NATIONAL GUIDELINE CLEARINGHOUSE™ (NGC) GUIDELINE SYNTHESIS

DIAGNOSIS AND TREATMENT OF GASTROESOPHAGEAL REFLUX DISEASE (GERD)

Guidelines

1. **American Society for Gastrointestinal Endoscopy (ASGE)**. Role of endoscopy in the management of GERD. Gastrointest Endosc 2007 Aug;66(2):219-24. [41 references]
2. **New Zealand Guidelines Group (NZGG)**. Management of dyspepsia and heartburn. Wellington (NZ): New Zealand Guidelines Group (NZGG); 2004 Jun. 119 p. [333 references]
3. **University of Michigan Health System (UMHS)**. Gastroesophageal reflux disease (GERD). Ann Arbor (MI): University of Michigan Health System; 2007 Jan. 10 p. [9 references]

INTRODUCTION

A direct comparison of American Society for Gastrointestinal Endoscopy (ASGE), New Zealand Guidelines Group (NZGG), and University of Michigan Health System (UMHS) recommendations for diagnosis and management of GERD is provided in the tables, below.

The guidelines differ slightly in scope. The ASGE and UMHS guidelines address only GERD, whereas the NZGG guideline addresses other causes of dyspepsia, including undifferentiated and non-ulcer dyspepsia, peptic ulcer disease, and *H. pylori*. The ASGE guideline also includes recommendations for Barrett's esophagus. This synthesis is limited to recommendations for the diagnosis and treatment of GERD.

The tables below provide a side-by-side comparison of the key attributes of each guideline, including specific interventions and practices that are addressed. The language used in these tables, particularly in Table 4, Table 5 and Table 6, is in most cases taken verbatim from the original guidelines:

- Table 1 provides a quick-view glance at the primary interventions considered by each group.
- Table 2 provides a comparison of the overall scope of the guidelines.
- Table 3 provides a comparison of the methodology employed and documented by the groups in developing their guidelines.
- Table 4 provides a more detailed comparison of the specific recommendations offered by each group for the topics under consideration in this synthesis, including:
    - Clinical Presentation and Diagnostic Testing
    - Diagnostic Classification Schemes

    - Initial Empiric Trial and Pharmacologic Treatment
    - Lifestyle Modification and Adjunctive Therapy
    - Surgery and Endoscopic Therapies
    - Supporting References
- Table 5 lists the potential benefits and harms associated with the implementation of each guideline as stated in the original guidelines.
- Table 6 presents the rating schemes used by the guideline groups to rate the level of evidence and/or the strength of the recommendations.

A summary discussion of the areas of agreement and areas of differences among the guidelines is presented following the content comparison tables.

Abbreviations used in the text and table:

- ASGE, American Society for Gastrointestinal Endoscopy
- BE, Barrett's esophagus
- BID, twice a day
- EGD, esophagogastroduodenoscopy
- GERD/GORD, gastroesophageal reflux disease
- GI, gastrointestinal
- *H. pylori, helicobacter pylori*
- H_2RA, histamine H_2 receptor antagonist
- NERD, non-erosive reflux disease
- NZGG, New Zealand Guidelines Group
- OGD, oesophago-gastro duodenoscopy
- OTC, over the counter
- PPI, proton pump inhibitor
- RCT, randomized controlled trial
- UMHS, University of Michigan Health System

TABLE 1: COMPARISON OF INTERVENTIONS AND PRACTICES CONSIDERED
("✓" indicates topic is addressed)

	ASGE (2007)	NZGG (2004)	UMHS (2007)
Clinical Presentation and Diagnostic Testing	✓	✓	✓
Diagnostic Classification Schemes	✓	✓	✓
Initial Empiric Trial and Pharmacologic Treatment	✓	✓	✓
Lifestyle Modification and Adjunctive Therapy		✓	✓
Surgery and Endoscopic Therapies	✓	✓	✓

TABLE 2: COMPARISON OF SCOPE AND CONTENT	
Objective and Scope	
ASGE (2007)	To discuss the use of endoscopy for the diagnosis and management of GERD
NZGG (2004)	To promote up-to-date recommendations for the safe and efficient management of individuals with dyspepsia and heartburn
UMHS (2007)	To implement a cost-effective and evidence-based strategy for the diagnosis and treatment of GERD
Target Population	
ASGE (2007)	• United States • Patients with GERD
NZGG (2004)	• New Zealand • Individuals with dyspepsia and heartburn
UMHS (2007)	• United States • Adults with suspected or confirmed GERD
Intended Users	
ASGE (2007)	Physicians
NZGG (2004)	Advance Practice Nurses Health Care Providers Nurses Pharmacists Physician Assistants Physicians
UMHS (2007)	Advanced Practice Nurses

	Nurses Pharmacists Physician Assistants Physicians

TABLE 3: COMPARISON OF METHODOLOGY	
Methods Used To Collect/Select the Evidence	
ASGE (2007)	*Hand-searches of Published Literature (Primary Sources)* *Searches of Electronic Databases* *Described Process:* In preparing this guideline, a search of the medical literature was performed using PubMed, supplemented by accessing the "related articles" feature of PubMed. Additional references were obtained from the bibliographies of the identified articles and from recommendations of expert consultants. When little or no data exist from well-designed prospective trials, emphasis is given to results from large series and reports from recognized experts. *Number of Source Documents:* Not stated *Number of References:* 41
NZGG (2004)	*Hand-searches of Published Literature (Primary Sources)* *Hand-searches of Published Literature (Secondary Sources)* *Searches of Electronic Databases* *Searches of Unpublished Data* *Described Process:* Groups developing the guideline conducted literature searches, including current computer searches (Medline, EMBASE) and surveys of review publications (Cochrane Library, Bandolier). Unpublished papers and research still under way were examined, as well as published papers. Other dyspepsia guidelines published between 1998 and June 2003 were perused to ensure appropriate information was considered in developing the New Zealand version of the Guideline. As updates of

	Cochrane Reviews became available, they were also included in the review process to ensure new developments had been considered. *Number of Source Documents:* Not stated *Number of References:* 333
UMHS (2007)	*Hand-searches of Published Literature (Primary Sources)* *Searches of Electronic Databases* *Described Process:* The literature search began with the results of the literature search performed through September 2000 for the previous version of this guideline. The results of two more recent literature searches were reviewed: • American College of Gastroenterology: Updated Guidelines for the diagnosis and treatment of gastroesophageal reflux disease (2005), literature search through early 2004. • VA/DOD Clinical Practice Guideline for the Management of Adults with Gastroesophageal Reflux Disease in Primary Care Practice (2003), literature search through May 2002. A search of more recent literature was conducted prospectively on Medline from January 2004 through May 2006 using the major keywords of: gastroesophageal reflux disease (or GERD, NERD, NEED [non-erosive esophageal disease]), human adults, English language, clinical trials, and guidelines. Terms used for specific topic searches within the major key words included: symptoms (atypical symptoms, heartburn, retrosternal burning sensation precipitated by meals or a recumbent position, hoarseness, laryngitis, sore throat, chronic cough, chest pain, bronchospasm/asthma, dental erosions) nocturnal (or nocturnal breakthrough, night time), endoscopy, pH recording, manometry, provocative testing (Bernstein's), video esophagography, empiric/therapeutic trial to acid suppression, lifestyle measures/treatment (avoiding fatty foods, chocolate, peppermints, ethanol-containing beverages; recumbency for 3 hours after a meal; elevating head of bed; weight loss), antacids, alginic acid (gaviscon), carafate, prokinetic agents (cisapride, metoclopramide, bethanechol, domperidone), H2 receptor antagonists (nizatidine, ranitidine, famotidine, cimetidine), proton pump inhibitors (omeprazole, lansoprazole, rabeprazole, pantoprazole, esomeprazole), fundoplication (open vs. laparoscopy; endoscopic antireflux procedures), Barrett's esophagus (screening, surveillance). Detailed search terms and strategy available upon request. The search was conducted in components each keyed to a specific causal link in a formal problem structure (available upon request). The search was supplemented with very recent information available

