VHA/DoD Clinical Practice Guideline for the Management of Adults with **Gastroesophageal Reflux Disease** in Primary Care Practice

Pharmacy Benefits Management
Strategic Healthcare Group
and Medical Advisory Panel
Veterans Health Administration
Department of Veterans Affairs

Pharmacoeconomic Center
Department of Defense

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EXECUTIVE SUMMARY

1. Gastroesophageal reflux disease (GERD) is a complex and common chronic gastrointestinal disorder. The majority of patients with GERD symptoms in community or general practice have a macroscopically normal endoscopic examination (nonerosive reflux disease, NERD), while less than half of patients with GERD symptoms are found to have erosive esophagitis. Complicated GERD includes Barrett's esophagus, esophageal strictures, hemorrhage, or perforation, and extraesophageal complications (such as aspiration, asthma, chronic coughing, chest pain, and laryngopharyngitis). The natural history of GERD is variable among patients; however, the disease course is chronic and non-progressive in most individuals.
2. Alarm symptoms are those that suggest cancer. Alarm symptoms include dysphagia, odynophagia, weight loss, hematemesis, black or bloody stools, chest pain, or choking (acid reflux causing coughing, hoarseness, or shortness of breath). Patients with alarm symptoms require immediate referral for further diagnostic testing.
3. The diagnosis of GERD is usually based on symptoms and associated risk factors. Heartburn, regurgitation, or both, which often occur after meals (particularly large or fatty meals) and that are present as the sole or predominant symptoms, are highly specific for GERD. Initiation of treatment can generally be based on the presence of typical reflux symptoms. Clinicians should be aware, however, that evidence for the positive predictive value of heartburn for diagnosing GERD is sub-optimal mainly because of the lack of a diagnostic gold standard. The presence of heartburn, acid regurgitation, and relief of heartburn with antacid or acid suppressive agents (a response that suggests an acid-peptic disorder) reinforces a diagnosis of GERD. It is important to remember that the intensity and frequency of reflux symptoms are poor predictors of the presence or severity of esophagitis.
4. The goals of treatment are to relieve symptoms, heal esophagitis if present, manage or prevent complications, and avoid progression and recurrence.
5. Empiric therapy for GERD is reasonable without diagnostic testing. Further diagnostic testing (including endoscopy, proton pump inhibitor [PPI] trial, ambulatory pH monitoring, or other tests) is recommended in patients who have an inadequate response to therapy, need continuous chronic therapy, have chronic symptoms (e.g., > 5 years) and are at risk for Barrett's esophagus, or have alarm symptoms (e.g., bleeding, chest pain, choking, dysphagia, or weight loss), or have complicated GERD. Repeated endoscopy is usually not indicated, as sustained symptom resolution reasonably reflects healing of esophagitis and is the accepted primary clinical end point.
6. If a patient has extraesophageal and esophageal symptoms of GERD, this guideline recommends starting standard-dose PPI and, if symptoms persist, referring the patient for further evaluation. The need for double-dose PPI may then be based on patient response to standard-dose PPI, confirmation of a presumptive diagnosis of extraesophageal GERD, and any diagnostic findings.
7. This guideline suggests that empiric initial treatment may consist of either a histamine H_2 receptor antagonist (H_2RA) or PPI based on the patient's response to any previous therapy with H_2RAs. Standard-dose PPIs are superior to standard-dose H_2RAs in terms of relieving heartburn and healing esophagitis; however, there is a lack of evidence and consensus to support using one treatment *approach* (step-up, step-down, or no-step therapy) over the others. Expert opinion supports either step-up therapy (H_2RAs first) or step-down therapy (PPIs first) for initial therapy of patients with GERD. Arguments can be made for either treatment approach. There is also a lack of evidence to support the practice of stratifying empiric initial therapy based on intensity or frequency of symptoms.
8. In patients who incompletely respond to a trial of either nonprescription or prescription H_2RA, PPIs are preferred over continuing H_2RA therapy because of their greater efficacy and faster symptom

control, and the limited additional benefit gained from extending therapy with the same or higher dose of H_2RA.

9. An inadequate response to a 4- to 8-week course of standard-dose PPI may indicate longer treatment is needed, more severe disease, or incorrect diagnosis. Patients who have an inadequate response to standard-dose PPI should be referred for further diagnostic testing. Additional benefit may be obtained by extending treatment for another 4 to 8 weeks with either the same or double doses of a PPI.
10. This guideline suggests two possible pharmacologic options for maintenance therapy: (1) step-down management with attempted discontinuation of therapy (preferred); or (2) no-step management; i.e., continuation of the current medication regimen. The decision to undergo a trial of step-down management and discontinuation of therapy should be individualized. The choice of approach should take into consideration such factors as the patient's clinical status, the presence or likelihood of complications, the patient's previous response to treatment, the likelihood of follow-up (to monitor patients after therapy is stepped down or discontinued), and overall costs. Since a substantial proportion of patients may remain in prolonged remission without maintenance therapy, and patients who relapse regain symptom control after reinstitution of therapy, an attempt to discontinue therapy is considered to be a reasonable option in most patients. Patients who require continuous, long-term maintenance therapy should be referred for further diagnostic testing.
11. Two methods of stepping down therapy may be used in patients who have achieved symptomatic remission: (1) attempt treatment discontinuation first; or (2) attempt treatment discontinuation after step-wise reduction in treatment intensity. There is no standardized method for stepping down therapy, and no consensus on the optimal duration of initial therapy before attempting to step down therapy once symptoms are controlled. This guideline suggests reinstituting treatment upon relapse to provide symptomatic therapy while the patient is awaiting further evaluation. If patients relapse within 2 weeks of discontinuing or stepping down therapy, this guideline suggests restarting the initial drug regimen that was effective. For relapses occurring after the first 2 weeks, this guideline suggests stepping up drug therapy. Referral for further diagnostic testing should be considered for all patients who relapse or require continuous, long-term maintenance therapy.
12. Other pharmacologic options include antacids, nonprescription H_2RAs, and prokinetics. Antacids with or without alginic acid may be useful as rapid-acting, on-demand treatment of heartburn. The on-demand, short-term use of nonprescription H_2RAs, taken in doses generally one half of standard doses, may be useful in controlling heartburn and preventing reflux symptoms provoked by certain foods or drinks, but are ineffective as maintenance therapy of GERD. Metoclopramide is generally of limited usefulness in the management of GERD.
13. Surgical intervention may be an alternative to medical maintenance therapy in a minority of patients and is based on individual patient considerations and preferences. A specialist should be consulted to help determine the appropriateness of antireflux surgery versus pharmacologic therapy. Many surgically treated patients still use regular antireflux medication. Antireflux surgery should not be advised with the expectation that antisecretory therapy will no longer be needed or that it is a cancer-preventing procedure.
14. Most nonpharmacologic measures are not considered to be generally recommendable as sole therapy of GERD; but certain dietary or lifestyle modifications may be helpful as adjunctive therapy in individual patients. Nonpharmacologic measures (and antacids) are considered to be of minimal benefit or not sufficiently effective to justify their use as sole initial or long-term therapy of GERD; however, evidence is lacking in this area. Dietary or lifestyle modification should be considered an adjunctive measure and not a distinct step in the treatment of GERD. Practitioners should consider the potential for positive and negative consequences of dietary and lifestyle modifications on the patient's quality of life, and the possibility that any beneficial effects may be small compared with the acid suppressive effects of PPIs and H_2RAs.

PHARMACY BENEFITS MANAGEMENT STRATEGIC HEALTHCARE GROUP

VHA's Pharmacy Benefits Management Strategic Healthcare Group (PBM SHG or "PBM") has been directed by the Under Secretary for Health to coordinate the development of guidelines for the pharmacologic management of common diseases treated within the VA, establish a national VA formulary, manage pharmaceutical costs and utilization, and measure outcomes as they apply to patient care. The MAP provides support and direction to the PBM staff, located in Washington, DC and Hines, Illinois.

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MISSION

The mission of the Pharmacoeconomic Center (PEC) is to improve the clinical, economic, and humanistic outcomes of drug therapy in support of the readiness and managed care missions of the Military Health System.

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ACKNOWLEDGMENTS

This guideline was developed in consultation with members of the PBM-MAP, members of the PEC, and specialists in Gastroenterology. The VA/DoD Guideline Steering Committee and Office of Quality and Performance will be considering adoption of this guideline for a joint VA/DoD guideline on the management of GERD. This guideline was prepared by Francine Goodman, PharmD, BCPS, VA PBM, Hines, Illinois; Kevin Roberts, PharmD, Clinical Coordinator, Dallas VA Medical Center; and Angela Allerman, PharmD, BCPS, DoD PEC.

The following clinicians provided comments on drafts of this report. The list does not include all clinicians who reviewed this guideline, only those who agreed to be acknowledged. The final document incorporates reviewers' comments; however, the PBM–MAP and PEC take full responsibility for the content of this guideline.

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ABBREVIATIONS

ASGE	American Society for Gastrointestinal Endoscopy
CIS	cisapride
CTD	cimetidine
CYP	cytochrome protein; specifically, cytochrome P450
EGD	esophagogastroduodenoscopy
ESO	esomeprazole
FDA	Food and Drug Administration
FSS	Federal Supply Schedule
GER	gastroesophageal reflux
GERD	gastroesophageal reflux disease
GI	gastrointestinal
Hp(+)	*Helicobacter pylori*-positive
H_2RA	histamine H_2 receptor antagonist
ITT	intent-to-treat
LAN	lansoprazole
LNF	laparoscopic Nissen fundoplication
MAP	Medical Advisory Panel
MUSE	Metaplasia-Ulceration-Stricture-Erosion (classification system of esophageal lesions)
NERD	nonerosive reflux disease
NR	not reported
NSD	no (statistically) significant difference
OME	omeprazole
ONF	open Nissen fundoplication
OQ	overall quality (of evidence)
PAN	pantoprazole
PBM	Pharmacy Benefits Management
PMC	Pantoprazole-Metronidazole-Clarithromycin combination therapy
QE	quality of evidence
PEC	Pharmacoeconomic Center
PLAC	placebo
PPCACG	Practice Parameters Committee of the American College of Gastroenterology
PPI	proton pump inhibitor
RAB	rabeprazole
RTD	ranitidine
SHG	Strategic Healthcare Group
SLS	simplified lansoprazole suspension
SOS	simplified omeprazole suspension
SR	strength of recommendation
VISN	Veterans Integrated Service Network

DEFINITIONS

Gastroesophageal reflux disease (GERD) can be defined as chronic symptoms or mucosal damage secondary to abnormal reflux of gastric contents into the esophagus.[1] According to Dent, *et al.*, the term GERD should be used to include all individuals who are exposed to the risk of physical complications from gastroesophageal reflux, or who experience clinically significant impairment of health related well being (quality of life) due to reflux related symptoms, after adequate reassurance of the benign nature of their symptoms.[2]

Alarm symptoms are those that suggest cancer. Alarm symptoms include dysphagia, odynophagia, weight loss, hematemesis, black or bloody stools, chest pain, or choking (acid reflux causing coughing, hoarseness, or shortness of breath).

Barrett's epithelium refers to the replacement of squamous epithelium with metaplastic columnar epithelium. Barrett's esophagus may occur in 10% of patients with GERD and is associated with an increased risk of adenocarcinoma.

Complicated GERD includes Barrett's esophagus, erosive esophagitis, esophageal strictures, hemorrhage, perforation, and extraesophageal complications such as aspiration, asthma, chronic coughing, chest pain, and laryngopharyngitis.

Extraesophageal GERD is the reflux of gastric contents affecting tissue other than the esophagus.

Nonerosive reflux disease (NERD) or endoscopy negative reflux disease refers to the presence of typical GERD-related symptoms caused by intraesophageal acid without endoscopic evidence of Barrett's esophagus or definite esophageal mucosal breaks (esophageal mucosal erosion or ulceration).[2,3]

Reflux esophagitis is inflammation of the esophageal mucosa resulting from exposure to gastric contents.

INTRODUCTION

THE MANAGEMENT OF ADULTS WITH GASTROESOPHAGEAL REFLUX DISEASE IN PRIMARY CARE PRACTICE

GERD is a complex and common chronic gastrointestinal disorder. It has been estimated that heartburn, a typical symptom of GERD, is experienced by about 10% of American adults daily, about 20% weekly, and about 40% at least monthly.[4-6] The annual incidence of GERD has been estimated to be 6%.[7] The true prevalence and incidence of GERD, however, are uncertain.[7]

While the risk of GERD-related death is low, GERD can have a great impact on a patient's day-to-day functional ability. Untreated GERD has been associated with a greater impairment in health-related quality of life than duodenal ulcers, angina pectoris, congestive heart failure, menopause, diabetes mellitus, and hypertension.[8-10]

The economic burden associated with GERD is substantial in the U.S. Almost $2 billion per year are spent on over-the-counter antacids and histamine-2 receptor antagonists (H_2RAs), and about $6 billion per year are spent on prescription H_2RAs and proton pump inhibitors (PPIs).[11] In the VA and DoD, pharmacy prime vendor purchases for antacids, H_2RAs, and PPIs during 2001 exceeded $134 million.

The alleviation of pain, healing of injured esophageal mucosa (if present), prevention of progression and complications of GERD, the prevention of disease recurrence, and restoration of a patient's normal quality of life are important goals for providers who care for patients with GERD. The typical chronic relapsing-remitting nature of GERD means that providers must plan and implement long-term management for many patients.

Since primary care practitioners have assumed a greater share of responsibility in the medical management of patients with GERD, this guideline is targeted to the needs of primary care practitioners but is directed to providers at all levels. Many advances are being made in the pharmacologic and surgical treatment of GERD. Still, there are many controversies about the best management approach, particularly for uninvestigated GERD. Rather than propose a single approach, this guideline presents options for the initial and long-term management of GERD from a primary care perspective. It is intended to serve as a tool to aid primary care practitioners in making informed decisions about the diagnosis and pharmacologic treatment of GERD.

Goals of the Guideline

The goal of evidence-based guidelines in the Veterans Health Administration (VHA) and the Department of Defense (DoD) health care systems is to improve patient outcome. The desired outcomes of successful implementation of this guideline are to reverse impairment in the patient's health-related quality of life and prevent GERD-associated morbidity and mortality. To achieve these goals, this guideline addresses the following key points:

- Identify and refer patients who require further evaluation or may need long-term follow-up by an appropriate specialist.
- Develop a plan for empiric initial therapy to relieve symptoms and promote esophageal healing.
- Optimize drug therapy to control symptoms if initial therapy did not provide adequate symptomatic relief.
- Develop a plan for maintenance drug therapy to prevent relapse and keep symptoms under control.
- Minimize complications due to GERD.

This guideline is not intended to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technologic advances and patterns evolve. The ultimate judgment regarding a particular clinical procedure

or treatment course must be made by the individual provider in light of the patient's clinical presentation, patient preferences, and the available diagnostic and treatment options. This guideline can assist providers in the care of an individual patient, but the use of a clinical practice guideline must always be considered as a recommendation within the context of a provider's clinical judgment.

Guideline Development Process

Whenever possible, the PBM–MAP and PEC rely upon evidence-based, multidisciplinary, nationally recognized consensus statements for the basis of clinical practice guidelines. Relevant literature was reviewed and assessed with consideration given to the VA and DoD populations. Drafts of the full guideline or only the treatment algorithm were sent to DoD and VA gastroenterologists and members of the PBM and PEC for comment and to identify pivotal decision points in treatment pathways. Prior to being finalized, the guideline was made available on the Web through the Office of Quality and Performance to obtain comments from the field.

The original guidelines that were merged in the creation of this document were (1) *The Pharmacologic Management of Gastroesophageal Reflux Disease* (PBM-MAP Publication No. 98-0010, dated September 1998, last updated March 2000) and (2) a draft update (last modified 20 January 2001) of *Improving the Clinical and Economic Outcomes of Gastroesophageal Reflux Disease (GERD)* (PEC Update, Vol. 98, Issue 4).

Updates of the present guideline relied primarily on two evidence-based publications on the diagnosis and management of GERD, one developed by the American College of Gastroenterology[12] and revised in June 1999,[1] and the other prepared by an international panel of experts participating in the Genval Workshop[2] and updated (with focus on primary care practice) in 2001.[13]

Sources of Evidence

Literature searches were performed to obtain updated, general information on the management of GERD and to obtain problem-directed evidence to support decision points and treatment pathways. Electronic searches were performed on all Evidence Based Medicine reviews available on OVID (included the Cochrane Database of Systematic Reviews, ACP Journal Club, Database of Abstracts of Reviews of Effectiveness, and Cochrane Controlled Trials Register) and the National Library of Medicine's (NLM's) MEDLINE/PubMed database (1966 to May 2002). Preference was given to meta-analyses, systematic reviews, and randomized controlled trials. The Clinical Queries service of PubMed was used for focused searches for well-designed (e.g., double-blind or placebo-controlled) trials on therapy, diagnosis, or prognosis, usually with emphasis on specificity of searches. Relevant articles were also obtained from reference lists of retrieved articles.

In an attempt to find other up-to-date evidence-based clinical practice guidelines on medical management of GERD, the Web sites of the Agency for Healthcare Research and Quality (http://www.ahcpr.gov), the National Guideline Clearinghouse (http://www.guidelines.gov), and the National Institute for Clinical Excellence (http://www.nice.org.uk) were searched using American or British spellings of the term *gastroesophageal reflux*. A search was also performed via the Centre for Evidence-Based Medicine, University Health Network, Mount Sinai Hospital Web site (http://www.cebm.utoronto.ca/index.htm) and the Evidence Based Medical Practice Directory of the Family Medicine Department at Laval University (http://www.medecine.quebec.qc.ca). Guidelines for dyspepsia were not considered to be specifically applicable to GERD, although there is some overlap between the two conditions.

The main terms and limits applied in the literature searches are provided in Appendix 1. A complete list of references used in the development of the treatment algorithm, annotations, supplements, and appendix tables starts on page 47.

Rating the Evidence

Articles supporting diagnostic or therapeutic interventions were reviewed for relevance and graded according to a rating scheme based on the methods of the third U.S. Preventive Service Task Force.[14] Ratings were based on the quality of evidence (QE), overall quality (OQ), net effect of the intervention, and grade of the strength of recommendation (SR) (see Table 1 to Table 4. The SR depends on the OQ of evidence and on the magnitude of net benefit.

