response (none, partial, or complete) to antacids, H₂RAs, or PPIs, is critical for providing the right guidance in resource-poor areas, to avoid unnecessary diagnostic investigations.

The Cascade shown in Table 7 assumes that there are no alarm features and no alternative, non-GI causes of the symptoms, that *H. pylori* infection has been sought and eradicated if indicated, and that NSAID use has been excluded as a cause of symptoms.

APPENDIX

Abbreviations and Definitions (Table A1)

TABLE A1. List of Abbreviations (Acronyms) and Definitions

Abbreviation	Definition
ACG	American College of Gastroenterology
BE	Barrett esophagus
bid	bis in die (twice a day)
BMI	Body mass index
ECG	Electrocardiogram, electrocardiography
EE	Erosive esophagitis
EGD	Esophagogastroduodenoscopy (upper gastrointestinal endoscopy)
EoE	Eosinophilic esophagitis
ESEM	Endoscopic suspicion of esophageal metaplasia
FDA	Food and Drug Administration (United States)
GERD	Gastroesophageal reflux disease
GERS	Gastroesophageal reflux symptoms
GI	Gastrointestinal
H ₂ RA	Histamine H ₂ -receptor antagonist
LA	Los Angeles (classification)
MR-PPI	Modified release PPI (includes all delayed-release PPIs)
NERD	Nonerosive gastroesophageal reflux disease
NSAID	Nonsteroidal anti-inflammatory drug
od	omni die (daily)
OTC	Over the counter
PPI	Proton-pump inhibitor
PUD	Peptic ulcer disease
RDQ	Reflux disease questionnaire
UBT	Urea breath test
WDHD	World Digestive Health Day

Gold Standard Guidelines on GERD

- 2013 American College of Gastroenterology guidelines for diagnosis and management: Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol.* 2013;108:308–328; quiz 329. Doi: 10.1038/ajg.2012.444. National Guideline Clearinghouse NGC 009639.
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Los Angeles Classification of EE (Table A2)

TABLE A2. Los Angeles Classification of Erosive Esophagitis

Grade A	One or more mucosal breaks, no longer than 5 mm, none of which extends between the tops of the mucosal folds
Grade B	One or more mucosal breaks, more than 5 mm long, none of which extends between the tops of 2 mucosal folds
Grade C	Mucosal breaks that extend between the tops of 2 or more mucosal folds, but which involve < 75% of the esophageal circumference
Grade D	Mucosal breaks that involve at least 75% of the esophageal circumference

Prague Criteria for BE

The Prague criteria for BE provide a consensus-based endoscopic classification system that has undergone extensive internal and external validation by trained endoscopists. The criteria represent a simple system for assessing the extent of BE, based on the length of the distal esophagus involved circumferentially (C) and maximally (M) by Barrett epithelium relative to the gastroesophageal junction, characterized by the proximal ends of the gastric mucosal folds and/or the lower esophageal sphincter “pinch.” These criteria are identified and measured reliably by different endoscopists. The location of gastroesophageal landmarks is central to this classification and can also be reliably identified and located by different endoscopists. This standardized classification enhances the ability of physicians to gauge the efficacy of treatments for BE in individual patients and the classification of patients with BE in clinical trials.^{71,72}

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