	to expert members of the panel, including abstracts from recent meetings and results of clinical trials. Negative trials were specifically sought. The search was a single cycle. *Number of source documents:* Not stated *Number of references:* 9
Methods Used to Assess the Quality and Strength of the Evidence	
ASGE (2007)	Expert Consensus (Committee)
NZGG (2004)	Weighting According to a Rating Scheme (Scheme Given - Refer to Table 6)
UMHS (2007)	Weighting According to a Rating Scheme (Scheme Given - Refer to Table 6)
Methods Used to Analyze the Evidence	
ASGE (2007)	*Systematic Review* *(Process not described)*
NZGG (2004)	*Review of Published Meta-Analyses* *Systematic Review with Evidence Tables* *Described Process:* The Core Committee of the Dyspepsia and GORD Working Party established four regional committees, each including general practitioner, gastroenterology and surgical input, to develop the guidelines for specific areas: Dunedin/Christchurch for GORD; Wellington for undifferentiated dyspepsia and non-ulcer dyspepsia (NUD); Waikato/Rotorua/Bay of Plenty for non-steroidal anti-inflammatory drug (NSAID)-related dyspepsia; and Auckland for *Helicobacter pylori* and peptic ulcer. The four regional working groups each established a systematic search of the literature. Each developed their evidence tables from which their recommendations were made. When the core committee convened they made a decision that the evidence tables would not be published nor would they include the level of evidence for each study in the guideline text. Rather, the committee would put its emphasis on producing a workbook style guideline with detailed references for those who wish to delve into the original research.
UMHS (2007)	*Review of Published Meta-Analyses*

	Systematic Review *Described Process:* Conclusions were based on prospective RCTs if available, to the exclusion of other data. If RCTs were not available, observational studies were admitted to consideration. If no such data were available for a given link in the problem formulation, expert opinion was used to estimate effect size.
Methods Used to Formulate the Recommendations	
ASGE (2007)	*Expert Consensus* *Described Process:* Guidelines for appropriate utilization of endoscopy are based on a critical review of the available data and expert consensus.
NZGG (2004)	*Expert Consensus* *Described Process:* The drafts of the four regional working groups were developed between 1998 and 2001 by which time they had been submitted to the Core Committee for review. Decisions were made by consensus of the various groups, and eventually with the Core Committee. These were then collated and edited by members of the Core Committee and a professional editor/writer. The edited copies were returned to the four working groups to ensure they had maintained their original interpretation. Opportunity was given to update the information with the final drafts being returned in mid-2002.
UMHS (2007)	*Expert Consensus* *(Process not described)*
Major Outcomes Considered	
ASGE (2007)	• Accuracy and specificity of diagnostic tests • Incidence and economic impact of GERD • Cost-effectiveness of endoscopic evaluation, screening and/or treatment • Safety of endoscopic procedures
NZGG (2004)	• Sensitivity and specificity of OGD and diagnostic tests for *H. pylori* • Healing rates with various treatments for erosive oesophagitis • Effect of proton pump inhibitors and histamine type$_2$ receptor antagonists on dyspepsia and heartburn • *H. pylori* eradication rates with various drug regimens

	• Recurrence rates of GORD and peptic ulcer • Metronidazole resistance rates
UMHS (2007)	• Sensitivity and specificity of diagnostic tests • Rate of symptomatic relief • Esophagitis healing rates • Medication and treatment side effects
Financial Disclosures/Conflicts of Interest	
ASGE (2007)	Not stated
NZGG (2004)	No current competing interests were reported by any member of the guideline development team.
UMHS (2007)	The University of Michigan Health System endorses the Guidelines of the Association of American Medical Colleges and the Standards of the Accreditation Council for Continuing Medical Education that the individuals who present educational activities disclose significant relationships with commercial companies whose products or services are discussed. Disclosure of a relationship is not intended to suggest bias in the information presented, but is made to provide readers with information that might be of potential importance to their evaluation of the information. **Team Members; Relationship; Company** Joel J. Heidelbaugh, MD (None) Arvin Gill (None) R. Van Harrison, PhD (None) Timothy T. Nostrant, MD; Consultant; Astra-Zeneca, Janssen (J & J), Sartoris, Tapp (Takeda), Wyeth

TABLE 4: COMPARISON OF RECOMMENDATIONS FOR THE EVALUATION/DIAGNOSIS AND TREATMENT/MANAGEMENT OF GERD
CLINICAL PRESENTATION AND DIAGNOSTIC TESTING

ASGE (2007)	**Summary** GERD can be diagnosed on the basis of typical symptoms without the need for diagnostic testing, including endoscopy **(1C)**. Endoscopy is recommended for patients who have symptoms suggesting complicated GERD or alarm symptoms **(2A)**. Endoscopic findings of reflux esophagitis should be classified according to an accepted grading scale or described in detail **(3)**. Endoscopy should be considered in patients at risk for BE **(2C)**. Biopsy must be performed to confirm endoscopically suspected BE **(2B)**. Endoscopic biopsy specimens should not be obtained from an endoscopically normal tissue to exclude BE **(2B)**. For patients with established BE of any length and with no dysplasia, after 2 consecutive examinations within 1 year, an acceptable interval for additional surveillance is every 3 years **(3)**. **Indications for Endoscopic Evaluation** A diagnosis of GERD can be made based on a history of classic symptoms and favorable response to antisecretory medical therapy. It is important to note that epigastric pain can be the major symptom of GERD. If the patient's history is typical for uncomplicated GERD, an initial trial of empiric medical therapy is appropriate prior to endoscopy in most patients. Endoscopy at presentation should be considered in patients who have symptoms suggestive of complicated disease or those at risk for BE. Failure to respond to appropriate antisecretory medical therapy or the presence of other clinical signs suggestive of complicated GERD should prompt evaluation with EGD and consideration of other diagnostic modalities, including ambulatory pH monitoring, esophageal manometry, and multichannel impedance testing. The indications for EGD in patients with GERD are listed in Table 2 of the original guideline document. Endoscopy should also be considered in the evaluation and management of patients with suspected extra-esophageal manifestations of GERD who present with symptoms such as choking, coughing, and hoarseness. Additionally, EGD may be necessary for the detection or exclusion of erosive esophagitis, peptic strictures, esophageal cancer, gastric outlet obstruction, and other potentially significant upper-GI tract findings. It has been proposed that a baseline EGD should be performed in patients with GERD requiring continuous acid-suppressive therapy, especially after recurrence of symptoms upon