Table 1 Quality of Evidence (QE) Rating Scale

I	Evidence obtained from at least one properly randomized controlled trial.
II-1	Evidence obtained from well-designed controlled trials without randomization.
II-2	Evidence obtained from well-designed cohort or case-controlled analytic studies, preferably from more than one center or research group.
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments could also be regarded as this type of evidence.
III	Opinion of respected authorities, based on clinical experience, descriptive studies and case reports, or reports of expert committees

Table 2 Overall Quality (OQ)

I	Good	High-grade evidence (I or II-1) directly linked to health outcome
II	Fair	High-grade evidence (I or II-1) linked to intermediate outcome OR Moderate-grade evidence (II-2 or II-3) directly linked to health outcome
III	Poor	Level III evidence or no linkage of evidence to health outcome
IV	—	Insufficient evidence

Table 3 Net Effect of the Intervention

Substantial	More than a small relative impact on a frequent condition with a substantial burden of suffering OR A large impact on an infrequent condition with a significant impact on the individual patient level
Moderate	A small relative impact on a frequent condition with a substantial burden of suffering OR A moderate impact on an infrequent condition with a significant impact on the individual patient level
Small	A negligible relative impact on a frequent condition with a substantial burden of suffering OR A small impact on an infrequent condition with a significant impact on the individual patient level
Zero or Negative	Negative impact on patients OR No relative impact on either a frequent condition with a substantial burden of suffering OR An infrequent condition with a significant impact on the individual patient level

Table 4 Grade for Strength of Recommendation (SR)

Overall Quality of Evidence	Net benefit of intervention			
	Substantial	Moderate	Small	Zero or Negative
I	A	B	C	D
II	B	B	C	D
III	C	C	C	D
IV	I	I	I	D

Key:

A A strong recommendation that the intervention is always indicated and acceptable
B A recommendation that the intervention may be useful/effective
C A recommendation that the intervention may be considered
D A recommendation that a procedure may be considered not useful/effective, or may be harmful
I Insufficient evidence to recommend for or against—the clinician will use their clinical judgment

Content of the Guideline

This guideline consists of the following five sections:

1. Introduction
2. Treatment Algorithms and Annotations
   - Algorithm 1: Initial Therapy
   - Algorithm 2: Maintenance Therapy
3. Supplements
   - Diagnostic Tests
   - Pharmacotherapeutic Agents
   - Costs of Antireflux Agents
   - Surgical Interventions
4. References
5. Appendices

This guideline uses an algorithmic method to depict the clinical logic behind treatment pathways. Annotations explain the underlying rationale and provide evidence tables. The supplements provide additional details on diagnostic tests and pharmacotherapeutic information on individual antireflux agents. All references used throughout this guideline are listed after the supplements. A list of main search terms and reference tables summarizing studies on maintenance therapy are provided in the appendices.

This guideline focuses on patients with uninvestigated GERD. It does not specifically address the management of Barrett's esophagus, NERD, reflux esophagitis, complicated GERD, and extraesophageal GERD, as patients with diagnoses of these conditions should be evaluated by an appropriate specialist and should be treated in consultation with the specialist. Also, the management of dyspepsia is excluded from this guideline because it is managed using other treatment pathways.

Important Changes to the Guideline Since the Last Update

To focus on primary care practice, one of the major changes made to this guideline was a redirection from mainly using evidence derived from a subset of patients with reflux esophagitis, in whom endoscopic response was emphasized, to preferring evidence applicable to a mixed population of patients with

different types of GERD, particularly patients with uninvestigated GERD, in whom symptomatic response has become more clinically relevant.

Studies that evaluated mixed populations may have performed endoscopy as part of the protocol, but endoscopic findings were not used to allocate treatment. Most of these studies excluded patients with severe or ulcerative esophagitis, esophageal stricture, Barrett's esophagus, or peptic ulcer disease. Of 10 efficacy studies that included patients with NERD and non-ulcerative or ulcerative reflux esophagitis,[15-24] 5 evaluated initial therapy and reported the proportion of enrolled patients who were excluded.[15-19] The proportion of patients excluded from these trials ranged from 3% to 12%. Since the excluded conditions are expected to occur in a minority of patients in general practice, and the proportions of patients excluded from the studies tend to support this assumption, the patients included in these studies may approximate patients seen in primary care.

Since the last updates to the guidelines by the PBM-MAP (March 2000) and the PEC (draft update, January 2001), much information has been learned about the epidemiology of GERD and effective therapeutic strategies. Major changes to the previous guidelines include the following:

- NERD has become recognized as a distinct type of GERD.
- Lifestyle modifications are no longer considered to be primary treatment, but are instead adjunctive measures in the overall treatment strategy of GERD.
- The choices of H_2RAs and PPIs have expanded with the Food and Drug Administration (FDA) approval of a number of new agents, while the choices of prokinetic agents have been reduced by the implementation of a limited access program for cisapride.
- Doubling the dose of H_2RAs has been demonstrated to produce marginal benefits.
- Recent federal contracting initiatives have resulted in reductions in the drug acquisition costs of rabeprazole and lansoprazole, making these agents more cost-effective in the treatment of severe GERD.

Another major part of updating this guideline consisted of completely reformatting the text to make it more consistent with recommendations on clinical algorithm development proposed by the Society for Medical Decision Making and the Agency for Healthcare Research and Quality (formerly, Agency for Health Care Policy and Research).[25,26]

Referencing the Guidelines

This guideline should be referenced as follows:

> *VHA/DoD Clinical Practice Guideline for the Management of Adults with Gastroesophageal Reflux Disease in Primary Care Practice*. Washington, DC: Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel, Veterans Health Administration, Department of Veterans Affairs, and the Pharmacoeconomic Center, Department of Defense. March 12, 2003. PBM-MAP Publication No. 03-0016.

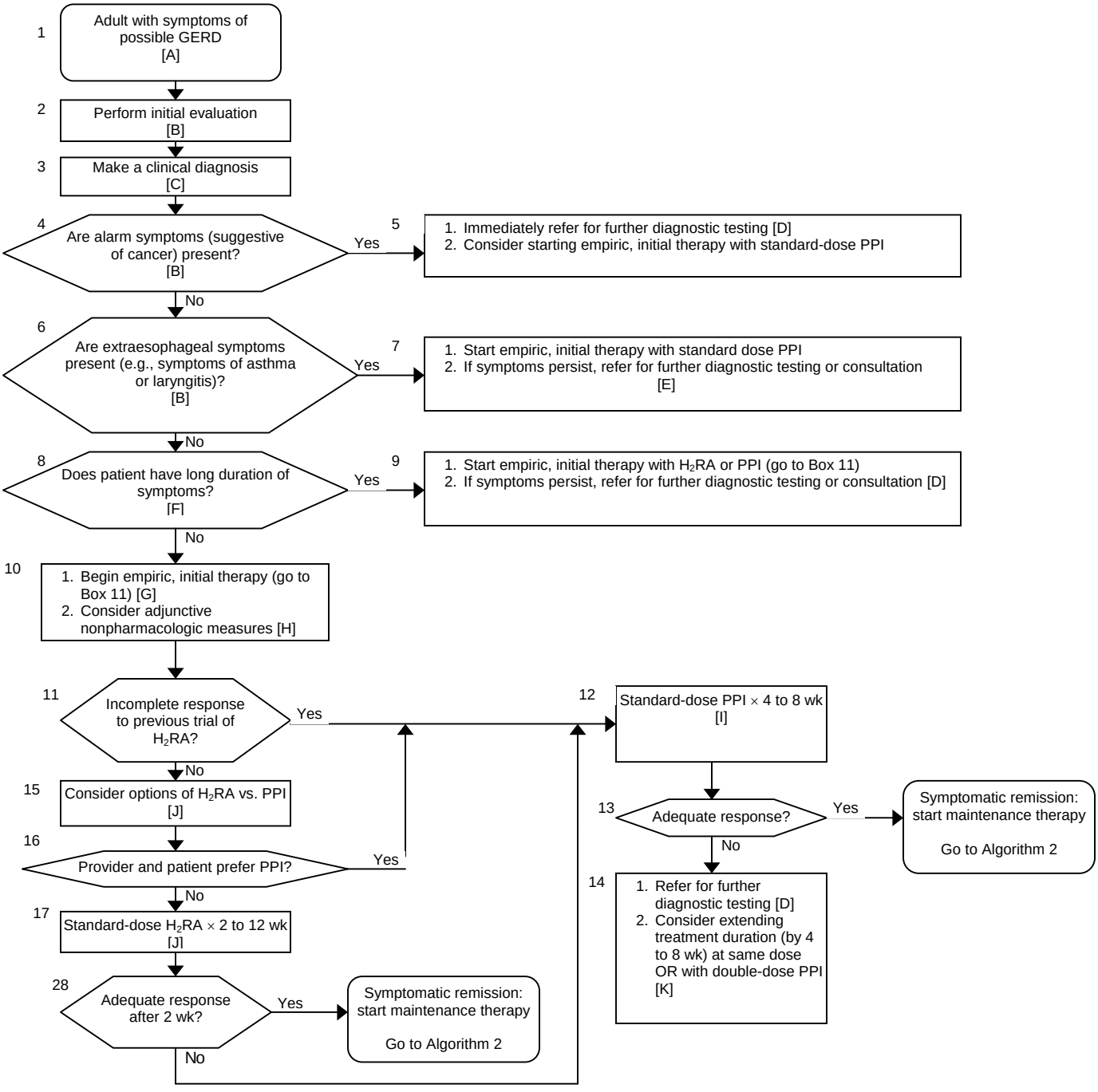
Updating the Guidelines

The PBM–MAP and PEC will review this guideline routinely. Updating will occur as new information is made available from well-designed, scientifically valid studies, and as outcome data may direct.

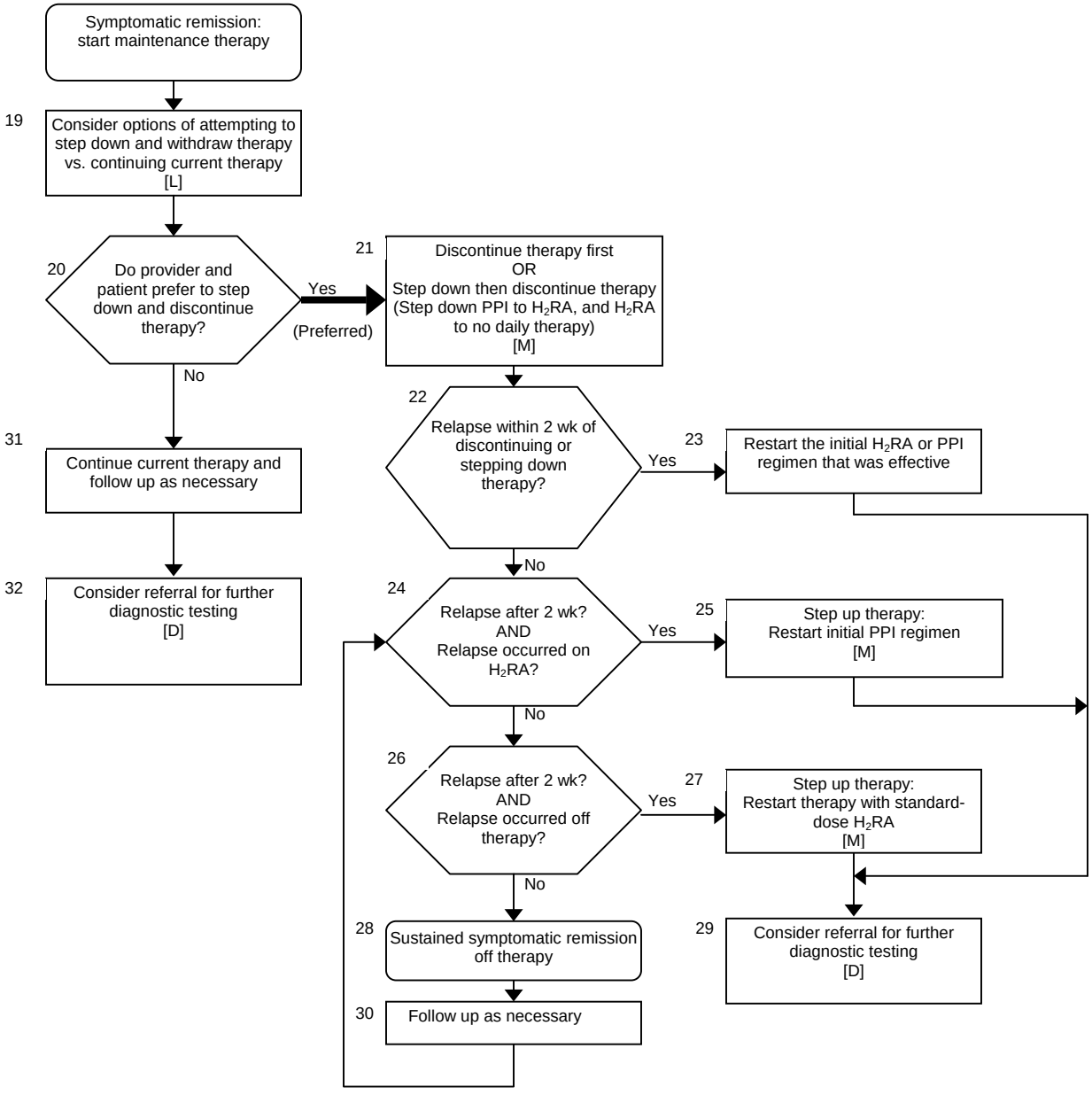
A current copy of the clinical practice guideline can be obtained from the Office of Quality and Performance home page at http://www.oqp.med.va.gov; the PBM home page at http://www.vapbm.org; or the PEC home page at http://www.pec.ha.osd.mil.

TREATMENT ALGORITHMS AND ANNOTATIONS

Algorithm 1 VHA/DoD Clinical Practice Guideline for the Management of Adults with Gastroesophageal Reflux Disease in Primary Care Practice: INITIAL THERAPY (GERD Final.doc)



Algorithm 2 **VHA/DoD Clinical Practice Guideline for the Management of Adults with Gastroesophageal Reflux Disease in Primary Care Practice: MAINTENANCE THERAPY (GERD Final.doc)**



VHA/DOD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF ADULTS WITH GASTROESOPHAGEAL REFLUX DISEASE IN PRIMARY CARE PRACTICE

ANNOTATIONS

A. Adult with symptoms of gastroesophageal reflux disease

OBJECTIVES

- To define gastroesophageal reflux disease (GERD)
- To list the causal mechanisms of gastroesophageal reflux (GER)
- To provide epidemiologic and other background information on GERD

ANNOTATION

Definition of GERD

There is a lack of consensus on the definition of GERD at least partly because there is no diagnostic gold standard and there is disagreement about how to determine when occasional heartburn becomes the disease due to GER. GERD can be defined as chronic symptoms or mucosal damage secondary to abnormal reflux of gastric contents into the esophagus.[1] According to Dent, *et al.*, the term GERD should be used to include all individuals who are exposed to the risk of physical complications from gastroesophageal reflux, or who experience clinically significant impairment of health related well being (quality of life) due to reflux related symptoms.[13]

Causal mechanisms of GER

- Transient relaxation of the lower esophageal sphincter
- Increased intra-abdominal pressure that overpowers a decrease in lower esophageal sphincter tone
- Impaired esophageal or gastric motility

In the majority of patients, GERD-related symptoms are caused by the abnormally prolonged exposure of the esophageal mucosa to acid and pepsin. In a minority of patients, normal levels of esophageal acid exposure may produce reflux symptoms.

Epidemiology

Possible complications of GERD and their respective prevalence or incidence rates are shown in Table 5.

Table 5 Rate of complications from GERD

Complication	Rate of occurrence
Barrett's esophagus	10% to 15%
Esophageal stricture	4% to 20%
Esophageal ulceration	2% to 7%
Esophageal hemorrhage	< 2%
Esophageal perforation	< 0.2%
Esophageal adenocarcinoma	
With Barrett's esophagus	0.5% / y
Without Barrett's esophagus	0.07% / y

Sources: Spechler (1992), Spechler (2001), Shaheen (2000), Provenzale (1999)[27-30]

The majority (up to 50% to 70%) of patients with frequent GERD symptoms in community or general practice have a macroscopically normal endoscopic examination (nonerosive reflux disease, NERD).[22,31,32] NERD may not simply be a mild form of GERD, but may represent a distinct and

heterogeneous subset of GERD in which increased esophageal sensitivity to acid may play a more prominent role in symptom production.[2,3]

Up to one half (about 30% to 50%) of patients with GERD symptoms in community or general practice are found to have reflux esophagitis,[22,31-33] and the majority (66%) of those with esophagitis have mild erosive changes.[32]

The more severe forms of GERD—erosive esophagitis, ulcerative esophagitis, stricture, and Barrett's esophagus—are more common in older Caucasian males.[34] Barrett's esophagus may occur in patients with NERD or erosive esophagitis. In a community practice study, 11 (6%) of 178 screened or evaluated patients with frequent, chronic heartburn were found to have Barrett's esophagus.[32]

The natural history of GERD is variable among patients; however, the disease course is chronic and non-progressive in most individuals. At the same time that pathologic reflux persists, symptoms tend to decline over the long term (17 to 22 years).[35]

Recent evidence suggests that NERD and esophagitis follow their own disease course with little crossover, and there appears to be little temporal progression of disease severity, with the maximal severity of each type of GERD occurring at the time of diagnosis.[2,34,36,37] Patients who have Barrett's esophagus with high-grade dysplasia also tend to have a relatively stable course.[38]

GERD and Barrett's esophagus are strongly associated with esophageal adenocarcinoma.[39-41] Estimates of the risk of esophageal adenocarcinoma among patients with Barrett's esophagus vary widely, from 0.2% to 4% per year.[28-30] The calculated risk, however, may overestimate the true incidence in the general population because of publication bias, and 0.5% per year may be a more reasonable estimate.[29] In U.S. veterans, the risk of adenocarcinoma among patients with Barrett's esophagus was found to be 0.4% per year.[28] The incidence of adenocarcinoma was 2.3% per year among patients with high-grade dysplasia and no cancer after 1 year of intensive endoscopic surveillance, and only 0.3% per year among the entire Barrett's population with no cancer after 1 year of intensive endoscopic surveillance.[38]

The rate of reflux esophagitis-related deaths has been increasing (from 1.0 per million living population during 1968 to 1972 to 2.1 per million during 1988 to 1992),[42] but even in an older population of U.S. veterans with severe GERD it seems to be low (4% over a mean of 10 years).[28] The rate of deaths associated with esophageal cancer in patients with Barrett's esophagus not undergoing surveillance has also been reported to be relatively low (1.3% over a mean of 9 years),[43] and available evidence suggests that Barrett's esophagus does not shorten survival.[38,44,45] In contrast, the prognosis for esophageal adenocarcinoma is poor with an estimated five-year survival of 17%.

While GERD has a minimal effect on survival, it can have a great impact on a patient's day-to-day functional ability. Untreated GERD has been associated with a greater impairment in health-related quality of life than duodenal ulcers, angina pectoris, congestive heart failure, menopause, diabetes mellitus, and hypertension.[8-10]

B. Perform initial evaluation

OBJECTIVES

To discuss the initial evaluation of a patient with GERD symptoms

ANNOTATION

History

A detailed history should be obtained from all patients regarding

- symptom description,
- exacerbating factors,
- measures taken to relieve symptoms, and
- response to previous treatments.

Symptom description

The classic or typical symptoms of GERD are those of heartburn and/or acid regurgitation (Table 6).

