Medical Treatment for GERD in Asia

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Abstract

Evidence shows that gastroesophageal reflux disease (GERD) is rapidly rising in Asia. Recent globalization of economies and the associated lifestyle changes may have tipped the balance in favor of the development of GERD. Medical treatment consisting of lifestyle and dietary modifications and pharmacologic therapy are the mainstays of treatment. Only elevation of the head of the bed, left lateral decubitus positioning, and weight loss have been associated with GERD improvement. There is insufficient evidence to support restriction of alcohol, tobacco, caffeine, spicy foods, chocolate, citrus, and carbonated drinks. Avoidance of these may help with GERD symptoms. Acid suppression therapy with PPI is still the cornerstone of pharmacologic treatment of erosive esophagitis, NERD, and extraesophageal symptoms of GERD. Adjunctive treatment with H2 antagonists, antacids, alginates, and prokinetics may be used in GERD patients refractory to PPI.

Keywords

GERD • Erosive esophagitis • Reflux esophagitis • NERD • PPI • H2RA • Prokinetics • Antacid • Alginate

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Introduction

Medical treatment is the mainstay of treatment of GERD and includes lifestyle and dietary modifications and pharmacologic therapy. Acid suppression therapy is the cornerstone of pharmacological treatment of GERD since the advent of H2 antagonists. Currently, proton pump inhibitors (PPIs) offer the most effective acid suppression and are used widely throughout the world for the treatment of GERD.

Lifestyle and Dietary Modification

Lifestyle interventions are part of therapy for GERD. Counseling is provided regarding weight loss, head of bed elevation, tobacco and alcohol cessation, avoidance of late-night meals, and cessation of foods that can potentially aggravate reflux. Physiologic studies show that these maneuvers enhance esophageal acid clearance, decrease acid reflux-related events, or ease heartburn symptoms [1]. However, in case-controlled studies, only elevation of the head of the bed, left lateral decubitus positioning, and weight loss have been associated with GERD improvement [1].

Studies have shown improvement in GERD symptoms and esophageal pH values with head of bed elevation using blocks or foam wedges (Table 7.1) [2–4]. Weight gain, even in subjects with a normal BMI, has been associated with new onset of GERD symptoms [5]. Morbidly obese patients have been shown to have statistically more GERD symptoms compared to nonobese subjects [6]. Weight loss has also been shown to reduce GERD symptoms [7, 8]. One large case-controlled study

Table 7.1 Efficacy of lifestyle interventions adapted from 2013 ACG guidelines for the diagnosis and management of GERD

Lifestyle intervention	Effect of intervention on GERD parameters	Sources of data	Recommendation
Weight loss	Improvement of GERD symptoms and esophageal pH	Case control	Strong recommendation for patients with BMI>25 or patients with recent weight gain
Head of bed elevation	Improved esophageal pH and symptoms	Randomized controlled trial	Head of bed elevation with foam wedge or blocks in patients with nocturnal GERD
Avoidance of late evening meals	Improved nocturnal gastric acidity but not symptoms	Case control	Avoid eating meals with high-fat content within 2–3 h of reclining
Tobacco and alcohol cessation	No change in symptoms or esophageal pH	Case control	Not recommended to improve GERD symptoms
Cessation of chocolate, caffeine, spicy foods, citrus, carbonated beverages	No studies performed	No evidence	Not routinely recommended for GERD patients. Selective elimination could be considered if patients note correlation with GERD symptoms and improvement with elimination

showed there was a 40% reduction in frequent GERD symptoms for women who reduced their BMI by 3.5 or more compared with controls [5]. Roux-en-Y gastric bypass was considered an effective method to alleviate symptoms of GERD [9].

Consumption of tobacco, chocolate, and carbonated beverages and lying in the right lateral decubitus position have been shown to decrease lower esophageal sphincter pressure (LESP), whereas consumption of alcohol, coffee, caffeine, and spicy and fatty foods had no effect. There was an increase in esophageal acid exposure times with tobacco and alcohol consumption in addition to ingestion of chocolate and fatty foods. However, tobacco and alcohol cessation were not shown to raise LESP, improve esophageal pH, or improve GERD symptoms. There have been no studies that have shown clinical improvement in GERD symptoms with cessation of coffee, caffeine, chocolate, spicy foods, citrus, carbonated beverages, fatty foods, or mint [1].