	withdrawal of successful medical therapy. Such a recommendation is not universally accepted, however, and one must also consider associated drawbacks of EGD, such as the potential physical risks, financial costs, and limited access to the procedure. There is also a paucity of outcomes research to suggest that early or even once-in-a-lifetime EGD has a favorable effect upon the management, course, or health-related quality of life of patients with typical symptoms of GERD without alarm features. Endoscopy is often performed as part of the preoperative evaluation of patients being considered for antireflux surgery, for the placement of a wireless esophageal pH monitoring system (as described in a recent technology status evaluation report), and is an inherent part of various endoscopic antireflux procedures. **Diagnosis and Classification of GERD** When esophagitis is defined endoscopically, biopsy specimens of the mucosa should be obtained under the following circumstances: underlying immunocompromised state, irregular or deep ulceration present, proximal distribution of esophagitis, presence of a mass lesion or nodularity, an irregular or malignant-appearing stricture. In these situations, forceps biopsy and/or brush cytology specimens are necessary to exclude other diagnoses, including infectious etiologies and malignancy. Historically, follow-up EGD for patients with GERD with esophagitis was reserved for patients whose symptoms failed to respond to medical therapy, those who had severe esophagitis or an esophageal ulcer, or for those who needed additional biopsy to clarify a diagnosis. It has recently been suggested, however, that there may be a role for repeat EGD after adequate medical therapy has achieved mucosal healing in patients with esophagitis, specifically to exclude BE.
NZGG (2004)	**<u>Initial Management of Undifferentiated Dyspepsia</u>** **GPP** - If there is heartburn and dyspepsia, treat as GORD in the first instance. **<u>GORD</u>** **GORD Symptoms** Consider GORD in people with: • Heartburn (burning sensation radiating from the epigastrium towards the neck) **(A)** • Non-cardiac chest pain, asthma, chronic cough, hoarseness of voice, and erosion of teeth. **(B)** **GPP** - Exclude people with alarm signals from empiric therapy, and

	refer for OGD. Alarm Signals • Weight loss • Persistent regurgitation of food or vomiting • Dysphagia • Symptoms of GI bleeding (haematemesis or melaena). **Initial Management: Empiric Therapy** The presence of alarm symptoms should result in urgent referral for OGD. People with persistent heartburn and no alarm features may be further evaluated with a simple questionnaire (Appendix A in the original guideline document). Although this has been shown to substantially facilitate the diagnosis of GORD, it is seldom used in clinical practice. OGD Investigation As the incidence of cancer is extremely low in younger people but increases with age, the person's age becomes a risk factor for cancer, and the age of 50 years should be considered as a guide for referral for OGD. In addition, all people with alarm signals (see Chapter 2: *Undifferentiated Dyspepsia* in the original guideline document) should be investigated with OGD. Findings at OGD should not be used as the definitive criteria for the primary diagnosis of GORD. As at least 50% of people with symptomatic GORD do not have inflammatory damage at OGD, the procedure is not a sensitive tool for diagnosis. **Further Investigation** *24-Hour Ph Telemetry* Currently, 24-hour pH telemetry should be used to investigate high-dosage treatment failures or to assess individuals with grade-0 GORD prior to considering surgery (usually combined with manometry). People with GORD (all grades) not responding to high-dosage twice-daily PPIs and with signs of "acid break-through" (particularly at night) demonstrated on pH telemetry while on medication, need the maximum twice-daily dose of PPIs, as well as nocturnal H_2RA.
UMHS (2007)	**Diagnosis** **History.** A well-taken history is essential in establishing a diagnosis

	of GERD. If the classic symptoms of heartburn and acid regurgitation clearly dominate a patient's history, they can help establish the diagnosis of GERD with sufficiently high specificity, although sensitivity of clinical history remains low compared to 24-hour pH monitoring. The presence of atypical symptoms (see Table 1 in the original guideline document), although common, cannot sufficiently support the clinical diagnosis of GERD. *[B]* **Testing.** No gold standard exists for the diagnosis of GERD *[A]*. Although pH probe is accepted as the standard with a sensitivity of 85% and specificity of 95%, false positives and false negatives still exist *[B]*. Endoscopy lacks sensitivity in determining pathological reflux. Barium radiology has limited usefulness in the diagnosis of GERD and is not recommended *[B]*. **Rationale for Recommendations** **Endoscopy.** Endoscopy should be considered in those who present with warning symptoms (see Table 2 in the original guideline document) and who are suspected to have complications from GERD. Further testing should also occur for patients who do not respond to therapy, need continuous chronic therapy and have risk factors for BE. Repeating endoscopy is likely not to be worthwhile following a normal result. **PH probe.** Patients with endoscopic-negative GERD and who do not respond to medications are best evaluated by ambulatory pH monitoring. The purpose for pH probe must be defined before proceeding: is it to diagnose GERD or to determine the adequacy of therapy. The test should be performed off therapy if the diagnosis is under question. The test should be performed on therapy if one is trying to determine the adequacy of treatment. The major indication for performing 24 ambulatory pH monitoring is in documenting treatment failures, either to antireflux surgery or medical management. **Other diagnostic modalities.** Other diagnostic modalities include manometry, Bernstein's test, and gastroesophageal scintigraphy. Due to their many limitations, these tests should not be routinely ordered. Barium swallow should not be used in the evaluation of GERD although it was commonly used in the past. It is useful in the evaluation of dysphagia but limited in its ability as a screening test for GERD, as are all the aforementioned modalities.
DIAGNOSTIC CLASSIFICATION SCHEMES	

ASGE (2007)	Endoscopic findings of reflux esophagitis should be classified according to an accepted grading scale or described in detail **(3)**. **Diagnosis and Classification of GERD** There are several classification systems for grading the endoscopic severity of erosive reflux esophagitis and associated complications (see below). These classification systems have been primarily used in clinical trials to study the efficacy of medical therapy as treatment of reflux esophagitis. However, these systems are useful in clinical practice for documenting disease severity. Currently, the most commonly used systems are the Los Angeles (LA) classification and the Savary-Miller classification, with the latter being used predominantly in Europe. The LA classification has several advantages. First, it has been shown to be reliable, with good intra- and inter-observer agreement when tested among expert and inexperienced endoscopists. Second, when using this system, the severity of esophagitis has been demonstrated to correlate with the extent of esophageal acid exposure determined by 24-hour pH monitoring. These 2 systems avoid the use of erythema as a descriptor due to its nonspecific language. It is strongly recommended that the endoscopist describe the extent of endoscopic abnormalities, either through the use of an accepted grading system or by a detailed description of the endoscopic findings. **The modified Los Angeles classification of GERD** A. One (or more) mucosal break no longer than 5 mm that does not extend between the tops of 2 mucosal folds B. One (or more) mucosal break more than 5 mm that does not extend between the tops of 2 mucosal folds C. One (or more) mucosal break that is continuous between the tops of 2 or more mucosal folds but that involves less than 75% of the circumference D. One (or more) mucosal break that involves at least 75% of the esophageal circumference **The modified Savary-Miller classification of GERD** I. Single or isolated erosive lesion, oval or linear, but affecting only 1 longitudinal fold II. Multiple erosive lesions, noncircumferential, affecting more than 1 longitudinal fold, with or without confluence III. Circumferential erosive lesions IV. Chronic lesions including ulcer(s), stricture(s), and/or short esophagus, alone or associated with lesions of grades I to III V. Columnar epithelium in continuity with the Z line, noncircular, star-shaped, or circumferential, alone or associated with lesions

	grades I to IV
NZGG (2004)	The appearance of mucosal breaks on inspection at OGD is usually defined using the Los Angeles classifications (see below). Grades 0 to B indicate that complications are most unlikely to develop, while stricture and bleeding are almost always confined to people with grades C and D. The older Savary-Miller classification (see below) of oesophagitis is still used by many endoscopists. It has similar gradings of oesophagitis (I to IV), although grade II is roughly equivalent to the Los Angeles classification C. People with a history of heartburn (2 or more times a week for over 6 months) and normal OGD are considered to have grade 0 GORD. **Los Angeles endoscopic classifications of oesophagitis** 0. Normal endoscopic findings A. One or more mucosal breaks confined to the mucosal folds, each no longer than 5 mm B. At least 1 mucosal break more than 5 mm long confined to the mucosal folds but not continuous between the tops of 2 mucosal folds C. At least 1 mucosal break continuous between the tops of 2 or more mucosal folds but not circumferential D. Circumferential mucosal break **Savary-Miller endoscopic classification of oesophagitis** I. One or more supravestibular, non-confluent mucosal lesions accompanied by erythema, exudate, or superficial erosion II. Erosive and exudative mucosal lesions are confluent but do not cover the entire circumference of the oesophagus III. Erosive and exudative lesions cover the entire circumference of the mucous membrane leading to inflammatory infiltration of the wall without stricture IV. Appearance of chronic mucosal lesions (ulcers, fibrosis of walls, stricture, short oesophagus, scarring without columnar epithelium)
UMHS (2007)	Esophagitis is best defined by the LA classification system and identifies the degree to which mucosal breaks (erosions or ulcerations) occur, graded in severity from A to D, with D being the most severe. Specific definitions are: A. One or more mucosal breaks no longer than 5 mm, none of which extends between the tops of the mucosal folds B. One or more mucosal breaks more than 5 mm long, none of which extends beyond the tops of two mucosal folds C. Mucosal breaks that extend between the tops of two or more