Table 6 Signs and Symptoms of GERD and Potential Complications

Common symptoms	Heartburn Regurgitation Dysphagia (difficulty swallowing)
Unusual symptoms	Hypersalivation (waterbrash) Nausea Odynophagia (painful swallowing)
Extraesophageal manifestations	Asthma Chest pain, noncardiac Chronic cough Dental disease Globus sensation Hoarseness Laryngitis Respiratory symptoms
Signs and symptoms of potential complications	Abdominal mass Anemia Hemorrhage Weight loss
Alarm symptoms (suggestive of cancer)	Dysphagia Odynophagia Weight loss Hematemesis Black or bloody stools Chest pain Choking

A predominance of heartburn, regurgitation, or both, which often occur after meals (particularly large or fatty meals) are highly specific for GERD.

Typically, symptoms are characterized by a hot or burning sensation located in the retrosternal region (pyrosis, heartburn), often related to body position and sometimes associated with regurgitation or hypersalivation (water brash). It may be relieved by antacids and has an upward moving quality. Heartburn should be distinguished from dyspepsia, which is characterized by postprandial distress in the abdomen, not the chest.

Less frequently, patients may have extraesophageal GERD with chest pain, hoarseness, asthma, or cough. Of note is that some patients with GERD may present with minimal or no symptoms.

Clinicians should be aware that the word “heartburn” might be misinterpreted by patients, partly due to cultural variations in the interpretation and translation of the word. Using the description “a burning

feeling rising from the stomach or lower chest up towards the neck" may be more useful in identifying patients with heartburn than using the word itself.[46]

Complicated GERD includes Barrett's esophagus, esophageal strictures, hemorrhage, or perforation, and ***extraesophageal complications*** such as aspiration, asthma, chronic coughing, chest pain, and laryngopharyngitis.

Alarm symptoms are those that suggest cancer. Alarm symptoms include dysphagia, odynophagia, weight loss, hematemesis, black or bloody stools, chest pain, or choking (acid reflux causing coughing, hoarseness, or shortness of breath). Patients with alarm symptoms require immediate referral for further diagnostic testing.[1,2]

Dysphagia, odynophagia, and weight loss suggest malignancy, ulceration, or stricture. Black or red stools suggest erosive esophagitis or ulceration; cancer is also in the differential but is less common. Choking, coughing, hoarseness, or asthma suggests aspiration of acid.

Exacerbating factors

Reflux symptoms most often occur after meals, while a small proportion of patients experience nocturnal reflux symptoms. Although dietary and lifestyle factors have been implicated in the pathogenesis of GERD, evidence of their role has been poorly documented.[47] In some individuals, however, ingestion of certain foods and specific lifestyle factors may precipitate or worsen symptoms of GERD. (Also see Annotation H, page 19.) Factors that may exacerbate or contribute to symptoms include the following:

- gastric distension (e.g., voluminous meals)
- supine position, particularly the right lateral decubitus position
- bending over
- certain foods or beverages (e.g., alcohol, caffeinated beverages, carbonated beverages, peppermint/spearmint, chocolate, citrus, high-fat foods, milk, onions, garlic, spicy foods, tomato juices)
- excessive physical activity (e.g., running)

Risk factors associated with GERD include the following:[48-50]

- psychological stress
- psychiatric disease
- alcohol
- smoking
- obesity (body mass index > 30 kg/m^2)
- an immediate family history of heartburn or gastroesophageal disease
- use of nonsteroidal anti-inflammatory drugs

A medication history should be obtained to identify agents that may contribute to symptoms of GERD (Table 7).

Table 7 Medications Contributing to Symptoms of GERD

Mechanism	Medications		
Decrease lower esophageal sphincter pressure	α-Adrenergic antagonists Anticholinergic agents (or medications with significant anticholinergic effects)	β_2-adrenergic agonists Calcium channel blockers Diazepam Dopamine Estrogen	Misoprostol Nitrates Progesterone Theophylline
Direct injury of esophageal mucosa	Alendronate Aspirin Chloral hydrate Iron	Nonsteroidal anti-inflammatory agents Potassium supplements (slow-release)	Quinidine Tetracyclines

Factors possibly protective against GERD include chronic gastritis[34,51] and *Helicobacter pylori* infection.[42,52-54]

Measures taken to relieve symptoms

Many patients who present with GERD have mild or infrequent symptoms and do not seek medical intervention unless they have failed a trial of nonprescription drug therapy, such as antacids or half-dose H_2RAs, or have not obtained adequate relief after discontinuing foods, beverages, or medications that exacerbate their symptoms.

Response to previous treatments

A history of partial or complete relief of reflux symptoms with antacids or half-dose H_2RAs suggests an acid-peptic disorder, and may be helpful in making a clinical diagnosis.

Physical Exam

The provider should search for any signs of extraesophageal disease, complications of advanced disease, or diseases that may present with GERD symptoms (e.g., gastric or esophageal carcinoma).

Laboratory Tests

No routine laboratory tests are required. However, hemoglobin and hematocrit would be helpful to detect anemia, particularly in patients with hematemesis, other signs of gastrointestinal bleeding, or severe, unremitting symptoms. Further diagnostic work-up is warranted in patients presenting with atypical symptoms or when manifestations of more severe or complicated disease are apparent.

Routine testing for *H. pylori* (with subsequent eradication of the organism if present) is of little benefit in patients with GERD.

C. Make a clinical diagnosis

OBJECTIVE

To discuss the clinical diagnosis of GERD

ANNOTATION

Base diagnosis on symptoms and response to previous antireflux therapy

There is no gold standard for the diagnosis of GERD, and no standardized, symptom-based, diagnostic algorithm for making a diagnosis of GERD.

Since there is a lack of physical, physiologic, or biochemical markers for GERD, the diagnosis of GERD is usually based on symptoms and associated risk factors, although many symptoms of GERD are nonspecific.

Heartburn, regurgitation, or both, which often occur after meals (particularly large or fatty meals) and that are present as the sole or predominant symptoms, are highly specific for GERD. However, the predictive value of reflux symptoms depends on the reference standard. When acid reflux on ambulatory 24-hour pH monitoring is used as the diagnostic standard, the typical symptoms (heartburn and acid regurgitation), when present as the predominant or sole symptoms, have been found to have relatively high positive predictive value (59% to 75%).[55,56] When endoscopy is used as the standard, the same symptoms have been shown to have low positive predictive value (37%) and high negative predictive value (90%).[51]

The results of these studies suggest that initiation of treatment can generally be based on the presence of typical reflux symptoms. Clinicians should be aware, however, that evidence for the positive predictive value of heartburn for diagnosing GERD is sub-optimal mainly because of the lack of a diagnostic gold standard.[2]

The presence of heartburn, acid regurgitation, and relief of heartburn with antacid or acid suppressive agents (a response that suggests an acid-peptic disorder) reinforces a diagnosis of GERD.[1]

It is important to remember that the intensity and frequency of reflux symptoms are poor predictors of the presence or severity of esophagitis.[21,22,57] GERD may be present without the concomitant findings of mucosal breaks (erosions) in the esophagus (NERD), just as tissue damage may be identified in the absence of typical symptoms of heartburn or regurgitation.[58]

Conditions to exclude (not covered by these guidelines)

There can be considerable overlap in symptoms between functional dyspepsia and GERD, particularly NERD, depending on the definitions used for either disorder. Dent, et al. recommend that patients with heartburn should be distinguished from those with dyspepsia as defined by the Rome criteria, which excludes heartburn from the definition of dyspepsia.[2] Patients experiencing dyspepsia rather than heartburn should be managed according to a different decision pathway, recognizing that true dyspepsia may be caused by GER.

D. Refer for further diagnostic testing

OBJECTIVE

To discuss the indications for further diagnostic testing.

ANNOTATION

Empiric therapy for GERD is reasonable without diagnostic testing. Patients who present with typical symptoms of GERD in the absence of longstanding, frequently recurring, progressive, or alarm symptoms or complicated disease may be started on empiric treatment and rarely need a confirmatory diagnostic test since symptom resolution is the primary clinical end point.

The recommendations of the Practice Parameters Committee of the American College of Gastroenterology (PPCACG) for further diagnostic testing are shown in Table 8.[1]

Table 8 Indications for further diagnostic testing (PPCACG)

Lack of response to therapy
Need for continuous chronic therapy
Chronic symptoms in a patient at risk for Barrett's esophagus[†]
Alarm symptoms suggesting complicated GERD:
bleeding
chest pain
choking (acid causing coughing, shortness of breath, or hoarseness)
dysphagia
weight loss

Source: DeVault (1999)[1] PPCACG = Practice Parameters Committee of the American College of Gastroenterology

[†] Endoscopy to screen for Barrett's esophagus is recommended in patients with a long duration of GERD symptoms (e.g., > 5 years), particularly white males who are 50 or more years of age.[59]

Patients with alarm symptoms may receive initial therapy with a PPI while they are awaiting further evaluation. The presence of alarm symptoms, however, requires immediate referral for diagnostic testing.[1,2]

Repeated endoscopy is usually not indicated,[60] as sustained symptom resolution reasonably reflects healing of esophagitis[61-64] and is the accepted primary clinical end point. The absence of heartburn has a high predictive value (91.4%) for endoscopic remission; however, the presence of heartburn has a low predictive value (26.8%) for relapse of esophagitis.[62] Symptom response (control or complete relief of heartburn) may be more frequently associated with healing of esophagitis after treatment with a PPI than with an H_2RA.[23,62] Among patients with persistent heartburn, a smaller proportion of PPI-treated patients than H_2RA-treated patients still have unhealed erosions.[15]

GERD that is refractory to drug therapy is rare.[1] Nonresponders to adequate trials of drug therapy, particularly PPI therapy, should have their symptoms reassessed, undergo endoscopy if it was not previously done, and be considered for additional diagnostic work-up.[1,2,60]

For further discussion on indications for repeat endoscopy and information on specific diagnostic tests for GERD, see Diagnostic Tests, page 33.

Intervention	Reference(s)	QE	OQ	SR
Immediate referral for diagnostic testing if alarm symptoms are present	DeVault (1999)[1] Dent (1999)[2]	III III	III	C
Repeated endoscopy is usually not indicated	ASGE (1999)[60] Vigneri (1995)[61] Carlsson (1997)[62] Richter (2000)[63] Vakil (2001)[64]	III I I I I	II	C
Reassessment and further diagnostic testing in nonresponders	DeVault (1999)[1] Dent (1999)[2] ASGE (1999)[60]	III III III	III	C

E. Start standard-dose PPI; if symptoms persist, refer for further diagnostic testing or consultation

OBJECTIVE

To discuss the management of patients with possible extraesophageal GERD

ANNOTATION

Effective treatment for extraesophageal GERD is not standardized. Well-designed studies comparing different pharmacologic treatments of extraesophageal GERD are lacking. The literature search found no well-designed trials comparing H_2RAs with PPIs or standard doses with higher doses of PPIs in the treatment of extraesophageal GERD. This guideline recommends considering empiric, standard-dose PPI as initial therapy.

For initial management of extraesophageal symptoms of GERD, expert consensus opinion favors empiric therapy with double-dose PPI (in two divided doses for at least 2 to 3 months) over invasive diagnostic testing because (1) ambulatory pH testing lacks diagnostic accuracy in patients with extraesophageal GERD, (2) a diagnostic trial of PPI is at least as sensitive as pH testing for diagnosing GERD, and (3) ambulatory pH testing or qualified personnel to interpret the test results may not be locally available.[65,66] This guideline suggests that the need for double-dose PPI should be based on patient response to standard-dose PPI, confirmation of a presumptive diagnosis of extraesophageal GERD, and any diagnostic findings.

Some patients may require higher doses and longer duration of acid suppressive therapy for adequate control of extraesophageal symptoms,[67,68] and response to treatment may partly depend on the type of extraesophageal GERD.[65]

Adjunctive therapy with antacids and postural lifestyle modifications may be considered but cannot be recommended for asthma or other types of extraesophageal GERD symptoms because of the lack of well-designed trials, inconsistent effects on asthma symptoms, and lack of improvement in pulmonary function tests.[69,70]

Patients with persistent symptoms of GERD and extraesophageal symptoms deserve further diagnostic testing (also see Annotation D) or consultation.[1] Diagnostic tests in addition to those performed for GERD may be required.

Intervention	Reference(s)	QE	OQ	SR
Trial of standard-dose PPI if a patient has esophageal and extraesophageal symptoms of GERD	GERD guideline expert opinion	III	III	C
Prefer empiric therapy with double-dose PPI over invasive diagnostic testing for initial management of possible extraesophageal symptoms of GERD	Johnson (2000)[65] Hogan (2001)[66]	III III	III	C
Antacids and postural lifestyle modifications for extraesophageal GERD symptoms	Gibson (2002; systematic review that includes only one study [Kjellen, 1981]) of nonpharmacologic measures[69] Kjellen (1981)[70]	I I	II	C
Patients with persistent symptoms of GERD and extraesophageal symptoms should undergo further diagnostic testing	DeVault (1999) [1]	III	III	C

F. Does patient have long duration of symptoms?

OBJECTIVE

To discuss the standard of practice and outcome evidence related to screening for Barrett's esophagus

ANNOTATION

Endoscopy to screen for Barrett's esophagus is recommended in patients with a long duration of GERD symptoms (e.g., > 5 years), particularly white males who are 50 or more years of age.[59] Furthermore, the duration of therapy may need to be included in calculating when to screen for Barrett's esophagus because acid suppression may not alter progression, and symptoms may not predict the presence of Barrett's esophagus.[1]

The use of endoscopy to detect or screen for Barrett's esophagus and at what point a patient should be evaluated are controversial issues. There is a lack of evidence that screening prevents death from esophageal adenocarcinoma. The associated time, effort, and costs to perform wide-scale screening of patients at risk would be prohibitive.[71,72] In addition, screening for Barrett's esophagus would miss up to 40% of patients with Barrett's esophagus who have no symptoms of GERD.[39]

Decisions to screen for Barrett's esophagus should be made with the understanding that there is a lack of evidence that these recommendations favorably affect patient survival or quality of life.

Intervention	Reference(s)	QE	OQ	SR
Endoscopy to screen for Barrett's esophagus in patients with a long duration of GERD symptoms (e.g., > 5 years), particularly white males who are 50 or more years of age.	Sampliner (1998)[59]	III	III	C
Screening endoscopy to prevent death from esophageal adenocarcinoma	Lack of evidence	IV	IV	I

G. Begin empiric, initial therapy

OBJECTIVE

To discuss reasons for stratified therapy based on results of early endoscopy vs. empiric treatment with delayed endoscopy in patients without alarm symptoms

ANNOTATION

There is a lack of data on the relative value of performing pre-treatment endoscopy upon the initial diagnosis versus starting empiric therapy, and the choice of strategy is controversial.[2] There are reasons favoring either approach (Table 9). (Note: The reasons for early endoscopy given here in the context of timing of endoscopy are different from the *indications* for endoscopy. Indications for endoscopy are discussed in Annotation D and under Diagnostic Tests, page 34.)

Table 9 Reasons for early endoscopy vs. empiric treatment

Reasons for early endoscopy–stratified therapy	Reasons for empiric therapy–delayed endoscopy
To confirm the clinical diagnosis	Endoscopy has a relatively limited diagnostic role, since less than half of patients with GERD have macroscopic abnormalities
To exclude other possible diagnoses such as peptic ulcer and gastric cancer	Patients destined to achieve remission on empiric therapy may not need endoscopy, thereby avoiding associated costs and possible negative effects on quality of life
To obtain information (e.g., degree of esophageal injury or presence of Barrett's esophagus or malignancy) that may predict disease relapse and need for maintenance therapy	Empiric therapy may facilitate identification of Barrett's esophagus (by reducing any tissue inflammation)
To direct treatment from an early stage in disease management, stratifying treatment based on grade of esophageal injury	

Sources: Dent (1999)[2]; Dent (2001)[13]

The Second Canadian Consensus Conference on the Management of GERD proposed a once-in-a-lifetime endoscopy mainly to detect Barrett's esophagus or esophageal cancer rather than erosive esophagitis.[73] However, the risk of developing esophageal adenocarcinoma associated with Barrett's esophagus is very

low in nonselected patients in primary care. Experts generally agree that detection of Barrett's esophagus should not be the primary reason for endoscopy.[2] (Also see Annotation F.)

At some facilities, early endoscopy would be chosen, but for the purposes of this guideline—in the absence of evidence to favor early, invasive diagnostic testing—empiric therapy is the preferred option.

Intervention	Reference(s)	QE	OQ	SR
Empiric treatment in patients without alarm symptoms	GERD guideline expert opinion	III	III	C

H. Consider adjunctive nonpharmacologic measures

OBJECTIVE

To discuss nonpharmacologic measures as adjuncts to acid-suppressive therapy

ANNOTATION

Although certain dietary and lifestyle factors may precipitate or exacerbate symptoms of GERD, most nonpharmacologic measures are not considered to be generally recommendable as sole therapy of GERD (Table 10).[47]

Table 10 Nonpharmacologic Measures to Reduce GERD Symptoms

MODIFICATION	RECOMMENDABLE	NOT GENERALLY RECOMMENDABLE[†]	NOT ASSESSED
Dietary	Avoid carbonated beverages Avoid voluminous meals	Avoid fatty meals Avoid sweets (including chocolate) Avoid spicy food and raw onions Avoid caffeinated beverages Avoid citrus products and juices	Avoid peppermint/spearmint, milk, garlic, and tomato juices
Lifestyle	Lose weight[‡] Quit smoking[‡] Avoid excessive physical activity (running)[§] Sleep lying on the left side of the body	Avoid alcoholic beverages Sleep with head elevated	Avoid the recumbent position for 3 hours after a meal

Source: Meining (2000)[47] Meining and Classen assessed the recommendability of dietary and lifestyle modifications based on the strength of scientific evidence and pathophysiologic mechanism. Nonpharmacologic measures that were not assessed by Meining and Classen are shown in the column labeled "Not Assessed."

† Dietary and lifestyle modifications that may not be generally recommendable might be helpful in individual patients.

‡ Recommendable because obesity and smoking may be risk factors for cancer of the distal esophagus

§ Avoidance of excessive physical activity, particularly running, is recommendable in affected persons.

Nonetheless, certain dietary or lifestyle modifications may be helpful as adjunctive therapy in individual patients. Expert opinion advocates checking individual patients for potentially important exposure to dietary and lifestyle factors[2,47] and educating patients about such factors.[1]

Nonpharmacologic measures (and antacids) are considered to be of minimal benefit or not sufficiently effective to justify their use as sole initial or long-term therapy of erosive esophagitis.[2] Similarly, they are not considered to be sufficiently effective to use as sole initial or maintenance therapy for NERD.[2] However, evidence in this area is lacking. The possible negative effects of these modifications on quality of life have not been adequately assessed. A number of randomized trials have found a placebo response rate of 20% to 30%, which is often attributed to lifestyle changes (despite the lack of supporting evidence).