	mucosal folds, but which involves less than 75% of the esophageal circumference D. Mucosal breaks which involve at least 75% of the esophageal circumference
INITIAL EMPIRIC TRIAL AND PHARMACOLOGIC TREATMENT	
ASGE (2007)	In patients with uncomplicated GERD, an initial trial of empiric medical therapy is appropriate **(1C)**.
NZGG (2004)	**Initial Management with Empiric Therapy** **A** - If the person's symptoms are suggestive of GORD, treat with a step-down drug regimen, usually in 4- to 8-week steps: • Step 1. Full-dose PPI (omeprazole 20 mg, lansoprazole 30 mg, pantoprazole 40 mg) daily • Step 2. Half-dose PPI • Step 3. H_2RAs (famotidine 20 to 40 mg, ranitidine 150 to 300 mg) twice daily • Step 4. Antacids/alginate **B** - If there is no response to full-dose PPI therapy, double the dose. **B** - Continue treatment for at least 3 to 6 months. **B** - If the person fails to respond or if symptoms recur within 1 month after end of treatment, consider OGD rather than long-term empiric therapy. **GPP** - Exclude people with alarm signals from empiric therapy, and refer for OGD. <u>Initial Management: Empiric Therapy</u> A trial of empiric therapy is justified in people aged <50 years presenting with typical GORD symptoms in the absence of alarm signals. In ascending order of potency and efficacy, the choice of drugs available includes: antacid/alginate, H_2RAs (single then double dose, both twice daily), prokinetics, PPIs (half, standard, double doses), and combinations of PPIs and H_2RAs or prokinetic agents (see Appendix B in the original guideline document). Prokinetics (e.g., domperidone and cisapride) are comparable in efficacy with H_2RAs, but cisapride is no longer favoured because of rare but potentially serious adverse effects. It also requires specialist recommendation in New Zealand. Many studies have demonstrated that PPIs provide more symptom

	relief and better healing than the other treatments. **"Step-Down" and "Step-Up" Treatment Options** There is a choice between the so-called "step-down" and "step-up" treatment regimens. The step-down approach, starting with a standard dose of PPI (taken 15 to 30 minutes before breakfast with water) and then gradually stepping down to less potent drugs, is recommended. The initial treatment trial should cover at least 2 to 4 weeks, but the dosage may be continued for 6 to 8 weeks in total before step-down is attempted, according to symptom control. Eventual withdrawal of medication is recommended after 3 to 6 months, as approximately 20% of people may not experience recurrence of symptoms. If the symptoms persist or recur after three months of high-dose empiric treatment, the person should be referred for OGD. **Treatment of GORD Diagnosed After OGD** **A** - People with grades 0, A, and B • Treat with a step-down drug regimen (See Algorithm 3 in the original guideline document) • If symptoms recur at stepped-down dosage, continue on lowest effective dose; intermittent therapy may control symptoms. People with grades C and D • Treat with ongoing continuous full-dose PPI treatment. **B** - If high dose PPI treatment fails, reevaluate symptoms and consider 24-hour pH telemetry. **B** - In people with Barrett's oesophagus or unresolved complications (grade D), reevaluate with OGD if necessary.
UMHS (2007)	**<u>Diagnosis</u>** **Therapeutic trial.** An empiric trial of acid suppression therapy can identify patients with GERD who do not have alarm symptoms *[A]* and may be helpful in the evaluation of those with atypical manifestations of GERD, specifically, noncardiac chest pain (NCCP) *[B]*.

Treatment

Pharmacologic treatment. H_2RAs, PPIs, and prokinetics have proven efficacy in the treatment of GERD *[A]*. Past prokinetics have been as effective as H_2RAs but are currently unavailable *[A]*. Carafate and antacids are ineffective *[A]*, but may be used as supplemental acid-neutralizing agents for certain patients with GERD *[D]*.

- NERD. Step-up (H_2RAs followed by a PPI if no improvement) and step-down (PPI followed by the lowest dose of acid suppression) therapy are equally effective for both acute treatment and maintenance *[C]*. Costs for step-down treatment are mainly medications, while step-up treatment requires more frequent endoscopy. On demand (patient-directed) therapy is the most cost-effective strategy.
- Documented erosive esophagitis. Initial PPI therapy is the treatment of choice for acute and maintenance therapy for patients with documented erosive esophagitis *[A]*.
- PPIs should be taken 30 to 60 minutes prior to a meal to optimize effectiveness *[B]*.

Follow up

Symptoms unchanged. If symptoms remain unchanged in a patient with a prior normal endoscopy, repeating endoscopy has no benefit and is not recommended *[C]*.

Warning signs. Patients with warning signs and symptoms suggesting complications from GERD (refer to Table 2 in the original guideline document) should be referred to a GERD specialist.

Risk for complications. Further diagnostic testing (e.g., EGD, pH monitoring) should be considered in patients who do not respond to acid suppression therapy *[C]* and in patients with a chronic history of GERD who are at risk for complications (e.g., BE, adenocarcinoma, stricture). Chronic reflux has been suspected to play a major role in the development of Barrett's esophagus, yet it is unknown if outcomes can be improved through surveillance and medical treatment *[D]*. Anti-reflux therapy has been shown to reduce the need for recurrent dilation from esophageal stricture formation *[A]*.

Rationale for Recommendations

PPI diagnostic test. A response to a short course of PPIs is commonly considered to support a diagnosis of GERD. PPIs have been studied and tried more often than H_2RAs given their higher efficacy.

Empiric/therapeutic trial. Diagnostic modalities cannot reliably

exclude GERD even if they are negative. Therefore an empiric trial may be the most expeditious way in which to diagnose GERD in those with classic symptoms and who do not have symptoms suggestive of complications (e.g., carcinoma, stricture). (Also see the discussion of "step-up" therapy and "step-down" therapy in treatment Section of the original guideline document.)

Empiric therapy should be tried for two weeks for patients with typical GERD symptoms. Treatment can be initiated with standard dosage of either an H_2RAs BID (on demand) or a PPI (30 to 60 minutes prior to first meal of the day), with drug selection depending on clinical presentation and appropriate cost effectiveness and the end point of complete symptom relief. (See Figure 1 and Table 4 in the original guideline document). If symptom relief is not adequate and H_2RAs BID was initially used, then PPI daily should be used. If PPI daily was initially used, then increase to maximum dose PPI daily or BID (30 to 60 minutes prior to first and last meals).

For those patients who initially present with more severe and more frequent symptoms of typical GERD, treatment may be initiated with higher and more frequent dosages of an H_2RAs or PPI. If symptom relief is not adequate from initial dose, then increase potency/frequency as needed to obtain complete symptom relief: high-dose H_2RAs to PPI daily, PPI daily or maximum dose PPI daily or BID. If there is no response when using higher dosages, then diagnostic testing should be performed. If patient responds, give 8 to 12 weeks of therapy, i.e., enough to heal undiagnosed esophagitis. If patient has complete symptom relief at 8-12 weeks, taper over 1 month to lowest effective dose of the medication that gives complete relief, e.g., H_2RAs on demand, PPI every other day (QOD). If symptoms reoccur, put patient back on initial effective medication and dose, and consider further testing depending on clinical presentation and course.

Patients who present with atypical or extraesophageal manifestations take a longer time to respond to empiric therapy. If there is no improvement at all in symptoms after one month, further testing should be pursued.

OTC remedies. Antacids and OTC acid suppressants are appropriate, initial patient-directed therapy for GERD. Antacids (Tums, Rolaids, Maalox) and combined antacid/alginic acid (Gaviscon) have been shown to be more effective than placebo in the relief of daytime GERD symptoms.

H_2RAs. Both higher doses and more frequent dosing of H_2RAs appear to be more effective in the treatment of reflux symptoms and healing of esophagitis. If the patient is on maximal therapy, the disadvantages include cost, which may exceed or equal the cost of a proton-pump inhibitor, as well as compliance.

	Patients seem to develop some tolerance to the H_2RAs, with some decreased efficacy observed after 30 days of treatment. **PPIs.** Solid evidence from numerous randomized controlled trials has shown that PPIs are more effective than both H_2RAs and placebo in controlling symptoms from erosive reflux disease (83% compared to 60% and 27%, respectively) over a 4 to 8 week period. **Treatment Failure** Empiric trials should be limited if no response is seen. Treatment response should be present in 2 to 4 weeks for patients with typical symptoms. Patients with atypical symptoms also have an initial response in one month, but may require 3 to 6 months for maximal response. Patients with atypical symptoms may require higher PPI doses for response. Empiric treatment in patients with atypical symptoms is appropriate if typical symptoms are also present. Esophageal pH monitoring off of anti-reflux medications might be the best approach initially in patients with atypical symptoms only since <30% of patients will have GERD associated symptoms. If patients with atypical symptoms do not respond to treatment in 1 to 3 months, then GERD is not likely the cause and the other diagnoses should be entertained.
LIFESTYLE MODIFICATION AND ADJUNCTIVE THERAPY	
ASGE (2007)	No recommendations offered.
NZGG (2004)	Although the traditional lifestyle measures usually recommended to people with GORD, such as raising the head of the bed, decreasing fat intake (to reduce body weight and to prevent delayed gastric emptying), cessation of smoking, moderation of alcohol intake, and avoiding tight clothing, may have some place in overall management, there are no systematic studies on these treatments, and published data are based on disputable methodology.
UMHS (2007)	**Lifestyle modifications.** Lifestyle modifications should be recommended throughout the treatment of GERD, but there is little evidence-based data to support their efficacy *[D]*. (Refer to Table 3 in the original guideline document for details). **<u>Rationale for Recommendations</u>** **Lifestyle modifications.** For a history typical for uncomplicated GERD, expert opinion is to **discuss and offer** various lifestyle modifications throughout the course of GERD therapy (see Table 3 in the original guideline document). Neither the efficacy nor the potential negative effects of lifestyle changes on a patient's quality of life have been adequately examined for any of these

	modifications. With relatively little data available, it is reasonable to educate patients about factors that may precipitate reflux. Refer to the original guideline topic for discussion of the following lifestyle modifications: • Head elevation • Avoid certain foods • Weight loss • Smoking cessation and alcohol minimization • Avoid medications that lower LES (lower esophageal sphincter) pressure • Avoid tight clothing around waist
SURGERY AND ENDOSCOPIC THERAPIES	
ASGE (2007)	Endoscopic antireflux therapy may be considered for selected patients with uncomplicated GERD after careful discussion with the patient regarding potential side effects, benefits, and other available therapeutic options **(3)**. **Endoscopic Antireflux Procedures** The endoluminal treatment of GERD is evolving and may have the potential to decrease the need for long-term antisecretory medications in selected patients. Most studies of endoluminal therapies for GERD have involved small numbers of PPI-dependent patients and have provided relatively limited follow-up information, so the durability of these therapies remains in question. Additionally, both short and long-term safety issues surrounding the endoluminal devices continue to be a concern, and the economics of their use are unknown. A technical review on the use of endoscopic therapies for GERD was recently published. The new endoscopic antireflux techniques represent a rapidly evolving area of GI endoscopy, but additional research is needed before they can be widely recommended. Appropriate patient selection and endoscopist experience should be carefully considered before pursuing these therapies. It is important that patients and practitioners alike be aware of the limitations in the evidence that exist with these devices at the present time.
NZGG (2004)	**Treatment of GORD diagnosed after OGD** **C** Consider surgery as alternative to long-term drug treatment if: • Age <50 years • Age 50 years and over and there is no comorbidity • There is inability or unwillingness to take medications.

	• There is inadequate control with medical therapy. **Surgery** Surgery should not be performed without a definitive diagnosis of GORD; 24-hour pH telemetry is advised in individuals with grade 0 GORD. Laparoscopic fundoplication has been recognised as a significant therapeutic advance. The choice of surgery over drug therapy should be made after evaluation of risks and benefits of both modes of therapy, and is usually made on the basis of a person's age, factors relating to compliance and acceptance of long-term drug therapy, cost, convenience and, of course, a person's preference. Surgery has the potential to cure GORD but it is important that the diagnosis is confirmed by OGD and/or pH telemetry. Oesophageal manometry is useful to exclude achalasia and other forms of oesophageal dysmotility. The decision to perform surgery should take into account the following factors: 1. The disease severity, in terms of symptoms and OGD findings, is predictive of the long-term prognosis on medical therapy; GORD grades 0, A and B have a good complication-free long-term prognosis, whereas complications may occur in grades C and D. 2. The recognised complications of uncontrolled reflux are stricturing, ulceration and intestinal metaplasia. Good drug treatment compliance is essential if these are to be avoided in people with severe GORD. 3. Surgery is more cost effective, and safer, in people of young biological age. 4. Comorbidity, such as cardio-pulmonary disease, increases the risk of surgery. This is more common in people aged 60 years and over. 5. Post-operatively, dietary restrictions may be necessary and flatulence and inability to vomit may be problems. Although dysphagia is usually self-limiting (within a few months), this can be a longer-term problem. 6. Previous abdominal surgery can make laparoscopic surgery difficult. 7. The morbidity of surgery must be compared with the known side effects of medical therapy. Although long-term PPI is considered safe, most long-term studies only extend to about 15 years. 8. The experience of the surgeon with this particular operation is a critical factor in the long-term success.
UMHS (2007)	**Treatment**

	Surgery. Anti-reflux surgery is an alternative modality in the treatment of GERD in patients who have documented chronic reflux with recalcitrant symptoms *[A]*. Surgery has a significant complication rate (10% to 20%). Resumption of pre-operative medication treatment (>50%) is common and will likely increase over time. **Other endoscopic modalities.** Some alternative endoscopic modalities are less invasive and have fewer complications, but are also likely to have lower response rates than antireflux surgery *[C]* and have not been shown to reduce acid exposure. **Rationale for Recommendations** **Surgical treatment.** The choice to consider anti-reflux surgery must be individualized. Patients should have documented acid reflux, a defective anti-reflux barrier in the absence of poor gastric emptying, normal esophagus motility and at least a partial response to acid reduction therapy. Surgery appears to be most effective for heartburn and regurgitation (75% to 90%) and less effective for extraesophageal symptoms (50% to 75%). **Newer endoscopic treatments.** Radiofrequency heating of the gastroesophageal (GE) junction (Stretta) and endoscopic gastroplasty (Bard, Wilson Cook), polymer injections to bolster the GE junction, and full thickness gastroplication have all been shown to improve symptoms and quality of life scores in sham controlled trials. None of these techniques have consistently reduced acid exposure. Polymer injections have been removed for safety concerns. Durability of response for all of these modalities (30% to 50% at 3 years) may limit long term usefulness. Complications are relatively rare in experienced hands and are less than with standard anti-reflux surgery.