The avoidance of certain foods or alcoholic drinks that provoke reflux symptoms is thought to be a potentially effective measure for reducing symptoms but is considered to be ineffective for healing of esophagitis[2] Elevating the head of the bed by 6 to 8 inches may be useful for the minority of patients who experience nocturnal reflux symptoms, have major nocturnal acid exposure, or have severe esophagitis, but is otherwise considered to be illogical for the majority of patients, who usually suffer reflux symptoms postprandially.[2]

Dietary or lifestyle modification should be considered an adjunctive measure and not a distinct step in the treatment of GERD. Practitioners should consider the potential for positive and negative consequences of lifestyle modifications on the patient's quality of life, and the possibility that any beneficial effects may be small compared with the acid suppressive effects of PPIs and H_2RAs.

Intervention	Reference(s)	QE	OQ	SR
Avoid carbonated beverages, avoid voluminous meals, lose weight, quit smoking, avoid excessive physical activity, and sleep lying on the left side of the body (based on scientific evidence and pathophysiologic mechanism).	Meining (2000)[47]	III	III	C
Check individual patients for potentially important exposure to dietary and lifestyle factors	Dent (1999)[2] Meining (2000)[47] DeVault (1999)[1]	III III III	III	C
Nonpharmacologic measures are of minimal benefit or not sufficiently effective	Dent (1999)[2]	III	III	C
Nonpharmacologic measures *as sole therapy*:				
Avoid alcoholic beverages	Feldman (1995)[74]	III	IV	I
Avoid carbonated beverages	Feldman (1995)[74]	III	IV	I
Avoid chocolate	Murphy (1988)[75]	I	II	C
Avoid citrus products and juices	Feldman (1995)[74]	III	IV	I
Avoid excessive physical activity	Lack of studies in patients with GERD	IV	IV	I
Avoid raw onions	Allen (1990)[76]	II-3	II	C
Avoid voluminous meals	Holloway (1985)[77]	I	II	C
Elevate the head of the bed	Stanciu (1977)[78] Harvey (1987)[79] Johnson (1981)[80]	I I II-3	II	C
Favor decaffeinated coffee	Pehl (1997)[81]	I	II	C
Lose weight (if obese)	Fraser-Moodie (1999)[82] Kjellin (1996)[83] Mathus-Vliegen (1996)[84]	II-3 I I	II	D
Quit smoking	Pehl (1997)[85] Kadakia (1995)[86] Waring (1989)[87]	II-2 II-3 II-3	II	C
Reduce coffee intake	Feldman (1995)[74]	III	IV	I
Reduce fat intake	Penagini (1998)[88] Becker (1989)[89]	I I	II	D
Sleep in the left lateral decubitus position	Shay (1996)[90]	II-3	III	C
Nonpharmacologic measures *as an adjunct* to acid-suppressive agents:				
Elevate the head of the bed	Harvey (1987)[79]	I	II	C

I. (Start) standard-dose PPI × 4 to 8 wk (in patients who have had an incomplete response to a previous trial of H_2RA)

OBJECTIVE

To explain the rationale for selecting standard-dose PPI over extending the treatment duration with either the same or higher dose of H_2RA in patients who have had an incomplete response to a previous trial of H_2RA

ANNOTATION

In patients who incompletely respond to a trial of either nonprescription or prescription H_2RA, PPIs are preferred over continuing H_2RA therapy because of their greater efficacy and faster symptom control, and the limited benefit gained from extending therapy with the same or higher dose of H_2RA.

As second-line therapy of refractory heartburn with or without esophagitis, standard-dose H_2RA therapy for an additional 2 to 4 weeks produces a limited increase in the cumulative rate of heartburn resolution (range of increase, 2% to 8%).[16,24] For refractory erosive reflux esophagitis, extending the duration of treatment by 4 to 12 weeks with standard-dose H_2RA produces modest increases in cumulative healing rates (median increase, 14%; range, 13% to 21%).[91-93]

A relatively flat dose-response relationship has been demonstrated with the H_2RAs during first-line therapy for esophagitis and second-line therapy in both a mixed population of patients with NERD or uncomplicated reflux esophagitis and a selected population of patients with erosive reflux esophagitis. When used as first-line therapy for esophagitis, higher than standard doses of H_2RAs have been demonstrated to produce minimal, if any, incremental improvement in cumulative response rates[91,92,94-100] (median of differences in healing rates between double and standard doses at 6 to 12 weeks: 3%).[18,91,92,94,95,99-102] In comparison with a standard dose of H_2RA as second-line therapy for heartburn with or without esophagitis, doubling the dose of H_2RA produces limited additional improvement (0% to 7%) in cumulative rates of complete heartburn relief over 2 to 8 weeks.[16,24]

A single study found quadruple doses of H_2RA to be more effective than standard doses (difference in healing rates: 21%).[98] Two other studies found quadruple doses to be not more effective than double doses of H_2RAs (difference in healing rates: –2% and –5%).[96,97]

In patients who had uninvestigated moderate to severe heartburn and remained symptomatic after 6 weeks of standard-dose H_2RA therapy, extending treatment with the H_2RA at the same dose was found to be inferior to switching to a PPI in terms of the proportion of patients achieving complete heartburn relief (16% vs. 46%, respectively, at 8 weeks).[103] Similarly, standard- or double-dose H_2RA has been shown to be inferior to switching to PPI therapy in a mixed population of patients with NERD or reflux esophagitis[104] and in a selected population of patients with erosive or ulcerative reflux esophagitis.[105]

Second-line therapy with H_2RAs also takes longer to achieve a response rate similar to that with PPIs. Patients who had inadequate responses to at least 12 weeks of standard-dose H_2RA may need to take an H_2RA for 8 to 12 weeks more (even at double doses) to achieve a cumulative healing or heartburn resolution rate close to that seen with just 4 weeks of PPI therapy.[93,104,105]

Nonprescription and standard doses of H_2RA taken on demand for 4 weeks are similar in efficacy in terms of relieving heartburn (median proportion of heartburn episodes relieved: 70% with famotidine 10 mg vs. 69% for 20 mg).[106] There also appears to be little difference between lower than prescription doses of H_2RAs.[106,107]

Considering the consistent documentation that limited benefit is gained from extending the duration of H_2RA therapy at the same or higher doses, and the superiority of PPIs over double-dose H_2RAs, this

guideline considers standard-dose PPI therapy to be the appropriate choice in patients who have had an incomplete response to a previous trial of either nonprescription or prescription H_2RA therapy.

Intervention	Reference(s)	QE	OQ	SR
If there is an incomplete response to initial H_2RA therapy, extending the duration of H_2RA therapy at the same or higher dose produces limited benefit	Hallerback (1998)[16]	I	I	C/D
	Kahrilas (1999)[24]	I		
	Pace (1990)[91]	I		
	Wesdrop (1993)[92]	I		
	Porro (1992)[93]	I		
	Simon (1994)[94]	I		
	Quik (1990)[95]	I		
	Roufail (1992)[96]	I		
	Euler (1993)[97]	I		
	Johnson (1989)[98]	I		
	Cloud (1994)[99]	I		
	Tytgat (1990)[100]	I		
Switch to a PPI if there is an incomplete response to H_2RA therapy	Maton (1999)[103]	I	II	B
	Richter (1996)[104]	II-2		
	Lundell (1990)[105]	I		
	Porro (1992)[93]	I		

J. Consider options of H_2RA vs. PPI

OBJECTIVE

To discuss issues to consider when choosing between H_2RAs and PPIs for empiric initial therapy

ANNOTATION

In patients who have not previously received H_2RAs or PPIs, there is insufficient evidence to support choosing one type of agent over the other as initial therapy of GERD. Expert opinion can provide reasonable justification for either a step-up or step-down treatment approach.

Stratifying treatment based on severity of symptoms is not supported by currently available information on the clinical and endoscopic manifestations of GERD. Similarly, the common recommendation to distinguish minor GER symptoms, which may be managed with nonprescription medication, from the more troublesome symptoms of GERD, which require prescription medication, poses a number of difficulties and lacks supporting evidence.

Therefore, these guidelines suggest that the individual provider should decide the treatment approach in consultation with the patient. Reasons for not advocating one treatment approach over the other in patients who have not previously received H_2RAs or PPIs and for not stratifying treatment based on symptom severity are presented below.

For empiric initial treatment of GERD, there is a lack of evidence and consensus to support using one treatment approach over the other

In studies comparing the H_2RAs and PPIs, 4 weeks' therapy with at least standard doses of H_2RAs achieves heartburn resolution in a substantial proportion (31% to 40%) of mixed populations of patients with NERD or uncomplicated esophagitis, although standard-dose PPIs are superior (response rate: 60% to 66%).[15,21,22]

Compared with H_2RAs, PPIs have also been shown to produce greater improvement in certain measurements of health-related quality of life at various time points in patients with uninvestigated GERD[108,109] and mixed populations of patients with NERD or reflux esophagitis.[109,110]

Studies comparing treatment *approaches* are limited. The literature search found a single study evaluating different treatment approaches in patients representative of a primary care population with uninvestigated

GERD. Howden, et al. found neither step-up therapy (starting with standard-dose ranitidine for 8 weeks then switching to standard-dose lansoprazole for 12 weeks) nor step-down therapy (starting with standard-dose lansoprazole for 8 weeks then switching to standard-dose ranitidine for 12 weeks) to be superior in the empiric treatment of patients with GERD.[111] The same trial found empiric therapy with a no-step PPI approach (lansoprazole for 20 weeks) to be superior to step-up, step-down, and no-step H_2RA therapy (ranitidine for 20 weeks). The duration of follow-up was relatively short (5 months), and the decision to switch drug was made according to protocol, not relief of reflux symptoms. The optimal approach—step-up, step-down, or no-step therapy—in the long-term management of patients with GERD remains to be determined.[112,113]

Most economic analyses, under a variety of conditions and assumptions, find the PPIs to be more cost-effective than H_2RAs as initial (or maintenance) therapy with or without endoscopy,[114] even when comparing a PPI (rabeprazole) to a generic H_2RA (ranitidine).[115] Cost-effectiveness studies applicable to the DoD and VA are lacking. The results of a model-based economic study that may have some relevance to the DoD or VA supports the use of a step-up approach for the initial treatment of GERD.[116] (For evidence on treatment approaches during maintenance therapy, see Annotation L.)

Expert opinion supports either step-up therapy (H_2RAs first) or step-down therapy (PPIs first) for initial therapy of patients with GERD,[1,13] although Dent, *et al.* supports a preference for PPIs followed by step down of treatment intensity.[2] Arguments can be made for either treatment approach (Table 11).

Table 11 Advantages and disadvantages of step-down and step-up treatment

Regimen	Advantages	Disadvantages
Step-down treatment (high initial therapy)	Rapid symptom relief Efficient for doctor Avoids overinvestigation and associated costs	Potential overtreatment Higher initial drug cost
Step-up therapy (minimum initial therapy)	Avoids overtreatment Lower initial drug cost	Patient may continue with symptoms unnecessarily Takes too long Inefficient for doctor May lead to overinvestigation Uncertain end point (partial symptom relief)

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There is a lack of evidence to support the practice of stratifying empiric initial therapy based on intensity or frequency of symptoms

Although an association between severity of esophageal lesions and the need for PPI therapy has been convincingly demonstrated,[57,117-122] a similar relationship has not been shown for heartburn severity. The severity or frequency of heartburn does not correlate with the presence or grade of esophagitis,[21,22,57,123-126] and there is little evidence that heartburn severity indicates the need for a specific type of therapy.

The literature search found a single published study and an abstract that provided data on treatment efficacy according to baseline symptom severity. In a mixed population of patients with NERD or uncomplicated erosive esophagitis, PPIs were found to be superior to H_2RAs in achieving heartburn remission regardless of the initial severity of heartburn.[21] After 4 weeks of treatment with omeprazole 20 mg q.d. or cimetidine 400 mg q.i.d., heartburn remission was achieved in 81%, 76%, and 57% of the PPI-treated patients with mild, moderate, or severe heartburn at study entry, respectively. The corresponding figures were 47%, 48%, and 17% for the H_2RA-treated patients. Treatment with omeprazole ($p < 0.0001$) and lower grade of heartburn at study entry ($p < 0.01$) statistically predicted heartburn relief at 4 weeks. In patients with severe heartburn, the absolute benefit increase in efficacy of 40% (57% minus 17%) suggests that PPIs may be preferred over H_2RAs in patients with more severe symptoms. However, as mentioned above, heartburn severity does not reflect the underlying disease

severity, and the additional benefit gained from PPI therapy was also substantial for mild (absolute benefit increase: 34%) and moderate (28%) symptoms. Similar documentation in empirically treated patients is lacking, and validation of the results by other studies is needed. Although the results may be applicable to a DoD patient population, the external validity of the results in U.S. veterans may be limited.

The study reported as an abstract found that baseline heartburn severity in patients with NERD does not influence heartburn resolution.[127] No significant differences in heartburn resolution were found between patients (N = 717) treated with standard- or double-dose esomeprazole for 4 weeks, regardless of the baseline heartburn intensity. Rates of heartburn resolution were similar in patients with mild, moderate, or severe heartburn at baseline for esomeprazole 40 mg (37.8%, 31.7%, and 40.7%, respectively) and esomeprazole 20 mg (31.0%, 37.9%, and 39.7%, respectively). The abstract concluded that the severity of heartburn should not influence the choice of treatment in patients with NERD.

A number of problems make it difficult to distinguish troublesome GERD from minor GER symptoms. There is no standard definition of GERD, no diagnostic gold standard for GERD, no standard method for determining severity of symptoms, no clear boundary distinguishing GERD from minor GER symptoms, and no standard method for differentiating between GERD and minor GER symptoms. It can be argued that the presence of any reflux symptoms may be GERD because physiologic reflux is asymptomatic.

Dent, *et al.* proposed that GERD was likely to be present when heartburn occurred on two or more days a week, and the occurrence of less frequent GER symptoms, which have not significantly impaired health related well-being, should not necessarily indicate GERD.[2] Although impairment of health-related quality of life has been shown to be associated with the frequency or intensity of heartburn with or without esophagitis,[10,128-130] data showing differences in health-related quality of life between patients who experience symptoms below vs. above a specific frequency are limited.

The literature search found a single international survey that distinguished between GERD and minor symptoms in terms of health-related quality of life. Based on completed surveys of 2056 American and Canadian subjects (20% of 10,334 eligible participants), Frank, *et al.* found statistically significant differences in nonprescription medication use, physician visits, and psychological well-being between surveyed patients who experienced heartburn and/or acid regurgitation (with or without dysmotility symptoms) at least once per week and/or of at least moderate intensity (arbitrarily classified as GERD) and those who had less frequent or lower symptom intensity (arbitrarily classified as minor symptoms).[131] The study was limited by the use of a survey instrument and the arbitrarily defined criteria for GERD and minor symptoms.

More importantly, however, symptoms less frequent than 2 days per week do not necessarily exclude GERD. As mentioned above, the intensity and frequency of symptoms do not reflect the presence or grade of esophageal disease. There is a lack of evidence that patients with minor or less frequent GER symptoms are not at risk for severe complications of GERD or esophageal cancer. To the contrary, mild symptoms may be experienced by patients with Barrett's esophagus more frequently than patients who have GERD without Barrett's esophagus.[129] One study found that 40% of patients with esophageal adenocarcinoma had no symptoms of GERD while 20% experienced reflux symptoms once per week.[39]

Distinguishing between GERD and minor GER symptoms on the basis of reflux symptom frequency (e.g., using 1 episode or 2 days per week as a threshold) or intensity (e.g., moderate to severe vs. mild symptoms), and allocating more effective therapy to patients classified as having GERD and less effective therapy to those classified as having minor GER symptoms, cannot be supported because of the lack of well-designed trials evaluating the validity of this approach. Endoscopic assessment of esophageal injury is currently the only available technique for grading GERD severity.

Intervention	Reference(s)	QE	OQ	SR
The intitial treatment approach may be either step-down therapy (PPI first) or step-up therapy (H_2RA first)	Bate (1997)[21]	I	II	C
	Armstrong (2001)[15]	I		
	Venables (1997)[22]	I		
	Kaplan-Machlis (2000)[108]	II-2		
	Revicki (1998)[109]	I		
	Wiklund (1998)[110]	I		
	Howden (2001)[111]	I		
	DeVault (1999)[1]	III		
	Dent (1999)[2]	III		
	Dent (2001)[13]	III		
	Bate (1997)[21]	I		
Initial treatment should not be stratified based on severity of symptoms	GERD guideline expert opinion	III	III	C

K. If response to PPI therapy is not adequate, consider extending treatment duration (by 4 to 8 wk) at same dose or with double-dose PPI

OBJECTIVE

To discuss the pharmacologic options for managing patients who do not adequately respond to initial therapy with standard-dose PPI

ANNOTATION

The recommended duration of therapy for PPIs in the treatment of GERD is 4 to 8 weeks. An inadequate response to a course of standard-dose PPI may indicate longer treatment is needed, more severe disease,[132] or incorrect diagnosis. Additional benefit may be obtained by extending treatment with either the same or double doses of PPI.[57,93,132-144] In either case, the patient should be referred for further diagnostic testing (also see Annotation D).[1,2]

Studies that compare treatment approaches for primary care patients who inadequately respond to standard-dose PPI are lacking. In a study of VA primary care and gastroenterology clinic patients who continued to experience heartburn more than once a week after at least 3 months' treatment with standard-dose lansoprazole, an additional 6 weeks' therapy with double-dose lansoprazole achieved complete relief of daytime and nighttime heartburn in 10 (22.7%) of 44 patients.[133]

More data is available for patients with erosive or ulcerative esophagitis. Comparing response rates at 4 and 8 weeks of standard-dose PPI treatment, a greater proportion of patients achieve complete heartburn relief at 8 weeks (64% to 86%) than at 4 weeks (60% to 73%) with differences ranging from 4% to 17% among studies.[93,134-138] Rates for healing of erosive reflux esophagitis are also greater at 8 weeks (70% to 96%) than at 4 weeks (39% to 88%) with differences of 7% to 34%.[57,93,132,134-136,139-145]

In patients who have inadequate responses to 8 weeks of standard-dose PPI, treatment with double-dose PPI for an additional 4 to 8 weeks has resulted in esophageal healing in all patients.[93] However, in one study, extension of therapy by an additional 4 weeks with double-dose omeprazole was not statistically different from standard-dose PPI in terms of overall healing and heartburn relief rates in patients who had unhealed esophagitis and persistent heartburn after the first 4 weeks of standard-dose omeprazole therapy.[137] In this situation, continuing therapy with standard-dose PPI may be the preferred option. The study evaluated a subset of patients with both persistent symptoms and unhealed esophagitis. Patients with asymptomatic unhealed esophagitis or healed esophagitis with persistent symptoms were not included in the study.

Additional studies comparing treatment approaches in patients who inadequately respond to standard-dose PPI therapy are needed. Available evidence suggests there may be incremental benefit from extending treatment with either standard or double doses of PPI in such patients.