SELECTED SUPPORTING REFERENCES **NOTE FROM NGC: BOLDED** REFERENCES ARE CITED IN MORE THAN ONE GUIDELINE. REFER TO THE ORIGINAL GUIDELINE DOCUMENTS FOR A COMPLETE LISTING OF SUPPORTING REFERENCES	
ASGE (2007)	American Society for Gastrointestinal Endoscopy. The role of endoscopy in the management of GERD: guidelines for clinical application. Gastrointest Endosc 1999;49:834-5.

Chotiprashidi P, Liu J, Carpenter S, *et al.* Wireless esophageal pH monitoring system. Gastrointest Endosc 2005;62:485-7.

Dent J, Brun J, Fendrick A, *et al.* An evidence-based appraisal of reflux disease management-the Genval Workshop Report. Gut 1999; 44(Suppl 2):S1-15.

DeVault KR, Castell DO. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. Am J Gastroenterol 2005;100:190-200.

Falk G, Fennerty MB, Rothstein RI. AGA institute technical review on the use of endoscopic therapy for gastroesophageal reflux disease. Gastroenterology 2006;131:1315-36.

Fock KM, Talley N, Hunt R, *et al.* Report of the Asia-Pacific consensus on the management of gastroesophageal reflux disease. J Gastroenterol Hepatol 2004;19:357-67.

Hanna S, Rastogi A, Weston AP, *et al.* Detection of Barrett's esophagus after endoscopic healing of erosive esophagitis. Am J Gastroenterol 2006;101:1416-20.

Kahrilas PJ, Pandolfino JE. Review article: oesophageal pH monitoring technologies, interpretation, and correlation with clinical outcomes. Aliment Pharmacol Ther 2005;22(Suppl 3):2-9.

Lieberman DA, Oehlke M, Helfand M. Risk factors for Barrett's esophagus in community-based practice. GORGE consortium. Gastroenterology Outcomes Research Group in Endoscopy. Am J Gastroenterol 1997;92:1293-7.

Lundell LR, Dent J, Bennett JR, *et al.* Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. Gut 1999;45:172-80.

Poelmans J, Feenstra L, Demedts I, *et al.* The yield of upper gastrointestinal endoscopy in patients with suspected reflux-related chronic ear, nose, and throat symptoms. Am J Gastroenterol 2004;99: 1419-26.

Rath HC, Timmer A, Kunkel C, *et al.* Comparison of interobserver agreement for different scoring systems for reflux esophagitis; impact of level of experience. Gastrointest Endosc 2004;60:44-9.

Vakil N, van Zanten SV, Kahrilas P, *et al.* The Montreal definition and classification of gastroesophageal reflux disease: a global evidence based consensus. Am J Gastroenterol 2006;101:1900-20.

Venables TL, Newland RD, Patel AC, *et al.* Omeprazole 10 milligrams

	once daily, omeprazole 20 milligrams once daily, or ranitidine 150 milligrams twice daily, evaluated as initial therapy for the relief of symptoms of gastro-oesophageal reflux disease in general practice. Scand J Gastroenterol 1997;32:965-73. Wo JM, Mendez C, Harrell S, *et al.* Clinical impact of upper endoscopy in the management of patients with gastroesophageal reflux disease. Am J Gastroenterol 2004;99:2311-6.
NZGG (2004)	Arvanitakis C, Nikopoulos A, Theoharidis A, *et al.* Cisapride and ranitidine in the treatment of gastro-oesophageal reflux disease-a comparative randomized double-blind trial. Aliment Pharmacol Ther 1993;7:635-41. Bardhan KD, Cherian P, Vaishnavi A, *et al.* Erosive oesophagitis: outcome of repeated long term maintenance with low dose omeprazole 10 mg or placebo. Gut 1998;43:458-64. Bate CM, Riley SA, Chapman RW, *et al.* Evaluation of omeprazole as a cost effective diagnostic test for gastro-oesophageal reflux disease. Aliment Pharmacol Ther 1999;13:59-66. Carlsson R, Dent J, Bolling-Sternevald E, *et al.* The usefulness of a structured questionnaire in the assessment of symptomatic gastroesophageal reflux disease. Scand J Gastroenterol 1998;33:1023-9. Crawley JA. Cost effectiveness of treatment for gastro-oesophageal reflux disease. Gut 1998;43:729-30. Dallemagne B, Weerts JM, Jeahes C, Markiewicz S. Results of laparoscopic Nissen fundoplication. Hepatogastroenterology 1998;45:1338-43. De Meester TR, Wang CI, Wernly JA, *et al.* Technique, indications, and clinical use of 24 hour esophageal pH monitoring. J Thorac Cardiovasc Surg 1980;79:656-70. **Dent J, Brun J, Fendrick A, *et al.* An evidence-based appraisal of reflux disease management-the Genval workshop report. Gut 1999; 44(Suppl 2):S1-16.** DeVault KR, Castell DO, *et al.* Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. Am J Gastroenterol 1999;94:1434-42. Enck P, Dubois D, Marquis P, *et al.* Quality of life in patients with upper gastrointestinal symptoms: results from the Domestic/International Gastroenterology Surveillance Study. Scand J

Gastroenterol 1999;S 231:48-54.

Fass R, Ofman JJ, Gralnek IM, *et al.* Clinical and economic assessment of the omeprazole test in patients with symptoms suggestive of gastro-esophageal reflux disease. Arch Intern Med 1999;159:2161-8.

GalmicheJ-P, Bruley DV. Symptoms and disease severity in gastro-oesophageal reflux disease. Scand J Gastroenterol 1994;29(Suppl 201):62-8.

Heudebert GR, Marks R, Wilcox CM, Centor RM. Choice of long-term strategy for the management of patients with severe esophagitis: a cost-utility analysis. Gastroenterology 1997;112:1078-86.

Inadomi JM, Jamal J, Murata GH, *et al.* Step-down management of gastroesophageal reflux disease. Gastroenterology 2001;121:1095-1100.

Kahrilas PJ, Quigley EM. Clinical esophageal pH recording: a technical review for practice guideline development. Gastroenterology 1996;110:1982-96.

Kromer W, Horbach S, Luhmann R. Relative efficacies of gastric proton pump inhibitors: Their clinical and pharmacological basis. Pharmacology 1999;59:57-77.

Kusano M, Ino K, Yamada T, *et al.* Interobserver and intraobserver variation in endoscopic assessment of GERD using the 'Los Angeles' classifications. Gastrointest Endosc 1999;49:700-04.

Kuster E, Ros E, Toledo-Pimentel V, *et al.* Predictive factors of the long term outcome in gastro-oesophageal reflux disease: six year follow-up of 107 patients. Gut 1994;35:8-14.

Laine L. *H. pylori* eradication in gastroesophageal reflux disease. Gastroenterology 1997;113:2019-20.

Locke GR, Talley NJ, Fett S, *et al.* Prevalence and clinical spectrum of gastroesophageal reflux: a population-based study in Olmsted County, Minnesota. Gastroenterology 1997;112:1448-56.

Locke GR, Talley NJ, Weaver AL, Zinsmeister AR. A new questionnaire for gastroesophageal reflux disease. Mayo Clin Proc 1994:69:539-47.

Perdikis G, Hinder RA, Lund RJ, *et al.* Laparoscopic Nissen fundoplication: where do we stand? Surg Laparosc Endosc 1997;1:17-21.