Intervention	Reference(s)	QE	OQ	SR
If there is an inadequate response to a course of standard-dose PPI, extend treatment with either the same or double dose of PPI.	Bate (1990)[57]	I	I	B
	Porro (1992)[93]	I		
	Fass (2000)[133]	I		
	Sandmark (1988)[134]	I		
	Sontag (1992)[135]	I		
	Mossner (1995)[136]	I		
	Bate (1993)[137]	II-2		
	Robinson (1993)[138]	II-2		
	Hetzel (1988)[132]	I		
	Corinaldesi (1995)[139]	I		
	Earnest (1998)[140]	I		
	Mee (1996)[141]	I		
	Castell (1996)[142]	I		
	Van Rensburg (1996)[143]	I		
	Mulder (1996)[144]	I		
The patient who does not respond to a course of standard-dose PPI should be referred for further diagnostic testing.	DeVault (1999)[1]	III	III	C
	Dent (1999)[2]	III		

L. Consider options of attempting to step down and discontinue therapy vs. continuing current therapy

OBJECTIVE

To discuss options for maintenance therapy

ANNOTATION

GERD is a chronic relapsing-remitting disease, and NERD may also be characterized by periods of exacerbation and remission.[36,37] Maintenance therapy constitutes both the cornerstone of GERD management and the main economic burden in the management of this often life-long disease. The goals of maintenance therapy are to keep symptoms under control, prevent relapse, and prevent progression of disease and complications. Failure to treat relapse may put the patient at risk for complications of GERD and progressive deterioration of esophageal function.

If a patient has an adequate, sustained response to initial therapy, this guideline suggests two possible options for maintenance therapy:

(1) step-down management with attempted discontinuation of therapy (preferred); or
(2) no-step management; i.e., continuation of the current medication regimen.

The optimal approach to maintenance therapy is unclear. The two choices suggested by this guideline have been more commonly evaluated in efficacy or economic studies. If relapse occurs, the choice of subsequent treatment approach also lacks consensus—to reinstitute continuous therapy, to reinstitute continuous therapy then step down, or to intermittently treat each relapse.

After symptomatic remission is achieved with initial therapy, the decision to undergo a trial of step-down management and discontinuation of therapy should be individualized. The choice of approach should take into consideration such factors as the patient's clinical status, the presence or likelihood of complications, the patient's previous response to treatment, the likelihood of follow-up (to monitor patients after therapy is stepped down or discontinued), and overall costs.

The reasons for stepping down therapy are cost minimization and avoidance of over-treatment. The fear of over-treatment may be unfounded, however, since the long-term use with PPIs seems to be safe (see

Proton Pump Inhibitors, page 40). The main advantage may be the ability to determine which patients may be adequately controlled on less acid suppressive and less expensive medication and thereby individualize therapy. Dent, *et al.* supports a trial of discontinuing therapy in all patients who have not undergone endoscopy to determine if GERD is a recurrent problem before considering long-term drug therapy or surgery.[2,13]

About 20% to 50% of patients may remain in symptomatic remission for 6 months without maintenance therapy.[17,33] Since patients who relapse regain symptom control after reinstitution of therapy,[17,20,146] an attempt to discontinue therapy is considered to be a reasonable option in most patients. For these reasons, this guideline prefers the step-down approach for maintenance therapy.

Reasons to continue current therapy include avoidance of at least temporary impairment in quality of life associated with possible relapse, prevention of complications due to untreated relapses, and possible decreased utilization of health care resources and their associated costs.

With either approach, patients who require continuous, long-term maintenance therapy should be referred for further diagnostic testing.[1,2]

Comparative studies and economic considerations

Studies comparing the two approaches to maintenance therapy are limited and differ in methods, making interpretation difficult. A single study included patients with uninvestigated heartburn. Howden, *et al.* found 20 weeks of empiric therapy with a no-step PPI approach to be superior to step-up, step-down, and no-step H_2RA therapy in terms of the percentage of 24-h heartburn-free periods (median: 82% vs. 74%, 67%, and 66%, respectively).[111] Step-down therapy and no-step H_2RA therapy were numerically similar. The study may not reflect clinical practice because the duration of follow-up was short and the timing for step-up or step–down therapy was dictated by protocol to occur at 8 weeks rather than based on symptom control. It is difficult to compare the results of this study with other efficacy studies because the proportions of patients in symptomatic remission were not reported. Continuing current PPI therapy may be superior to stepping down therapy in a general population; however, a step-down approach allows therapy to be individualized with the possibility of discontinuation of medication.

Another study evaluated initial and maintenance therapies in patients with NERD or mild reflux esophagitis.[147] Patients were randomized to initial treatment with standard-dose omeprazole or double-dose ranitidine for 4 to 8 weeks. Those in remission after 4 to 8 weeks were then re-randomized to treatment with half-dose omeprazole or standard-dose ranitidine for up to 12 months. The estimated proportion of patients in symptomatic remission after 12 months of maintenance therapy (according to initial therapy/maintenance therapy) was greatest with double-dose ranitidine/half-dose omeprazole (74%), followed by standard-dose omeprazole/half-dose omeprazole (65%), double-dose ranitidine/standard-dose ranitidine (45%), then standard-dose omeprazole/standard-dose ranitidine (35%) ($p < 0.0001$). Half-dose omeprazole was superior to standard-dose ranitidine based on the estimated remission rates during 12 months of maintenance therapy (68% vs. 39%; $p < 0.0001$).

Economic analyses have inconsistently favored different maintenance treatment approaches under various assumptions and conditions. A report from Sweden supported continuous over intermittent PPI therapy.[148] The results of an economic evaluation of "step-in" therapy (where maintenance therapy is withheld until the first relapse) depended on the grade of esophageal damage.[149]

The PPIs are generally superior to H_2RAs for maintenance therapy. However, the literature search found limited and conflicting information on the long-term efficacy rates of PPIs and H_2RAs in the maintenance of symptomatic remission in primary care patient populations. A randomized, open-label study (N = 268) found no statistically significant treatment differences in heartburn resolution rates after 24 weeks of empiric therapy with standard-dose omeprazole (31%) and standard-dose ranitidine therapy (29%).[108] In contrast, a double-blind, randomized controlled trial in a mixed population of patients with NERD or

nonulcerative esophagitis found half-dose omeprazole (10 mg q.d.) to be superior to standard-dose cimetidine (800 mg q.h.s.) in terms of heartburn remission rates at 24 weeks (53% vs. 16%, respectively).[23]

In patients with reflux esophagitis, continuous daily therapy for 1 year with half- or standard-dose PPIs has been consistently found to be superior to standard- or double-dose H_2RAs in terms of endoscopic[150-152] or symptomatic relapse.[147,151,153]

Most economic analyses, under a variety of conditions and assumptions, find the PPIs to be more cost-effective than H_2RAs as initial or maintenance therapy with or without endoscopy,[114] even when comparing a PPI (rabeprazole) to a generic H_2RA (ranitidine).[115]

One study that may be relevant to the VA showed that stepping down therapy from a PPI to H_2RAs, prokinetics, or both with a trial of drug discontinuation was successful in the majority (58%) of 71 evaluated patients. No significant changes in health-related quality of life or disease severity were observed 6 months after implementing step-down management, and the step-down approach resulted in a total annual cost savings of $15,069 for the cohort.[20]

Another study, which considered government procurement costs, favored PPIs over H_2RAs in patients with esophagitis when the difference in drug acquisition costs were small or when patients experienced substantial impairment in quality of life.[154]

In summary, there is currently no definitive evidence to support a particular approach in the maintenance therapy of DoD or VA patients with uninvestigated GERD. PPIs are superior to H_2RAs, and a no-step PPI approach may be superior to a step-down or no-step H_2RA approach for maintenance therapy in a population of patients. This guideline prefers a step-down approach, as it may individualize therapy to find the least acid-suppressive and least costly therapy needed for each patient. There has been no evidence of significant changes in quality of life or disease severity 6 months after initiating step-down management.

Intervention	Reference(s)	QE	OQ	SR
If a patient responds to intial therapy, either step down then discontinue therapy (preferred) or continue current medication regimen	GERD guideline expert opinion	III	III	C
Individualize decisions to undergo a trial of step-down management and discontinuation of therapy	GERD guideline expert opinion	III	III	C
Patients who require continuous, long-term maintenance therapy should be referred for further diagnostic testing	Dent (1999)[2] DeVault (1999)[1]	III III	III	C

M. Discontinue therapy first or step down then discontinue therapy

OBJECTIVE

To discuss two methods of stepping down therapy in patients who have achieved symptomatic remission

1. Attempt treatment discontinuation first
2. Attempt treatment discontinuation after step-wise reduction in treatment intensity

ANNOTATION

There is no standardized method for stepping down therapy, and no consensus on the optimal duration of initial therapy before attempting to step down therapy once symptoms are controlled. In efficacy trials, the duration of initial therapy is generally at least 4 to 8 weeks. Reports outlining protocols for step-down management or documenting the merits of step-down therapy in primary care patients are limited. There is also a lack of studies comparing patient outcomes resulting from different approaches to step-down management.

One reason for discontinuing therapy first is to determine early on which patients require any maintenance therapy. A step-down approach (discontinuation of PPI therapy or halving the PPI dose if tablet size made it possible, and reinstituting therapy upon relapse) has been associated with no significant changes in health-related quality of life measurements or disease severity at 6 months compared with baseline, despite a high relapse rate (85%).[20] Discontinuing therapy first is consistent with the recommendations by Dent, *et al*., who additionally recommend endoscopy if patients with uninvestigated GERD experience a relapse after stopping therapy (reinstitution of therapy before endoscopy is not specifically suggested).[2] While discontinuation of medication after successful initial therapy can evaluate whether long-term treatment is necessary, this strategy could not be routinely recommended by Dent, *et al.* because of conflicting data on the relapse rates of patients after stopping therapy.[2] Unlike the guideline proposed by Dent, *et al.*, this guideline suggests reinstituting treatment upon relapse to provide symptomatic therapy while the patient is awaiting further evaluation.

Reducing treatment intensity in a step-wise fashion before discontinuation reveals the specific type of drug the patient requires for maintenance therapy (i.e., patients who relapse after stepping down to H_2RA therapy are those who require PPI therapy) before determining which patients require any maintenance therapy.

Referral for further diagnostic testing should be considered for all patients who relapse or require continuous, long-term maintenance therapy.[1,2,60]

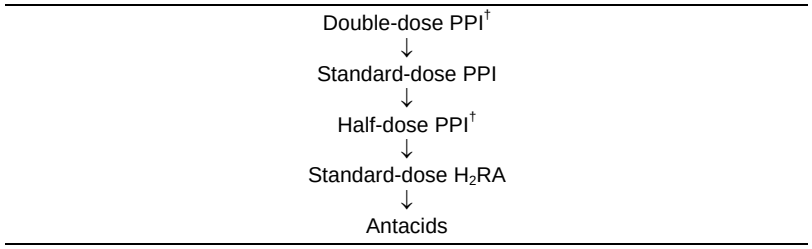
The two methods of stepping down therapy are modeled after the protocol used in U.S. veterans by Inadomi, *et al*., where relapse within the first 2 weeks of discontinuation or halving the dose of PPI (if tablet size made it possible) was managed by reinstituting initial effective PPI therapy, and relapse after 2 weeks was treated by stepping up drug therapy (to double-dose H_2RA, prokinetics, or a combination of both).[20] The 2-week period was chosen arbitrarily.

Both methods suggested by this guideline recommend restarting the initial drug regimen that was effective if patients relapse within 2 weeks of discontinuing or stepping down therapy. For relapses occurring after the first 2 weeks, this guideline suggests stepping up drug therapy.

There are important differences between the approach described here and the approach by Inadomi, *et al.* One difference is the recommendation to use standard-dose H_2RA instead of double-dose H_2RA or prokinetics. Double doses of H_2RA are not recommended because of limited additional benefit gained over standard doses (see Annotation H). Prokinetics are not recommended because of the market withdrawal of cisapride and limited evidence to support the use of other prokinetics (see Prokinetic Agents, page 43). Another key difference is the suggestion to refer the patient for further diagnostic testing if relapse occurs, whereas the protocol used by Inadomi, *et al.* was entirely based on symptoms. There is a lack of evidence that outcomes differ between symptom-based and endoscopy-based treatment of relapse. The provider should be aware that the specific methods suggested by this guideline have not been evaluated.

Both methods also use a step-wise decrease or increase in the degree of acid suppression based on a hierarchy of drug efficacy. For both NERD and erosive esophagitis, there is a hierarchy of efficacy for antireflux agents (from double-dose PPI down to standard-dose H_2RA).[2] A similar hierarchy (from double-dose PPI down to antacids) for primary care practice has been suggested by Dent, *et al.* (see Figure 1).[13]

Figure 1 Hierarchy of the efficacy of drug treatments for GERD



Source: Dent, et al. BMJ 2001;322:344-7.[13] Adapted with permission from the BMJ Publishing Group. © Copyright 2001, BMJ Publishing Group.

H_2RA = Histamine H_2 receptor antagonist; PPI = Proton pump inhibitor

† Double- and half-dose PPI therapies are NOT RECOMMENDED for uninvestigated GERD. Half doses are possible only with lansoprazole suspension, omeprazole suspension, and pantoprazole tablets. Also see text.

NOTE: Relapse on standard-dose PPI maintenance therapy and need for continuous long-term therapy are indications for further diagnostic evaluation.[1,2] *In this regard, the decision to use PPIs in either double or half doses for maintenance therapy should be made following diagnostic testing*. There is evidence to support the use of half-dose PPI over standard-dose H_2RA maintenance therapy in a mixed population of patients with NERD or mild erosive esophagitis[147]; but there is a lack of evidence in patients with uninvestigated GERD. The decision to use half-dose PPI therapy should be made after considering that half doses are currently possible only with lansoprazole suspension, omeprazole suspension, and pantoprazole tablets. (Also see Proton Pump Inhibitors, page 40.)

The evidence supporting the use of antacids as maintenance therapy is limited. In two small (N = 20 and 36) long-term (26- and 38-month)[155,156] and one large (N = 883) shorter-term (6-month)[157] study, about 20% of patients with reflux esophagitis experienced adequate symptomatic control on antacids after initial response to antireflux therapy. However, many patients have already found antacids (and lifestyle modifications) to be ineffective before they seek medical help (and lifestyle modifications may impair quality of life). For these reasons and because of insufficient evidence, Dent, *et al.* consider antacids (and lifestyle modifications) to be of minimal, if any, benefit as long-term (or initial) therapy for erosive esophagitis.[2] Similarly, a trial of their use for NERD is not supported.[2]

There is a remarkable lack of data on the long-term use of on-demand H_2RA maintenance therapy. Half-dose H_2RA given as a single daily dose has been found to be no different from placebo for maintenance therapy in mixed populations of patients with NERD or healed erosive esophagitis[158] and selected populations of patients with healed reflux esophagitis.[125] Similar studies in primary care patient populations are lacking.

The approach to maintenance therapy in patients who have been referred for further diagnostic testing (for example, because of alarm symptoms, extra-esophageal symptoms, long duration of symptoms, relapse on medication, or need for continued, long-term maintenance therapy) should be based on diagnostic test results.

Intervention	Reference(s)	QE	OQ	SR
For stepping down maintenance therapy, either discontinue therapy first or discontinue treatment after a step-wise reduction in treatment intensity	Inadomi (2001)[20] GERD guideline expert opinion	II-3 III	III	I
Refer patients who relapse or require continuous, long-term maintenance therapy for further diagnostic testing.	DeVault (1999)[1] Dent (1999)[2]	III III	III	C
Refer patients for consultation before considering the use of half-dose PPIs (only shown to be effective in patients with NERD or mild erosive esophagitis).	GERD guideline expert opinion	III	III	C
Antacids for maintenance therapy	Lieberman (1987)[155] Behar (1975)[156] Poynard (1993)[157] Dent (1999)[2]	II-3 II-2 II-3 III III	II	C
Half-dose H_2RA for maintenance therapy (no different from placebo)	Kaul (1986)[158] Koelz (1986)[125]	I I	II	D

SUPPLEMENTS

DIAGNOSTIC TESTS

The clinical diagnosis may be objectively confirmed by a number of diagnostic tests that quantify certain pathophysiologic aspects of the disease.

ENDOSCOPY

Description

Endoscopy (or esophagogastroduodenoscopy, EGD) allows direct visual assessment of mucosal damage, tissue sampling, and specific therapy (stricture dilation).

Mucosal breaks are indicative of esophagitis, while "minor" changes, such as erythema, edema, and friability, are not consistently identified as signs of esophagitis by different observers.[159] More than half of patients in community or general practice who experience frequent heartburn have no endoscopic evidence of mucosal breaks (erosion or ulceration).[22,31-33] Therefore, a negative endoscopy does not exclude a diagnosis of GERD.

Four classification systems have been commonly used for grading the extent and severity of esophageal lesions based upon the appearance of mucosal tissue on endoscopy: (1) Savary-Miller, (2) Hetzel-Dent, (3) Los Angeles, and (4) MUSE (**Table 12** to **Table 15)**.

Table 12 Savary-Miller Classification System of Esophageal Lesions

GRADE	DESCRIPTION
I	Lesions with erythema, exudates, or superficial erosions; non-confluent
II	Lesions with erosions or exudates; confluent without involving entire circumference
III	Circumferential erosive or exudative lesions
IV	Injury involving circumference of esophagus; deep ulceration, stricture, or development of columnar epithelium

Adapted from Savary (1978)[160]

Table 13 Hetzel-Dent Classification System of Esophageal Lesions

GRADE	DESCRIPTION
0	No mucosal abnormalities.
1	Erythema, hyperemia, mucosal friability without macroscopic erosions.
2	Superficial erosions involving less than 10% of the surface of the distal 5 cm of squamous epithelium.
3	Erosions or ulcerations involve 10% or 50% of the mucosal surface of the distal 5 cm of squamous epithelium.
4	Deep ulceration anywhere in the esophagus or confluent erosion involving more than 50% of the mucosal surface of the distal 5 cm of squamous epithelium.

Source: Hetzel (1988)[132]

Table 14 Los Angeles Classification System of Esophageal Lesions

GRADE	DESCRIPTION
A	One (or more) mucosal breaks no longer than 5 mm that do not extend between the tops of the mucosal folds.
B	One (or more) mucosal breaks more than 5 mm long that do not extend between the tops of two mucosal folds.
C	One (or more) mucosal breaks that are continuous between the tops of two or more mucosal folds, but which involve less than 75% of the esophageal circumference.
D	One (or more) mucosal breaks that involve at least 75% of the esophageal circumference.

Source: Lundell (1999)[124]

Table 15 MUSE Classification System of Esophageal Lesions

GRADE	DESCRIPTION			
	Metaplasia (M)	**Ulceration (U)**	**Stricture (S)**	**Erosion (E)**
0	Absent	Absent	Absent	Absent
1	1 fold	Junctional	> 9 mm	1 fold
2	> 2 folds	Barrett's ulcer	< 9 mm	≥ 2 folds
3	Circumferential	Combined	Stricture and shortening	Circumferential

Source: Armstrong (1993)[161]

While these classification systems are useful in stratifying patients by disease severity in clinical research trials, they tend to be less helpful in clinical practice because of inter- and intra-observer variation.[162,163] Careful, specific descriptions of esophageal observations and photo documentation provide more practical references for comparison.

Importantly, endoscopy is the most reliable method for detecting Barrett's esophagus but biopsy is required to check for metaplasia. Endoscopy can also detect malignancy. Histologic examination of apparently normal squamous mucosa has little role in diagnosing abnormal acid reflux.

Indications

The American Society for Gastrointestinal Endoscopy (ASGE)[60] specifically recommends endoscopy for the indications shown in Table 16.

Table 16 Indications for endoscopy (ASGE)

Persistent or progressive symptoms on therapy
Symptoms of dysphagia or odynophagia
Evidence of gastrointestinal bleeding or iron deficiency anemia
Presence of a mass, stricture, or ulcer in a patient with a previous esophagram
Extraesophageal symptoms of GERD
Esophageal symptoms in an immunosuppressed patient

Source: ASGE (1999)[60]

Repeat endoscopy to monitor esophagitis is generally not recommended. Follow-up endoscopy is recommended by the ASGE[60] in patients who

(1) have an inadequate symptomatic response to therapy;
(2) have an esophageal ulcer; and
(3) require additional biopsy and cytologic studies because the diagnosis is unclear.

PPI TRIAL

A "PPI test", consisting of a limited 1- to 2-week trial of omeprazole (40 to 80 mg per day in one or two divided doses)[164-166] or 5-day trial of lansoprazole (60 mg once daily),[167] may be a useful aid in ruling out a diagnosis of GERD either before endoscopy or after a negative endoscopy.[2] When endoscopy or 24-hour pH monitoring is used as the diagnostic standard, a 7-day trial of rabeprazole 40 mg per day in two divided doses has high sensitivity (83%) and specificity (75%) for detecting GERD-related noncardiac chest pain.[168] The PPI test may be at least as sensitive as

ambulatory esophageal pH monitoring in diagnosing GERD in patients with erosive esophagitis.[169]

A clinical and economic study in the VA found the PPI test (using omeprazole) to have acceptable sensitivity (80.0%; 95% confidence interval: 66.7% to 93.3%) and fair specificity (57.1%; 20.5% to 93.8%) for GERD.[170] The test reduced the use of endoscopies by 64% and ambulatory esophageal pH monitoring by 53%, and saved $348 per average evaluated patient.

High doses of PPIs are considered to be necessary for greater diagnostic sensitivity.[2] A 75% reduction in symptoms of NERD after at least 7 days' treatment has been shown to have higher sensitivity using quadruple–dose omeprazole (40 mg b.i.d.) (83.3%) than double-dose omeprazole (40 mg q.d., 27.2%), and both PPI regimens were more sensitive than standard-dose ranitidine (150 mg b.i.d., rate not reported).[164] The optimal diagnostic dose of PPI has not been determined.

Expert opinion advocates the strategy of using a PPI trial after endoscopy when needed to make a diagnosis of GERD because it is simpler and better tolerated than 24-hour ambulatory pH monitoring.[2] If endoscopy has excluded non-reflux–related abnormalities that respond to antireflux therapy, then a trial of high-dose PPI therapy should be reasonably specific for GERD. A diagnostic trial of PPI therapy without prior endoscopy is more controversial.[171,172]

AMBULATORY PH MONITORING

If doubt exists that the reflux of gastric contents is the cause of symptoms, a 24-hour ambulatory esophageal pH study may be performed.[58] Ambulatory esophageal pH monitoring may be useful for diagnosing GERD in patients with endoscopy-negative, persistent reflux symptoms or atypical symptoms, for monitoring esophageal acid exposure in patients with refractory symptoms, and for assessing response to medication. Ambulatory pH monitoring may also aid in identifying appropriate candidates for surgery by determining both the temporal relationship between reflux episodes and atypical symptoms, and the level to which acid reflux extends.[173-175]

However, the 24-hour esophageal acid exposure is not sensitive enough to serve as a gold standard for GERD. Up to one fourth of patients with erosive esophagitis and about one third of patients with NERD have normal acid exposure values.[2] Furthermore, acid exposure values may revert between normal and abnormal when pH monitoring is repeated,[176,177] or may differ when measured simultaneously by two attached probes.[178,179] Ambulatory pH monitoring is unlikely to aid in the diagnosis of GERD in patients with typical reflux symptoms, negative endoscopy, and positive response to antireflux therapy.

Unfortunately, neither pH monitoring nor the PPI test can reliably confirm or exclude a diagnosis of GERD. In difficult cases, both tests may be necessary to improve diagnostic certainty. Some experts consider pH monitoring to have the most utility in difficult patients if it is performed during PPI therapy.[2]

BARIUM ESOPHAGRAPHY

Barium esophagraphy is relatively inexpensive, and is of minimal practical value in the diagnosis of GERD. Barium esophagraphy is the most sensitive test for detecting esophageal strictures and calibrating the esophageal lumen. Additionally, a barium esophagram provides useful information on the presence or absence of a hiatal hernia but limited information on esophageal motor function. It is very insensitive in diagnosing mucosal inflammation or detecting the presence of Barrett's intestinal metaplasia (which requires biopsy and histologic confirmation). Depending on the desired information, a barium esophagram and/or endoscopy may be the preferred method to evaluate patients who present with dysphagia.

PROVOCATIVE TESTS

Provocative tests play a small role in the routine diagnosis of GERD. Mucosal sensitivity to acid can be assessed using a provocative test of the esophagus. The one most commonly used is the Bernstein test, which can indicate that symptoms are related to GERD if they are elicited by acid and not a normal saline control. The test is highly specific for GERD but much less sensitive,[180] and therefore cannot exclude reflux or distinguish between different degrees of reflux or esophagitis.

ESOPHAGEAL MANOMETRY

Esophageal manometry does not diagnose GERD; however, the test is helpful in assessing esophageal peristalsis in patients being considered for antireflux surgery or placement of ambulatory pH probes.[12]

PHARMACOTHERAPEUTIC AGENTS

ANTACIDS WITH OR WITHOUT ALGINIC ACID

Antacids with or without alginic acid may be useful as rapid-acting, on-demand treatment of heartburn.[181] Antacids neutralize gastric acid and, by neutralizing gastric acid, increase LES tone. Antacids with alginic acid (e.g., Gaviscon®) may be preferable even though their acid neutralizing capacity is small. The alginic acid forms a viscous layer that floats on top of the gastric contents and may mechanically prevent the reflux of acidic gastric contents into the esophagus, as well as shield the esophagus from gastric acid.

Antacids are widely used as self-treatment of reflux symptoms. Because many patients have already found lifestyle modifications and antacids to be ineffective before they seek medical help, expert opinion considers nonpharmacologic measures and antacids to be of minimal, if any, benefit as initial or long-term therapy for erosive esophagitis; similarly, their use for NERD is not supported.[2]

Whether an antacid or a combination of antacid with alginic acid is used, a dose equivalent to 80 mEq of acid neutralizing capacity (about 15 to 30 ml) should be administered q.i.d. (e.g., after meals and at bedtime) for 2 to 4 weeks. Agents should then be taken as needed. The onset of antacids is relatively rapid (within minutes) and their duration is 2 to 3 hours when given in close proximity to a meal.[182] The liquid form rather than tablets is preferred because of more rapid onset of action. If tablets are used, they should be chewed thoroughly and followed with a full glass of water.

Magnesium-containing antacids may cause diarrhea, and aluminum and calcium antacids may cause constipation. Hypophosphatemia may occur with chronic antacid use. Magnesium and aluminum retention may occur in patients with renal failure.

Antacids may form an insoluble complex with other drugs and decrease their bioavailability, or increase gastric pH, thereby interfering with the drug's disintegration, dissolution, solubility, ionization, or gastric emptying time (Table 17).

Table 17 Drug Interactions with Antacids

INTERACTING DRUG[†]	ANTACID COMPONENT					RECOMMENDATIONS FOR MANAGEMENT TO MINIMIZE RISK
	Aluminum	Calcium	Magnesium	Sodium bicarbonate	Magnesium / aluminum	
Allopurinol	↓					Administer allopurinol at least 3 hours before or 6 hours after the antacid
Aspirin		↓		↓	↓	Adjustments in salicylate dosage may be necessary
Atenolol	↓	↓	↓		↓	Administer atenolol at least 2 hours before or 6 hours after antacid
Atevirdine					↓	Separate doses by 2 to 3 hours
Cefpodoxime proxetil	↓			↓	↓	Do not administer antacids for at least 2 hours before or after the antibiotic
Flecainide				↑		Monitor flecainide concentrations
Iron	↓	↓	↓	↓	↓	Separate administration as much as possible
Isoniazid	↓					Administer isoniazid 2 hours before or 6 hours after antacid
Ketoconazole				↓	↓	Avoid antacids 2 hours before or after ketoconazole
Penicillamine	↓		↓		↓	Administer penicillamine 2 hours before or 6 hours after antacids
Quinidine		↑	↑	↑	↑	Monitor for altered effect of quinidine
Quinolones		↓			↓	Administer antibiotic at least 2 hours before or 6 hours after antacid
Sodium polystyrene sulfonate		↔[‡]	↔[‡]		↔[‡]	Consider alternative to antacid or space drugs apart as much as possible
Sulfonylureas			↑	↓	↑	Administer sulfonylurea 2 hours before or after antacid
Sympathomimetic amines				↑		Consider alternative antacid;monitor for enhanced effect of interacting drug
Tetracyclines	↓	↓	↓	↓	↓	Administer tetracyclines 2 hours before or 6 hours after antacids
Tocainide				↑		Monitor clinical status and electrocardiogram.

Sources: Anonymous (2001)[183]; Hansten (2001)[184] **This list is not all-inclusive.**

[†] Pharmacologic effect is ↓ (decreased) or ↑ (increased) by antacids.

[‡] Concomitant use may cause metabolic alkalosis

NONPRESCRIPTION HISTAMINE H_2 RECEPTOR ANTAGONISTS

The on-demand, short-term use of nonprescription H_2RAs, taken in doses generally one half of standard doses, are superior to placebo in controlling heartburn.[185,186] They are ineffective for preventing relapse in mixed patient populations with NERD or erosive esophagitis[158] and selected patient populations with reflux esophagitis.[125] Famotidine is also indicated for prevention of reflux symptoms provoked by certain foods or drinks.[187] In addition, famotidine 10 mg has been shown to be more effective than placebo in preventing postprandial reflux symptoms[188,189] and

reducing episodes of interrupted sleep due to nocturnal reflux.[190] The four H_2RAs that are currently approved for nonprescription use are considered to be interchangeable (see Table 18).[1]

Low-dose famotidine (10 mg) is superior to alginic acid in relieving heartburn symptoms.[191] Antacids may provide a marginally faster onset than H_2RAs; however, H_2RAs may be more palatable and longer lasting (up to 10 hours).

PRESCRIPTION HISTAMINE H_2-RECEPTOR ANTAGONISTS

Prescription H_2RAs are effective first-line drugs in a substantial proportion of patients with GERD. After 4 weeks of H_2RA therapy, symptom relief is obtained in about 31% to 40% of mixed populations of patients with NERD or uncomplicated esophagitis.[15,21,22] The H_2RAs reduce gastric acid secretion, decrease potential for esophageal mucosal damage, and promote healing. Expert opinion considers an H_2RA to be an appropriate first-line therapeutic option in patients without alarm symptoms or history of complicated GERD and who have not undergone endoscopy, have negative endoscopy, or have mild esophagitis.[2]

Some benefit may be obtained from more frequent dosing of H_2RAs[192,193]; however, most studies have found dosing frequency to have marginal effects on the efficacy of H_2RAs.[100,101,194,195] Higher than standard doses of H_2RAs provide minimal benefit over standard doses and are inferior to switching to a PPI. For further discussion on this topic, see Annotation H.

Exposure of healthy volunteers[196-200] or patients[201,202] to the H_2RAs for 1 day to several weeks has been associated with the development of tolerance to the acid suppressive effects. Previous treatment with a PPI has been reported to induce tolerance to H_2RAs.[203] Interestingly, absence of tolerance to the H_2RAs has been reported in patients with duodenal ulcers.[204,205] The mechanism of tolerance is unclear. Further studies are needed to determine the clinical impact of H_2RA tolerance in patients with GERD and other acid-related gastrointestinal disorders.

Short courses of bedtime H_2RA therapy decrease nocturnal acid breakthrough in patients being treated with twice daily PPIs for GERD.[206] After one week of therapy in healthy volunteers and patients with GERD, however, there is no difference between PPI twice daily and PPI twice daily plus bedtime H_2RA in terms of the proportion of individuals experiencing nocturnal acid breakthrough, probably due to the development of tolerance.[207] A sustained response to H_2RA therapy was observed after one month in a subgroup (4 of 16, 25%) of patients with GERD. Clinical outcomes remain to be evaluated in controlled trials. Although the addition of bedtime H_2RA to twice-daily PPI therapy has been suggested in situations where aggressive pH control may be necessary (such as extraesophageal symptoms, refractory esophagitis, and Barrett's esophagus),[208] there is insufficient evidence to support this practice for these conditions, and the available evidence suggests a lack of long-term benefit in the majority of patients with GERD.[207]

Recommended dosage regimens of the H_2RAs are shown in Table 18. Duration of acute therapy is generally 8 to 12 weeks. Patients may experience symptom relief within 2 weeks; however, most clinical trials were 6 to 12 weeks in duration, with the highest response rate seen at the end of the treatment period.

Table 18 Dosage Regimens of H_2RAs in the treatment of GERD

	RECOMMENDED ORAL DOSAGE REGIMEN	DOSAGE ADJUSTMENT IN RENAL / HEPATIC IMPAIRMENT	
DRUG	**Standard Dose**	**CrCl (ml/min)**	**Dose**
Cimetidine	400 mg b.i.d. or 800 mg q.h.s. × 12 wk	> 30 15 to 30 < 15	800 mg q.h.s. 600 mg q.h.s. 300-400 mg q.h.s.
Famotidine	20 mg b.i.d. or 40 mg q.h.s. × 6 to 12 wk	< 50	20 mg q.h.s. or 40 mg q 36 to 48 h
Nizatidine	150 mg b.i.d. or 300 mg q.h.s. × 6 to 12 wk	20 to 50	150 mg q.o.d. to q.h.s.
Ranitidine	150 mg b.i.d. or 300 mg q.h.s. × 6 to 12 wk	< 50	150 mg q.h.s.

The H_2RAs have a relatively low rate of adverse effects. Headache, dizziness, diarrhea, constipation, and mental status changes have occurred in patients taking these agents. Increases in liver enzymes may also occur. Gynecomastia has occurred in up to 1% of patients taking cimetidine for 1 month or longer, and may be related to the drug's weak antiandrogenic effect.

Drug interactions involving the H_2RAs are shown in Table 19. Cimetidine reduces the hepatic metabolism of certain drugs via inhibition of the cytochrome P450 (CYP) enzyme system. Ranitidine has intermediate affinity for the CYP system, while famotidine and nizatidine have none.

Table 19 Selected Drug Interactions with Histamine H_2 Receptor Antagonists

H_2RA	INTERACTING AGENT		EFFECT
Cimetidine	Alfentanil Amiodarone Benzodiazepines (diazepam, chlordiazepoxide, alprazolam and triazolam) β-blockers (propranolol, metoprolol, labetalol, and pindolol) Calcium channel blockers (verapamil, diltiazem, nifedipine, nimodipine, nisoldipine and nitrendipine) Carbamazepine Carmustine Cisapride Clozapine Flecainide	Lidocaine Meperidine Metformin Nicotine Sulfonylureas (glyburide, glipizide, tolbutamide) Paroxetine Phenytoin Praziquantel Procainamide Propafenone Quinidine Tacrine Theophylline Tricyclic antidepressants (desipramine, doxepin, imipramine, nortriptyline) Warfarin	↑ serum concentrations of interacting drugs; cause potentiation of therapeutic effects and in some cases, symptoms of toxicity. Monitor concurrent therapy with H_2RAs; draw serum concentrations of interacting drugs if appropriate; consider alternative to cimetidine if appropriate. Avoid concurrent use of warfarin and cimetidine.
Cimetidine	Fluconazole Itraconazole Ketoconazole		↓ serum concentrations of interacting drugs.
Ranitidine (and probably other H_2RAs.)	Cefpodoxime Cefuroxime Enoxacin Ketoconazole		↓ absorption due to ↑ intragastric pH.
Nizatidine	Salicylates		May increase salicylate concentrations in patients taking high doses of aspirin (3.9 g/d).
Ranitidine	Procainamide Sulfonylureas Warfarin		May ↑ serum concentrations or effect of interacting drugs.
Cimetidine Famotidine Nizatidine Ranitidine	Antacids Anticholinergics Metoclopramide		Interacting drugs may decrease the absorption of cimetidine and ranitidine; however, data conflict. Avoid simultaneous administration. Bioavailability of famotidine and nizatidine may be decreased, but no special precautions necessary.

Source: Anonymous (2001)[183]; Hansten (2001)[184] **This table lists the more commonly cited drug interactions and is not all-inclusive.**

PROTON PUMP INHIBITORS

The PPIs dramatically reduce gastric acid secretion by irreversibly binding to hydrogen/potassium adenosine triphosphatase in gastric parietal cells and inactivating this enzyme system. In mixed populations of patients with NERD or uncomplicated esophagitis, PPI therapy achieves symptom resolution in about 60% to 66% of patients after 4 weeks and are superior to H_2RAs.[15,21,22] In contrast to the H_2RAs, the efficacy of PPIs seems to be less affected by grade of esophagitis,[63] and the PPIs may exhibit a dose-related effect.[63,209]

Esomeprazole, the S-isomer of omeprazole, is currently indicated for the treatment or maintenance therapy of erosive esophagitis and symptomatic GERD. Although esomeprazole was found to be superior to omeprazole in a recent systematic review by the manufacturer,[210] a medical review by the FDA concluded that the results of four large, randomized trials (of which two favored esomeprazole and two showed no difference) do not support a superiority claim of esomeprazole over omeprazole.[211]

Dosing information for the PPIs is shown in Table 20.