	Sandmark S, Carlsson R, Fausa O, *et al.* Omeprazole or ranitidine in the short-term treatment of ulcerative reflux oesophagitis. Results of a double-blind randomised Scandinavian multicenter study. Scand J Gastroenterol 1988;23:625-32. Sonnenberg A, Delco F, El-Serag HB. Empirical therapy versus diagnostic tests in gastroesophageal reflux disease: a medical decision analysis. Dig Dis Sci 1998;43:1001-08. Spechler SJ. The role of gastric carditis in metaplasia and neoplasia at the gastroesophageal junction. Gastroenterology 1999;117:218-28. Van Pinxteren B, Numens ME, Bonis PA, Lau J. Short-term treatment with proton pump inhibitors, H2-receptor antagonists and prokinetics for gastrooesophageal reflux disease-like symptoms and endoscopy negative reflux disease. The Cochrane Library, Issue 2, 2000. Waring JP, Hunter JG, Oddsdottir M, *et al.* The preoperative evaluation of patients considered for laparoscopic antireflux surgery. Am J Gastroenterol 1995;90:35-8. Werdmuller BF, Loffeld RJ. *H. pylori* infection has no role in the pathogenesis of reflux esophagitis. Dig Dis Sci 1997;42:103-05.
UMHS (2007)	American College of Gastroenterology: DeVault KR. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. American Journal of Gastroenterology, 1999; 94(6):1434-1442. American College of Gastroenterology: DeVault KR, Castell DO. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. American Journal of Gastroenterology, 2005; 100:190-200. Heidelbaugh JJ, Nostrant TT. A cost-effective approach to the pharmacologic management of gastroesophageal reflux disease. Drug Benefit Trends 2004;16:463-471. Heidelbaugh JJ, Nostrant TT. Medical and surgical management of gastroesophageal reflux disease. In: Heidelbaugh JJ (ed). Clinics in Family Practice: Gastroenterology. Philadelphia, PA: Elsevier, September 2004, 6(3):547-568. Kahrilas, PJ. Gastroesophageal reflux disease. JAMA. 1996;276(12):983-988. Numans Me, Lau J, deWit NJ, Bonis PA. Short-term treatment with proton-pump inhibitors as a test for gastroesophageal reflux disease: a meta-analysis of diagnostic test characteristics. Annals of

	Internal Medicine, 2004; 140(7):518-27. Sridhar, S. Clinical economics review: cost-effectiveness of treatment alternatives for gastro-oesophageal reflux disease. Alim Pharmacol Ther 1996;10:865-873. VA/DoD clinical practice guideline for the management of adults with gastroesophageal reflux disease in primary care practice. Department of Veterans Affairs and Department of Defense, Draft 8a, March 12, 2003. Vaezi, M. Gastroesophageal reflux disease and the larynx. J Clin Gastroenterol, 2003; 36(3):198-203.

TABLE 5: BENEFITS AND HARMS	
Benefits	
ASGE (2007)	Appropriate utilization of endoscopy in the diagnosis and management of patients with GERD and BE
NZGG (2004)	Improved management and treatment of dyspepsia and heartburn including relief of symptoms, safer drug regimens, early identification of complications, early investigation and diagnosis of serious pathology, and reduced mortality from peptic ulcer disease
UMHS (2007)	Accurate diagnosis and appropriate, cost-effective treatment of GERD
Harms	
ASGE (2007)	• Drawbacks of EGD include the potential physical risks, financial costs, and limited access to the procedure. • Short- and long-term safety issues surrounding the endoluminal devices continue to be a concern, and the economics of their use are unknown.
NZGG (2004)	**"Step-down" treatment for GERD** Initial drug cost is higher and there is the possibility of some individuals being over-treated if an appropriate step-down procedure is not followed
UMHS (2007)	**Potential Harms**

	• H_2RAs have been associated with rare cytopenias, gynecomastia, liver function test abnormalities, and hypersensitivity reactions. • PPIs have been associated with rare vitamin B12 deficiencies, community-acquired pneumonia, Clostridium difficile colitis, and hip fracture. • Post antireflux surgical complications are common, but typically short term and manageable in most instances. Short term solid food dysphagia occurs in 10% of patients (2 to 3% have permanent symptoms) and gas bloating occurs in 7% to 10% of patients. Diarrhea, nausea, and early satiety occur more rarely. While some complication occurs in up to 20% of patients, major complications occur in only 3% to 4% of patients.

TABLE 6: EVIDENCE RATING SCHEMES AND REFERENCES

ASGE (2007)

Definitions

Grades of Recommendation

Grade	Clarity of Benefit	Methodologic Strength/ Supporting Evidence	Implications
1A	Clear	Randomized trials without important limitations	Strong recommendation; can be applied to most clinical settings
1B	Clear	Randomized trials with important limitations (inconsistent results, nonfatal methodologic flaws)	Strong recommendation; likely to apply to most practice settings
1C+	Clear	Overwhelming evidence from observational studies	Strong recommendation; can apply to most practice settings in most situations
1C	Clear	Observational	Intermediate-strength

		studies	recommendation; may change when stronger evidence is available
2A	Unclear	Randomized trials without important limitations	Intermediate-strength recommendation; best action may differ depending on circumstances or patients' or societal values
2B	Unclear	Randomized trials with important limitations (inconsistent results, nonfatal methodologic flaws)	Weak recommendation; alternative approaches may be better under some circumstances
2C	Unclear	Observational studies	Very weak recommendation; alternative approaches likely to be better under some circumstances
3	Unclear	Expert opinion only	Weak recommendation; likely to change as data become available

NZGG (2004)

Levels of Evidence

Ia: Evidence obtained from meta-analysis of RCTs

Ib: Evidence obtained from at least one RCT

IIa: Evidence obtained from at least one well-designed controlled study without randomisation

IIb: Evidence obtained from at least one other type of well-designed quasi-experimental study

III: Evidence obtained from well-designed descriptive studies, such as comparative studies, correlation studies, and case studies

IV: Evidence obtained from expert committee reports or opinions, and/or clinical experiences of respected authorities

	Grades of Recommendations **Grade A** *(Evidence levels Ia & Ib)* Requires at least RCT as part of the body of literature of overall good quality and consistency addressing specific recommendation **Grade B** *(Evidence levels IIa, IIb, & III)* Requires availability of well-conducted studies but no RCTs addressing specific recommendation **Grade C** *(Evidence level IV)* Requires evidence obtained from expert committee reports or opinions, and/or clinical experiences of respected authorities Indicates absence of directly applicable clinical studies of good quality **Good Practice Point.** Recommended best practice based on the clinical experience of the Dyspepsia and GORD Working Party.
UMHS (2007)	Levels of evidence reflect the best available literature in support of an intervention or test. A. Randomized controlled trials B. Controlled trials, no randomization C. Observational trials D. Opinion of expert panel

GUIDELINE CONTENT COMPARISON

ASGE, NZGG, and UMHS present recommendations for diagnosis and management of GERD in adults and provide explicit reasoning behind their judgments. The guidelines differ slightly in scope. The primary focus of the ASGE and UMHS guidelines is GERD, whereas the NZGG guideline addresses other causes of dyspepsia, including undifferentiated and non-ulcer dyspepsia, peptic ulcer disease, and *H. pylori*. The ASGE guideline also includes recommendations for BE. This synthesis is limited to recommendations for the diagnosis and treatment of GERD.

Methodology

Methods used to collect and select the evidence are similar in that all three groups performed searches of at least one electronic database and provide additional relevant information regarding this process. All three groups provide the names of databases searched; NZGG and UMHS also specify the dates over which evidence was obtained. All three groups performed hand-searches of published literature; NZGG also searched unpublished data.