Table 20 Dosage Regimens of Proton Pump Inhibitors in the Treatment of GERD

DRUG	RECOMMENDED ORAL DOSAGE REGIMEN		DOSAGE ADJUSTMENT IN RENAL / HEPATIC IMPAIRMENT	COMMENTS
	Initial Treatment	Maintenance		
Esomeprazole	20 to 40 mg q.d. × 4 to 8 wk; nonresponders may be treated for an additional 4 to 8 wk	20 mg q.d.	Do not exceed 20 mg/d in patients with severe hepatic impairment (Child Pugh Class C). No dosage adjustment necessary in mild to moderate hepatic impairment (Child Pugh Classes A and B).	Controlled studies of maintenance therapy did not extend beyond 6 mo. For patients who have difficulty swallowing capsules, the capsules may be opened and the intact pellets mixed with applesauce then swallowed without chewing.†
Lansoprazole	15 to 30 mg q.d. a.c. x ≤ 8 wk; nonresponders may be treated for an additional 8 wk	15 mg q.d.	Dosage adjustment should be considered in patients with severe hepatic disease	Patients with difficulty swallowing may open the capsule and sprinkle the intact granules on applesauce or mix with juice then swallow immediately.† Alternatively, a delayed release oral suspension or Simplified Lansoprazole Suspension (SLS) may be used.‡ Take doses before meals; if taken 30 min after meals, serum concentrations decrease by ~ 50%.
Omeprazole	20 mg q.d. x 4 to 8 wk; nonresponders may be treated for an additional 8 wk	20 mg q.d.	No adjustment necessary	The capsules may be opened and the granules mixed with acidic juices or applesauce and administered immediately. A Simplified Omeprazole Suspension (SOS)§ may be extemporaneously compounded.
Pantoprazole	40 mg q.d. × 8 wk; nonresponders may be treated for an additional 8 wk	40 mg q.d.	Modest drug accumulation (≤ 21%) may occur in patients with severe hepatic impairment; weigh risks of drug accumulation against potential loss of acid control if dosed q.o.d.	First PPI available for intravenous administration. Intravenous route approved for short-term (7 to 10 d), second-line treatment of GERD. There is no evidence of efficacy as first-line therapy. The intravenous dose is the same as the oral dose.
Rabeprazole	20 mg q.d. × 4 to 8 wk; nonresponders may be treated for an additional 8 wk	20 mg q.d.	Use caution in patients with severe hepatic impairment.	Controlled studies of maintenance therapy did not extend beyond 52 wk. The delayed-release tablets should be swallowed whole and not chewed, crushed, or split.

† The granules of lansoprazole and pellets of esomeprazole have also been shown to remain intact when exposed to yogurt, orange juice, or apple juice. Lansoprazole granules may also be mixed with Ensure pudding, cottage cheese, strained pears, or orange, tomato, apple, cranberry, grape, pineapple, prune, or V-8 vegetable juice.

‡ Simplified Lansoprazole Suspension (SLS): 3 mg/ml 8.4% sodium bicarbonate; stable for 14 days at room temperature or 28 days refrigerated (non-oral syringe).[212]

§ Simplified Omeprazole Suspension (SOS): 2 mg/ml 8.4% sodium bicarbonate; stable for 1 week at room temperature or 24 weeks frozen (non-oral syringe); protect from light.[213]

Some patients may require higher than standard doses to control reflux symptoms. The decision to use higher than standard doses of PPIs should be made after further diagnostic testing.

In healthy volunteers, divided-dose PPI therapy (i.e., daily dose given in two divided doses) has been shown to be superior to[214] or no different from[215] the same daily dose given once a day in terms of gastric acid suppression. An advantage in terms of clinical outcomes (symptom relief or

endoscopic healing) in patients with GERD, however, has not been demonstrated[216] or not been studied in a well-designed clinical trial.

The administration of PPIs 15 to 30 minutes before a meal is generally suggested for greater efficacy because these agents inhibit only proton pumps that have been activated, as occurs when parietal cells are stimulated by meals.[208,217]

"Resistance" to high doses of PPIs is uncommon (estimated to be 5%), and most cases are believed to probably represent inter- or intra-patient variability in pH control[208] or may be due to incorrect diagnosis. Improvement in pH control can be achieved with dosage increases. Alternative diagnoses should be considered when a patient does not respond to an adequate trial of PPI therapy.

Patients unable to take the oral PPI dosage forms have additional options for administration. The encapsulated products (esomeprazole, lansoprazole and omeprazole) allow for alternative administration through admixture of granular contents with certain foods and beverages (see Table 20). Additionally, a manufactured suspension has recently been approved (lansoprazole 15 mg and 30 mg delayed-release suspension). Patients with alternative enteral access (i.e., nasogastric tube, G-tube, etc.), may use an extemporaneously compounded, bicarbonate-based suspension of lansoprazole or omeprazole (Simplified Lansoprazole Suspension [SLS] or Simplified Omeprazole Suspension [SOS], respectively). These formulations have been demonstrated to have superior pH control and cost benefit in hospitalized patients.[218,219]

An intravenous formulation of pantoprazole is approved for the short–term (7- to 10-day), second-line treatment of GERD in hospitalized patients. The efficacy of i.v. pantoprazole in raising intragastric pH has been shown to be inferior to that of SLS in healthy volunteers[220]; clinical trials in patients with GERD have not been performed. The comparative treatment costs of i.v. pantoprazole, versus H_2RAs or suspensions, are expected to be considerably more expensive. The short-term use of i.v. pantoprazole would be appropriate for patients in whom the risk of stepping down to i.v. H_2RAs is considered to be unacceptable and who are unable to take their present PPI medication orally.

The PPIs are well tolerated. The most frequently reported side effects include diarrhea, nausea, abdominal pain, and headache. Regarding safety in pregnancy, omeprazole is category C and all other PPIs are category B.

Long-term therapy with a PPI in humans has generally not been associated with serious adverse events. Dose-related hypergastrinemia, hypochlorhydria, gastric aplasia, micronodular argyrophil cell hyperplasia, and subatrophic or atrophic gastritis have been seen in patients receiving long-term therapy with a PPI. PPI therapy increases serum gastrin concentrations by two- to four-fold. Dysplasia and neoplasia have not been observed in humans after PPI therapy for up to 11 years.[221,222] Adverse effects occurring after more than 11 years of treatment with PPIs are unknown. The drugs appear to be safe; however, there are still concerns about the long-term use of PPIs.[223] Cobalamin (vitamin B-12) absorption may be decreased in patients on long-term PPI therapy but no changes in serum concentrations have been reported to date after as many as 7 years of therapy.[224] Hypochlorhydria and long-term acid suppression have been associated with bacterial overgrowth.[225] Providers need to weigh the risks vs. benefits of using long-term PPI therapy in patients with GERD. To date, the benefits appear to outweigh the risks.

Drug interactions involving the PPIs are summarized in Table 21.

Table 21 Selected Drug Interactions with Proton Pump Inhibitors

PROTON PUMP INHIBITOR	INTERACTING DRUG(S)	EFFECT
Lansoprazole	Caffeine, Theophylline	Serum concentrations of interacting drugs may decrease due to an increase in clearance.
Esomeprazole Omeprazole	Benzodiazepines (diazepam, flurazepam, and triazolam)	Omeprazole inhibits metabolism and may cause ↑ serum concentrations of interacting drugs. May potentiate therapeutic effects and, in some cases, symptoms of toxicity.
Omeprazole	Carbamazepine, Cyclosporine, Phenytoin, Warfarin	Omeprazole inhibits metabolism and may cause ↑ serum concentrations of interacting drugs. May potentiate therapeutic effects and, in some cases, symptoms of toxicity. Monitor laboratory tests or serum concentrations of interacting drugs if appropriate; change interacting drug if needed.
Lansoprazole Omeprazole Rabeprazole	Digoxin	Inhibit acid secretion; ↑ bioavailability of interacting drug.
All agents	Delavirdine, Indinavir, Itraconazole, Ketoconazole	↓ absorption; ↓ serum concentration of interacting drug due to increase in gastric pH.
Lansoprazole Omeprazole	Sucralfate	↓ and delayed absorption of PPI; ↓ bioavailability by about 17%. Take PPIs ≥ 30 min before sucralfate.

Sources: Anonymous (2001)[183]; Hansten (2001)[184]

This list includes the more commonly cited drug interactions and is not all-inclusive.

The PPIs are metabolized by the CYP enzyme system. All of the PPIs are metabolized by the CYP3A4 and CYP2C19 enzyme subfamilies to different degrees. Omeprazole is the most likely to prolong elimination of drugs metabolized via hepatic oxidation. Lansoprazole, pantoprazole, and rabeprazole have not been involved in clinically significant CYP-mediated interactions. Esomeprazole has been involved in some interactions, but experience is limited. Reduced absorption of certain drugs may occur as a result of an increase in gastric pH due to the PPI.

PROKINETIC AGENTS

The prokinetic agents have been shown to be effective in the symptomatic treatment and prophylaxis of patients with GERD; however, their role in the treatment of GERD is limited. Prokinetic agents increase esophageal peristalsis, gastric emptying, and lower esophageal sphincter (LES) resting pressure. The pathogenesis of GERD may involve defects in esophagogastric motility, such as LES incompetence, poor esophageal clearance, and delayed gastric emptying. There is no evidence, however, that prokinetics are more effective in the presence of a documented motility disorder.

Two prokinetic agents are available for treatment of patients with GERD: metoclopramide and cisapride. Metoclopramide is FDA-approved for the short-term (4- to 12-week) treatment of adults with GERD who have had inadequate response to conventional therapy. Cisapride was withdrawn from the U.S. market in July 2000 because of the risk of serious cardiac arrhythmias and death,[226] and is obtainable only through an investigational limited access program.[a]

[a] Information on the limited access program for cisapride and enrolling patients may be obtained by calling the manufacturer and sponsor, Janssen Pharmaceutica, toll-free at (877) 795-4247.

Overall, prokinetics offer no major clinical advantages over H_2RAs alone[227] and are inferior to PPIs in terms of controlling heartburn.[228] Another study found no benefit with metoclopramide over placebo.[229]

The recommended doses of the prokinetic agents are shown in Table 22**.**

Table 22 Dosage Regimens of Prokinetic Agents in the Treatment of GERD

DRUG	RECOMMENDED ORAL DOSAGE REGIMEN	DOSAGE ADJUSTMENT IN RENAL / HEPATIC IMPAIRMENT	COMMENTS
Cisapride	Available only through limited access program and dosed according to investigational protocol.	Contraindicated in patients with renal failure.	Reports of serious adverse reactions including arrhythmias and death have occurred with cisapride in patients who are taking certain medications or have certain disorders. Refer to Table 23 for further details.
Metoclopramide	10 to 15 mg q.i.d. a.c. and q.h.s. × 8 to 12 wk	Reduce dose by 50% for CrCl < 40 ml/min	Administer 30 min prior to a meal. Metoclopramide is associated with a serious adverse effect (tardive dyskinesia) that may be irreversible; extended duration of therapy increases risk.

The frequency of adverse effects of prokinetic agents appears to be dose related. The most frequently reported adverse effects affect the gastrointestinal system, such as diarrhea and abdominal cramping, or central nervous system. Metoclopramide is associated with a 1% to 9% overall incidence of extrapyramidal side effects, including akathisia. The risk of developing tardive dyskinesia with metoclopramide and the possibility of these symptoms becoming irreversible may be related to the duration of therapy and total cumulative dose. Tardive dyskinesia may also occur following short-term therapy (i.e., months) at low doses, and is then more likely to be reversible. Cisapride is associated with potentially fatal cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation, torsades de pointes, and QT prolongation. Most (about 89%) of these patients had known risk factors, such as diseases that may predispose to arrhythmias or medications that either prolong the QT interval, inhibit the CYP3A4 enzyme system which metabolizes cisapride, or deplete electrolytes (see Table 23 for drug interactions).[226] Knowledge of these interacting drugs would be important when cisapride is prescribed under investigational protocols.

Table 23 Selected Drug Interactions with Prokinetic Agents

PROKINETIC AGENT	INTERACTING AGENTS		EFFECT / COMMENTS
Cisapride	Antidepressants (fluoxetine [controversial], fluvoxamine, nefazodone, maprotiline) Antiretroviral agents (protease inhibitors: amprenavir, indinavir, nelfinavir, ritonavir, saquinavir; and delavirdine) Azole antifungals (fluconazole, itraconazole, ketoconazole, miconazole [i.v.]) Calcium channel antagonists: diltiazem, verapamil	Histamine H_2 receptor antagonists: cimetidine Leukotriene formation inhibitors: zileutin Macrolide antibiotics (erythromycin, clarithromycin, troleandomycin) Other: grapefruit juice, isoniazid, metronidazole, quinine, quinupristin/dalfopristin, mibefradil	Inhibit cisapride metabolism Interacting agents are contraindicated with cisapride. Alternative agents Antidepressants: citalopram, paroxetine, sertraline Calcium channel antagonists: dihydropyridine calcium antagonists (except nifedipine immediate-release) Histamine H_2 receptor antagonists: Famotidine, nizatidine, ranitidine Macrolide antibiotics: azithromycin Leukotriene formation inhibitors: montelukast (a leukotriene receptor antagonist)
Cisapride	Antiarrhythmic agents Class 1A (such as quinidine and procainamide) Class III (amiodarone, sotalol) Adenosine Antidepressants (tricyclic agents such as amitriptyline; and tetracyclic agents such as maprotiline)	Antipsychotic agents (phenothiazines, haloperidol, and sertindole) Other: astemizole, bepridil, cyclobenzaprine, droperidol, nifedipine (immediate-release), sparfloxacin, terodiline, vasopressin	Prolong QT interval Interacting agents are contraindicated with cisapride.
Cisapride	Diuretics		Electrolyte abnormalities may ↑ risk of arrhythmias; any electrolyte disturbances should be corrected.
Metoclopramide	Cyclosporine		↑ concentration of cyclosporine
Metoclopramide	Alcohol, CNS depressants		↑ sedation
Metoclopramide	Narcotic analgesics		May ↓ effect of metoclopramide
Cisapride Metoclopramide	Anticholinergic agents		May ↓ effect of prokinetic agents

Sources: Anonymous (2001)[183]; Hansten (2001)[184] **This list includes the more commonly cited drug interactions and is not all-inclusive.**

Prokinetic agents increase gastrointestinal emptying and may affect the absorption and bioavailability of many drugs. Therefore, patients should be monitored frequently if they are also taking agents with a narrow therapeutic index or agents requiring special monitoring (e.g., digoxin, warfarin, cyclosporine).

COSTS OF ANTIREFLUX AGENTS

Federal contracting initiatives have reduced the cost of PPI (rabeprazole or lansoprazole) therapy. For instance, at the current federal drug prices, the monthly cost of standard-dose rabeprazole is about $5 more than that of standard-dose ranitidine (see Table 24).

Table 24 Selected Costs for Drug Therapy of GERD in Increasing Order of DoD Monthly Cost by Drug Category

DRUG	DAILY ORAL REGIMEN (Standard / High Dose)	LOWEST COST ($) PER MONTH†	
		DoD	VA
H_2 receptor antagonists			
Ranitidine	150 mg bid / 150 mg q.i.d.	1.02 / 2.04	1.41 / 2.82
Cimetidine	800 mg b.i.d. / 800 mg t.i.d.	5.16 / 7.74	5.13 / 7.70
Famotidine	20 mg b.i.d. / 40 mg b.i.d.	3.00 / 5.40	2.31 / 4.51
Nizatidine	150 mg b.i.d. / 300 mg b.i.d.	65.06 / 79.80	63.60 / 123.90
Proton pump inhibitors			
Rabeprazole	20 mg q.d. / 40 mg q.d.	19.50 / 39.00	19.50 / 39.00
Lansoprazole	30 mg q.d. / 30 mg b.i.d.	19.50 / 39.00	19.50 / 39.00
Pantoprazole	40 mg q.d. / 80 mg q.d.	26.70 / 53.40	39.90 / 79.80
Omeprazole	20 mg q.d. / 40 mg q.d.	63.30 / 100.20	63.30 / 95.40
Esomeprazole	20 mg q.d. / 40 mg q.d.	69.30 / 71.40	73.50 / 73.50
Other agents			
Metoclopramide	10 mg q.i.d.	1.38	1.09
Antacids	15 ml q.i.d. / 30 ml q.i.d.	4.80 / 9.60	4.90 / 9.80
Antacid + sodium alginate	15 ml q.i.d. / 30 ml q.i.d.	0.65 / 1.29	0.62 / 1.23

† Lowest acquisition cost (Federal Supply Schedule, National Contract, or Blanket Purchase Agreement price) as of February 2003. For current prices, check the VA Pharmacy Benefits Management Web site at http://www.vapbm.org or http://vaww.pbm.med.va.gov.

SURGICAL INTERVENTIONS

Medical therapy is the first-line management of GERD. Partly because of the concerns over the long-term safety and costs of PPI therapy, surgery performed by an experienced surgeon remains a valid alternative to long-term PPI maintenance therapy of well-documented GERD.[1] Surgical intervention, such as open or laparoscopic Nissen fundoplication (ONF or LNF, respectively), may be necessary in selected patients. A specialist should be consulted to help determine the appropriateness of antireflux surgery versus pharmacologic therapy.

Patients considering surgical treatment should be advised that surgery does not avoid the need for long-term medications in the majority of cases, and it should not be expected to be a cancer preventing procedure for those with GERD and Barrett's esophagus.[28]

A direct clinical comparison of LNF and medical therapy using PPIs is not yet available. The keys to success for LNF or other laparoscopic surgery are accurate diagnosis, proper selection of patients, and the skills and experience of the surgeon.

New, minimally invasive surgical techniques are being developed. The Bard endoscopic suturing system and the Stretta endoscopic radiofrequency device are both FDA approved. Longer term studies of the endoscopic radiofrequency technique have demonstrated good safety profile, improved quality of life scores, and decreased need for PPIs.[230-234] These techniques require further studies to determine their comparative efficacy and role in the management of GERD.

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APPENDICES

Appendix 1 Main Search Terms

Limits: English language, Human studies

Terms related to GERD: gastroesophageal reflux, gastro-esophageal reflux, gastro-oesophageal reflux, GERD, GORD, esophagitis, oesophagitis, heartburn, nonerosive, non-erosive, endoscopy-negative, NERD, ENRD, other similar terms listed on the PubMed index.

Terms related to extraesophageal GERD: extraesophageal, extra-oesophageal, supraesophageal, supra-oesophageal, asthma, cough, bronchitis, hoarseness, laryngitis, pharyngitis, sinusitis, other similar terms listed on the PubMed index.

Terms related to drugs: proton pump inhibitors, PPI, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole, H2 receptor antagonists, H2 antagonist drug(s), H2 receptor blockaders, H2 receptor blockers, H2 receptor blocking agents, histamine2 receptor antagonists, histamine2 antagonists, histamine2 blocker(s), cimetidine, famotidine, nizatidine, ranitidine, other similar terms listed on the PubMed index.