NZGG provides explicit, graded recommendation statements. They note, however, that the grades indicate the strength of the supporting evidence, rather than the importance of the recommendation. The recommendation statements are supplemented with narrative discussion of the rationale for the recommendations, which includes footnotes to the corresponding evidence in the reference list.

The ASGE guidance is provided primarily in narrative format with references to the corresponding supporting evidence in the reference list. At the end of the guideline a summary of key, graded recommendation statements is provided. ASGE's recommendation grades reflect both the strength of the supporting evidence as well as the strength of the recommendation.

Like NZGG, UMHS also provides graded recommendation statements in the form of "Key Points", for which the levels of evidence reflect the best available literature in support of an intervention or test. UMHS also provides narrative discussion and a list of annotated references, but does not link the evidence in the reference list directly to particular recommendations.

To analyze the evidence, all three groups performed a systematic review (NZGG used evidence tables; NZGG and UMHS also performed a review of published meta-analyses). All three groups used expert consensus to formulate their recommendations and all provide reference lists (41 for ASGE, 333 for NZGG, and 9 for UMHS).

Areas of Agreement

Clinical Presentation and Diagnosis

The guideline groups agree that GERD can be diagnosed on the basis of classic symptoms (heartburn, epigastric pain, regurgitation) and favorable response to antisecretory therapy, without the need for routine diagnostic testing. However, there is also overall agreement that referral for endoscopy is indicated for patients presenting with alarm signals (involuntary weight loss, persistent vomiting, dysphagia, evidence of GI bleeding) or symptoms of complicated GERD, or for those at risk for BE.

Diagnostic Classification Schemes

For patients in whom endoscopy is indicated, all three groups address the two best known schemes available to diagnose and classify GERD, the Los Angeles (LA) and the Savary-Miller classification schemes. There is overall agreement that the LA classification system is more widely used and has more advantages than the Savary-Miller. ASGE notes that the latter is used primarily in Europe. Advantages of the LA system, according to ASGE, include reliability, with good intra- and inter-observer agreement, and demonstration of the severity of the esophagitis that correlates with the extent of esophageal acid exposure determined by 24-hour pH monitoring. NZGG similarly notes that the appearance of the mucosal breaks on inspection at OGD is usually defined using the LA system, adding however that the older Savary-Miller classification is still used by many endoscopists. UMHS is in agreement with ASGE and NZGG, noting that esophagitis is best defined by the LA classification system.

Initial Empiric Trial and Pharmacological Management

There is overall agreement that in most cases, a diagnosis of GERD is considered to be confirmed in patients not requiring diagnostic testing if symptoms resolve with a trial of empirical drug therapy. UMHS notes that diagnostic modalities cannot reliably exclude GERD even if they are negative and that an empiric trial may therefore be the most expeditious way in which to diagnose GERD in patients with classic symptoms. UMHS recommends a 2-week trial (adding that patients with extraesophageal GERD may require a longer initial trial); and NZGG notes that the initial trial should cover at least 2 to 4 weeks, but the dosage may be continued for 6 to 8 weeks in total before step-down is attempted, according to symptom control. As the focus of the ASGE guideline is on diagnosis, they do not make specific recommendations regarding therapy, but state that a trial of empiric medical therapy is appropriate for patients with uncomplicated GERD. Recommendations regarding the specific therapies used during the initial empiric trial differ. See Areas of Differences below.

There is also overall agreement that diagnostic investigation is indicated for patients who fail to respond to appropriate antisecretory therapy. ASGE notes that this scenario should prompt evaluation with EGD and consideration of other diagnostic modalities, including ambulatory pH monitoring, esophageal manometry, and multichannel impedance testing. NZGG also recommends that EGD be performed in patients who fail to respond to therapy or whose symptoms recur within 1 month after treatment. In patients with GERD diagnosed after EGD, however, they recommend that 24-hour pH telemetry should be used to investigate high-dose treatment failures or to assess individuals with grade-0 GERD prior to considering surgery (usually combined with manometry).

Similar to ASGE and NZGG, UMHS recommends endoscopy for patients who do not respond to therapy, need continuous chronic therapy, and have risk factors for BE. They also note that patients with endoscopic-negative GERD and who do not respond to medications are best evaluated by ambulatory pH monitoring. According to UMHS, the major indication for performing 24-hour ambulatory pH monitoring is in documenting treatment failures, either to antireflux surgery or medical management.

Lifestyle Modification

UMHS recommends that lifestyle modifications (weight loss, tobacco use, head elevation) be encouraged throughout the treatment of GERD. They qualify this recommendation however, by noting that there is little evidence-based data to support their efficacy. NZGG similarly notes that although the traditional lifestyle measures usually recommended to people with GERD may have some place in overall management, there are no systematic studies on these treatments, and published data are based on disputable methodology. ASGE does not provide recommendations.

Surgery

NZGG and UMHS agree that surgery is an appropriate option for patients with a definitive diagnosis of GERD whose symptoms are inadequately controlled with drug therapy, or when there is inability or unwillingness to take medications.

NZGG specifies that within this population surgery should be further restricted to patients less than 50 years of age, or patients older than 50 years of age with no comorbidities. Both groups stress that the decision to undergo anti-reflux surgery must be individualized. UMHS specifies that patients should have documented acid reflux, a defective anti-reflux barrier in the absence of poor gastric emptying, normal esophagus motility and at least a partial response to acid reduction therapy. NZGG notes that the decision to choose surgery over drug therapy should be made after evaluation of risks and benefits of both modes of therapy, and is usually based on a person's age, factors relating to compliance and acceptance of long-term drug therapy, cost, convenience and patient preference.

Endoscopic Antireflux Therapies

Two groups, ASGE and UMHS, address newer endoscopic therapies, yet neither make explicit recommendations. ASGE states that endoscopic antireflux therapy may be considered for selected patients with uncomplicated GERD after careful discussion with the patient regarding potential side effects, benefits, and other available therapeutic options. They add that the endoluminal treatment of GERD is evolving and may have the potential to decrease the need for long-term antisecretory medications. They cite limited information about the durability and the safety of these procedures as reasons why they cannot be recommended at this time. UMHS similarly states that some alternative endoscopic modalities (Stretta, endoscopic gastroplasty, polymer injections, full thickness gastroplication) are less invasive and have fewer complications, but are also likely to have lower response rates than antireflux surgery and have not been shown to reduce acid exposure.

Areas of Differences

Clinical Presentation and Diagnostic Testing

NZGG differs from ASGE and UMHS in recommending non-urgent endoscopy for all patients aged 50 years or more at first presentation, regardless of the presence of alarm symptoms, noting the higher incidence of cancer in this population.

Initial Empiric Trial and Pharmacologic Management

Options for empiric treatment include step-down therapy (beginning with standard dose PPI and stepping down to lower dose PPI or H_2RAs if response is good) and step-up therapy (beginning with H_2RAs and stepping up to PPI if symptoms are not resolved). NZGG recommends step-down therapy, with the first step being full-dose PPI, followed by half-dose PPI, followed by H_2RAs twice daily. The last step recommended by NZGG is antacids/alginate.

In contrast to NZGG, the UMHS guideline makes empiric trial recommendations according to clinical presentation: step-up *or* step-down therapy is appropriate for patients with NERD; initial PPI therapy is recommended for patients with documented erosive esophagitis. While NZGG and UMHS are in agreement that PPIs have been proven more effective than H_2RAss in controlling symptoms of erosive reflux disease, UMHS recommends that the drug chosen for initial therapy be selected based on clinical presentation and appropriate cost effectiveness. Both

groups agree, however, that if there is inadequate response to initial therapy, the treatment duration should be extended or modified. If the initial response to standard dose PPI was poor, NZGG and UMHS recommend increasing to maximum dose before beginning the step down process. UMHS recommends that if H_2RAs BID was initially used, then PPI daily should be used.

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