Terms related to primary care practice: general practice, primary care, community practice, community practice setting(s)

Terms related to health-related quality of life: quality of life, health related quality of life, SF-36, gastrointestinal symptoms rating scale, psychological well-being, GSRS, PGWB, quality of life in reflux and dyspepsia, QOLRAD

Appendix 2 Evaluation of Maintenance Therapy for GERD: Randomized, Double-blind, PLACEBO-CONTROLLED Trials

REFERENCE	INITIAL DISEASE SEVERITY†	INITIAL TREATMENT REGIMEN AND DURATION	RESPONSE (% Healing)	MAINTENANCE THERAPY (n), DURATION OF FOLLOW-UP	ENDOSCOPIC (OR SYMPTOMATIC) RESPONSE	TREATMENT COMPARISONS > Superior to ($p < 0.05$) = Not different from ($p > 0.05$)
		(Dose in mg unless otherwise specified)				(Total daily dose in mg unless otherwise specified)
Continuous Daily Therapy						
Mixed patient populations						
Kaul (1986)[158]	NERD and erosive esophagitis Grade 0 to 3	CTD 1600/d CTD 800/d × 12 wk	~31% ~27%	CTD 400 q.d. (14) PLAC (10) × 6 mo	~25% ~20%	CTD 400 = PLAC (NSD)
Laursen (1995)[235]	NERD or erosive esophagitis Grade 1 to 4	OME 40 / d OME 20 / d × 4 to 8 wk (nonresponders received OME 40 / d for additional 4 wk)	69% 54%	OME 20 q.d. (67) OME 10 q.d. (68) PLAC (33) × 6 mo	59% remission 35% remission 0% remission	OME 20 > PLAC ($p < 0.002$) OME 10 > PLAC ($p < 0.002$) OME 20 > OME 10 ($p < 0.002$)
Selected patient populations with NERD						
Venables (1997)[236]	NERD Grade 0 to 1	OME 20 q.d. OME 10 q.d. RAN 150 b.i.d. × 4 to 8 wk	NR	OME 10 q.d. (242) PLAC (253) × 6 mo	(27% relapse) (52% relapse)	OME 10 > PLAC, $p = 0.0001$
Selected patient populations with erosive esophagitis						
Koelz (1986)[125]	Erosive or ulcerative esophagitis	RTD 150 b.i.d. RTD 300 b.i.d. × 12 wk	70%	RTD 150 q.h.s. (33) PLAC (28) × 6 mo	42% relapse 36% relapse	95% CI (%): 19 to 56 25 to 61 RTD 150 = PLAC (NSD)
Hegarty (1997)[237]	Moderate or severe esophagitis Grade ≥ 2	RTD 300 q.i.d. RTD 300 t.i.d. RTD 150 b.i.d. × 4 to 8 wk	Overall: 59%	RTD 300 b.i.d. (95) RTD 150 b.i.d. (92) PLAC (92) × 12 mo	27% relapse 37% relapse 60% relapse	RTD 600 > PLAC, $p < 0.001$ RTD 300 > PLAC, $p = 0.002$ RTD 600 = RTD 300, $p = 0.15$ (NSD)
Simon (1994, 1995)[94,187]	Moderate to severe erosive esophagitis	FTD 40 b.i.d. FTD 20 b.i.d. PLAC × 6 to 12 wk	69% 54% 29% (at 12 wk)	FTD 40 b.i.d. (72) FTD 20 b.i.d. (69) PLAC (31) × 6 mo	11% relapse 22% relapse 62% relapse	FTD 80 > PLAC, $p < 0.001$ FTD 40 > PLAC, $p < 0.001$ FTD 80 = FTD 40, $p = 0.103$ (NSD)
Toussaint (1991)[238]	Esophagitis Grade I–IV	CIS 10 q.i.d. × 8 to16 wk	69%	CIS 10 b.i.d. (37) PLAC (43) × 6 mo	80% remission 61% remission (by symptoms and endoscopy)	CIS 10 b.i.d. = PLAC, $p = 0.06$

REFERENCE	INITIAL DISEASE SEVERITY†	INITIAL TREATMENT REGIMEN AND DURATION	RESPONSE (% Healing)	MAINTENANCE THERAPY (n), DURATION OF FOLLOW-UP	ENDOSCOPIC (OR SYMPTOMATIC) RESPONSE	TREATMENT COMPARISONS > Superior to ($p < 0.05$) = Not different from ($p > 0.05$)
		(Dose in mg unless otherwise specified)				(Total daily dose in mg unless otherwise specified)
Johnson (2001)[239]	Erosive esophagitis	ESO 20 q.d. ESO 40 q.d. OME 20 q.d. × 8 wk	89.9% 94.1% 86.9%	ESO 40 (82) ESO 20 (82) ESO 10 (77) PLAC (77) × 6 mo	93.6% remission 93.2% remission 57.1% remission 29.1% remission	95% CI (%): 87.4 to 99.7 87.4 to 99.0 45.2 to 69.0 17.7 to 40.3 ESO 40, 20, and 10 > PLAC, $p < 0.001$ ESO 40 and 20 > ESO 10 (95% CIs do not overlap)
Vakil (2001)[64]	Esophagitis, *Hp*(–)	ESO 40 q.d. ESO 20 q.d. OME 20 q.d. × 8 wk	NR	ESO 40 q.d. (92) ESO 20 q.d. (98) ESO 10 q.d. (91) PLAC (94) × 6 mo	87.9% remission 78.7% remission 54.2% remission 29.1% remission	95% CI (%): 80.4 to 95.4 69.5 to 87.8 42.9 to 65.5 17.6 to 40.6 ESO 40, 20, and 10 mg > PLAC, $p < 0.001$ ESO 40 and 20 > ESO 10 (95% CIs do not overlap)
Robinson (1996)[240]	Erosive esophagitis Grade $\geq$ 2	LAN 30 q.d. (?) × 8 wk (or erosive esophagitis w/o LAN)	NR	LAN 30 q.d. (56) LAN 15 q.d. (59) PLAC (55) × 12 mo	90% remission 79% remission 24% remission	LAN 30 > PLAC, $p < 0.0001$ LAN 15 > PLAC, $p < 0.0001$ LAN 15 = LAN 30 (NSD)
Sontag (1996), Feldman (1993), Robinson (1990)[241-243]	Erosive esophagitis resistant to H_2RAs Grade 2 to 4	Ph. I: H_2RA ≥ RAN 150 b.i.d. × 12 wk Ph. II: LAN 30 q.d. or 150 b.i.d. × 8 wk Ph. III: LAN 30 to 60 q.d. × 8 to 12 wk	Ph. I: NR Ph. II: 64% Ph. III: 73% (cumulative response NR)	LAN 15 q.d. (53) LAN 30 q.d. (54) PLAC (56) × 12 mo	67% remission 55% remission 13% remission	Time to first relapse: LAN 15 and 30 > PLAC, $p < 0.001$ LAN 15 = LAN 30 (NSD)
Bate (1995)[244]	Erosive esophagitis Grade 2 to 4	OME 20 to 40 / d × 4 to 8 wk	NR	OME 20 q.d. (68) OME 10 q.d. (60) PLAC (62) × 12 mo	74% remission 50% remission 14% remission	95% CI (%): 62 to 86 34 to 66 2 to 26 OME 20 and 10 > PLAC, $p < 0.001$ OME 10 = OME 20 (NSD)
Bardhan (1998)[146]	Erosive esophagitis Grade ≥ 2	OME 20 q.d. × 12 wk OME 40 q.d. × 12 wk if necessary	95%	OME 10 q.d. (130) PLAC (133) × 18 mo	60% remission 15% remission	OME 10 > PLAC, $p < 0.0001$
Birbara (2000)[245]	Erosive or ulcerative esophagitis	NR	NR	RAB 20 q.d. (94) RAB 10 q.d. (95) PLAC (99) × 13 mo	86% remission 77% remission 29% remission	RAB 20 > PLAC, $p < 0.001$ RAB 10 > PLAC, $p < 0.001$ RAB 10 = RAB 20 (NSD; study not powered to detect a difference)

REFERENCE	INITIAL DISEASE SEVERITY†	INITIAL TREATMENT REGIMEN AND DURATION	RESPONSE (% Healing)	MAINTENANCE THERAPY (n), DURATION OF FOLLOW-UP	ENDOSCOPIC (OR SYMPTOMATIC) RESPONSE	TREATMENT COMPARISONS > Superior to (p < 0.05) = Not different from (p > 0.05)
		(Dose in mg unless otherwise specified)				(Total daily dose in mg unless otherwise specified)
Caos (2000)[246]	Erosive or ulcerative esophagitis	NR	NR	RAB 20 q.d. (69) RAB 10 q.d. (70) PLAC (70) × 12 mo	90% remission 73% remission 29% remission	RAB 20 > PLAC, p < 0.001 RAB 10 > PLAC, p < 0.001 RAB 20 > RAB 10, p < 0.04
Blum (1993)[247]	Mild to severe esophagitis without stenosis	RAN 300 / d or Cimetidine 1600 / d or OME 40 / d × average 10 wk	NR	CIS 20 q.h.s. (151) CIS 10 b.i.d. (149) PLAC (143) × 12 mo	32% relapse 34% relapse 51% relapse	CIS 20 > PLAC, p < 0.005 CIS 10 b.i.d. > PLAC, p < 0.02 p < 0.01 (Overall treatment difference)
Thrice Weekly Therapy						
Sontag (1997)[248]	Erosive esophagitis Grade ≥ 2	OME 40 q.d. × 4 to 8 wk	91%	OME 20 q.d. (138) OME 20 q.d. × 3 d/wk (137) PLAC (131) × 6 mo	70% remission 34% remission 11% remission	OME 20 q.d. > PLAC, p < 0.001 OME 20 q.d. × 3 d/wk > PLAC, p < 0.001 OME 20 q.d. > 3 d/wk, p < 0.001
On-demand Therapy						
Lind (1999)[249]	NERD	OME 10 q.d. OME 20 q.d. PLAC × 4 wk (nonresponders received OME 20 q.d. for an additional 4 wk)	57%	OME 20 q.d. p.r.n. (139) OME 10 q.d. p.r.n. (142) PLAC (143) × 6 mo	(83% remission) (69% remission) (56% remission)	95% CI (%): 77 to 89 95% CI (%): 61 to 77 95% CI (%): 46 to 64 p < 0.01 (all intergroup differences) OME 20 p.r.n. > PLAC OME 20 p.r.n. = OME 10 OME 10 p.r.n. = PLAC
Talley (2001)[250]	NERD	ESO 20 mg/d OME 20 mg/d × 4 wk	NR	ESO 20 q.d. p.r.n. (170) PLAC (172) × 6 mo	(14% discontinued) (51% discontinued) (because of inadequate relief)	ESO 20 p.r.n. > PLAC, p < 0.0001

Drug abbreviations: CIS = Cisapride; CTD = Cimetidine; RTD = Ranitidine; ESO = Esomeprazole; LAN = Lansoprazole; OME = Omeprazole; PLAC = Placebo; RAB = Rabeprazole. **Other abbreviations**: *Hp*(–) = *Helicobacter pylori*-negative; NERD = Nonerosive reflux disease; NR = Not reported; NSD = No (statistically) significant difference (p > 0.05). † See reference for definition of severity grading.

Appendix 3 Evaluation of Maintenance Therapy of GERD: Randomized, Double-blind, ACTIVE-COMPARATOR Trials

REFERENCE	INITIAL DISEASE SEVERITY†	INITIAL TREATMENT REGIMEN(S) AND DURATION	RESPONSE	MAINTENANCE THERAPY (n) DURATION OF FOLLOW-UP	ENDOSCOPIC (SYMPTOMATIC) RESPONSE	TREATMENT COMPARISONS > Superior to (p < 0.05) = Not different from (p > 0.05) ~ Similar to (statistics not reported)
		(Dose in mg)				(Total daily dose in mg)
Continuous Daily Therapy						
Mixed patient populations						
Howden (2001)[111]	Heartburn on > 50% of the days, including > 1 moderate to severe episode	1) LAN 30 q.d. 2) LAN 30 q.d. 3) RTD 150 b.i.d. 4) RTD 150 b.i.d. × 8 wk	~75% ~72% ~61% ~60% Represents % of 24-h heartburn-free periods.	1) LAN 30 q.d. (no-step; 146) 2) RTD 150 b.i.d. (step-down; 151) 3) LAN 30 q.d. (step-up; 144) 4) RTD 150 b.i.d. (no-step; 152) × 12 wk	1) (82%) 2) (67%) 3) (74%) 4) (66%) Represents median % of 24-h heartburn-free periods.	No-step LAN > Step-up, Step-down, and No-step RTD (p < 0.01) Step-down ~ No-step RTD
Festen (1999)[147]	NERD and esophagitis Grade I to II	OME 20 q.d. RTD 300 b.i.d. × 4–8 wk	74% healed 50% healed (at 8 wk)	OME 10 q.d. (134) RTD 150 b.i.d. (129) × 12 mo	(68% remission) (39% remission)	OME 10 > RTD 300, p < 0.0001
Bate (1998)[23]	NERD and non-ulcerative esophagitis	OME 20 q.d. × 4 to 8 wk CTD 400 q.i.d. × 4 wk (Additional 4 wk of OME 20 q.d. if necessary.)	NR	OME 10 q.a.m. (77) CTD 800 q.h.s. (79) × 24 wk	(60% remission) (24% remission)	OME 10 > CTD 800, p < 0.0001
Vigneri (1995)[61]	NERD and erosive esophagitis Grade 1 to 3	OME 40 q.d. × 4 to 8 wk	NR	OME 20 q.d.(35) CIS 10 t.i.d. (35) RTD 150 t.i.d. (35) OME + CIS (35) RTD + CIS (35) × 12 mo	80% remission 54% remission 49% remission 89% remission 66% remission	OME 20 > CIS 30, p = 0.02 OME 20 > RTD 450, p = 0.003 OME 20 + CIS 30 > CIS 30, p = 0.003 OME 20 + CIS 30 > RTD 450, p < 0.001 OME 20 + CIS 30 > RTD 450 + CIS 30, p = 0.03 RTD 450 + CIS 30 > RTD 450, p = 0.05

REFERENCE	INITIAL DISEASE SEVERITY†	INITIAL TREATMENT REGIMEN(S) AND DURATION	RESPONSE	MAINTENANCE THERAPY (n) DURATION OF FOLLOW-UP	ENDOSCOPIC (SYMPTOMATIC) RESPONSE	TREATMENT COMPARISONS > Superior to (p < 0.05) = Not different from (p > 0.05) ~ Similar to (statistics not reported)
		(Dose in mg)				(Total daily dose in mg)
Selected patient populations with erosive esophagitis						
Gough (1996)[152]	Erosive esophagitis Grade 2 or 3	LAN 30 q.d. × 8 wk	~83% healed	LAN 15 q.d. (86) LAN 30 q.d. (75) RTD 300 b.i.d. (74) × 12 mo	31.4% relapse 20.0% relapse 67.6% relapse	Time to endoscopic relapse: LAN 15 > RTD 600, p < 0.001 LAN 30 > RTD 600, p < 0.001 LAN 15 = LAN 30, p = 0.11
Hallerback (1994)[153]	Erosive esophagitis Grade ≥ 2	OME 20 to 40 q.d. × 8 to 12 wk	Up to 95%	OME 10 q.d. (133) OME 20 q.d. (131) RTD 150 b.i.d. (128) × 12 mo	(62% remission) (72% remission) (45% remission)	OME 10 > RTD 300, p < 0.005 OME 20 > RTD 300, p < 0.001
Annibale (1996)[251]	Erosive esophagitis Grade 2 to 3	OME 20 q.d. × 4, 8, or 12 wk	NR	OME 20 q.d. (102) RTD 150 b.i.d. (103) × 6 mo	(89.2% remission) (75.7% remission)	OME 20 > RTD 300, p < 0.001
Lundell (1991)[252]	Esophagitis unresponsive to H_2RAs Grade ≥ 2	OME 40 q.d. RTD 300 b.i.d. × 4 to 12 wk	90% healed 47% healed	OME 20 q.d. (46) RTD 150 b.i.d. (22) × 12 mo	67% remission 10% remission	OME 20 > RTD 300, p < 0.0001
Adamek (2001)[151]	Esophagitis Grade II to III	PAN 40 q.d. × 8 wk (If *Hp*(+), PMC x 1 wk for eradication therapy then PAN 40 q.d. × 7 wk.)	80.3% 95% CI: 76.0 to 84.1% (healed and symptomatically relieved)	ITT analysis: PAN 20 q.a.m. (178) RTD 150 q.p.m. (94) × 12 mo Did/did not receive eradication therapy: PAN 20 63/115 RTD 150 33/61	34% relapse 66% relapse Did/did not receive eradication therapy: 39%/31% relapse 47%/75% relapse	PAN 20 > RTD 150, p < 0.0001 Patients who received eradication therapy: PAN 20 = RTD 150 (p = 0.2978) Patients who did not receive eradication therapy: PAN 20 > RTD 150 (p = 0.0001)
Jaspersen (1998)[253]	Complicated esophagitis with stricture	OME 20 b.i.d. until esophagitis healing and dysphagia relief (in combination with weekly esophageal dilatation)	83% healed	OME 20 b.i.d. (10) LAN 30 b.i.d. (10) PAN 40 b.i.d. (10) × 4 wk	90% remission 20% remission 30% remission (by endoscopy and symptoms)	OME 40 > LAN 60, p < 0.01 OME 40 > PAN 80, p < 0.01
Thjodleifsson (2000)[254]	Erosive esophagitis	NR	NR	OME 20 q.d. (83) RAB 10 q.d. (82) RAB 20 q.d. (78) × 52 wk	5% relapse 5% relapse 4% relapse	OME 20 = RAB 10 = RAB 20 (NSD)

REFERENCE	INITIAL DISEASE SEVERITY†	INITIAL TREATMENT REGIMEN(S) AND DURATION	RESPONSE	MAINTENANCE THERAPY (n) DURATION OF FOLLOW-UP	ENDOSCOPIC (SYMPTOMATIC) RESPONSE	TREATMENT COMPARISONS > Superior to (p < 0.05) = Not different from (p > 0.05) ~ Similar to (statistics not reported)
		(Dose in mg)				(Total daily dose in mg)
Thrice Weekly Therapy						
Dent (1994)[255]	Erosive esophagitis, Grade ≥ 2	OME 20 q.d. × 4 to 8 wk	81% healed	OME 20 q.d. (53) OME 20 3 d/wk (weekends) (55) RTD 150 b.i.d. (51) × 12 mo	89% remission 32% remission 25% remission	Difference 57%, 95% CI (%): 42 to 71 (OME 20 q.d. > 3 d/wk) Difference 64%, 95% CI (%): 50 to 78 (OME 20 > RTD 300) p < 0.001 (Both treatment comparisons)
Intermittent Therapy						
Bardhan (1999)[17]	NERD or erosive esophagitis Los Angeles grade A to C	RTD 150 b.i.d. OME 10 q.d. OME 20 q.d. × 2 wk (nonresponders received an additional 2 wk of RTD 300 b.i.d. or OME 20 q.d.)	26% healed 40% healed 55% healed	RTD 150 b.i.d. (229) OME 10 q.d. (227) OME 20 q.d. (221) Treatment × 2 to 4 wk upon symptomatic relapse. Follow-up × 12 mo	(47% completed) (46% completed) (48% completed)	RAN 300 ~ OME 10 ~ OME 20 (p-value NR)

Drug abbreviations: CIS = Cisapride; CTD = Cimetidine; RTD = Ranitidine; ESO = Esomeprazole; LAN = Lansoprazole; OME = Omeprazole; PMC = Combination therapy with Pantoprazole 40 mg b.i.d., Metronidazole 400 mg b.i.d., and Clarithromycin 250 mg b.i.d.; PAN = Pantoprazole; PLAC = Placebo; RAB = Rabeprazole. **Other abbreviations**: *Hp*(+) = *Helicobacter pylori*-positive; ITT = Intent-to-treat; NERD = Nonerosive reflux disease; NR = Not reported; NSD = No (statistically) significant difference (p > 0.05). † See reference for definition of severity grading