Other measures that theoretically can improve symptoms, however, have not been shown to be effective, including (1) avoidance of tight-fitting garments to prevent increasing intragastric pressure and the gastroesophageal pressure gradient, (2) promotion of salivation through oral lozenges/chewing gum to neutralize refluxed acid and increase the rate of esophageal acid clearance [10], and (3) abdominal breathing exercise to strengthen the anti-reflux barrier of the lower esophageal sphincter [11].

Pharmacologic Agents

Proton Pump Inhibitors (PPIs)

PPIs are the most potent inhibitors of gastric acid secretion by irreversibly binding to and inhibiting the H-K-ATPase pump. PPIs are most effective when taken 30 min before the first meal of the day because the amount of H-K-ATPase present in the parietal cell is greatest after a prolonged fast [12]. They are the drugs of choice as recommended by the different practice guidelines (Table 7.2).

The 2008 Asia-Pacific consensus on the management of GERD recommends 4 weeks of PPI treatment for nonerosive reflux disease (NERD) patients and 4 to 8 weeks for erosive esophagitis. PPIs at standard doses for 8 weeks relieve symptoms of GERD and heal esophagitis in up to 86% of patients with erosive esophagitis [12]. PPI therapy has been associated with superior and faster healing rates and decreased relapse rates compared with H2RAs and placebo [13].

There are no major differences in efficacy among PPIs and no consistent increase in symptom resolution or esophagitis healing rates between different dosages or dosing regimens of PPI therapy [14]. All of the PPIs, with the exception of dexlansoprazole, should be administered 30–60 min before meals to assure efficacy. Dexlansoprazole, the newest PPI available for use, is a dual delayed-release PPI licensed for use in the Asian Pacific region recently. Comparative trials of dexlansoprazole compared with lansoprazole 30 mg demonstrated superior control in

Table 7.2 Medical therapy for GERD

	Recommendations	Comments
Lifestyle changes	Weight loss, elevation of head, and left lateral decubitus position	Insufficient evidence to support restriction of alcohol, tobacco, caffeine, spicy foods, chocolate, citrus, and carbonated drinks. Avoidance of these may help with GERD symptoms
Proton pump inhibitor therapy	Drug of choice in GERD	No major differences in efficacy among PPIs
	Erosive esophagitis, 6–8 weeks at standard dose	No consistent increase in symptom resolution or esophagitis healing rates between different dosages or dosing regimens of PPI therapy
	NERD, 4 weeks at standard dose	
	Extraesophageal GERD	
	Refractory GERD	
H2 antagonists	More effective in controlling nocturnal acid secretion	Esophagitis healing rates rarely exceeded 60%
		Tachyphylaxis within 2–6 weeks
Alginates	Reduces the postprandial acid pocket in the proximal stomach	Gaviscon Double Action Liquid was found to be more effective than an antacid without alginate in controlling postprandial esophageal acid exposure
	Found to be as effective as omeprazole in the treatment of NERD	
	Decreases reflux and dyspeptic symptoms in GERD patients	
Prokinetic agents	Increases LES pressure, acid clearance, or gastric emptying	Its use as either monotherapy or adjunctive therapy to PPIs may have a role in the treatment of GERD in Asia
	Modest benefit in controlling heartburn	May cause cardiac dysrhythmias
	Unreliable efficacy in healing esophagitis	
Antacids	For episodic, primarily postprandial heartburn and intermittent (on-demand), mild GERD symptoms	Relief of heartburn within 5 min but have a short duration of effect of 30–60 min.
Other agents	Sucralfate limited only pregnant patients with GERD	Insufficient studies for *rikkunshito*, anxiolytics and antidepressants, electroacupuncture, melatonin, and anti-osteoporosis medication elcatonin
	Baclofen may be used in PPI refractory GERD patients	

esophageal pH values and better efficacy in healing esophagitis, maintenance of healing, and symptom control. There is the added convenience of being able to dose the drug any time of the day regardless of food intake [15].

Histamine 2 Receptor Antagonists (H2RAs)

H2RAs are commonly used for episodic heartburn, primarily for postprandial heartburn. However, the development of tachyphylaxis within 2–6 weeks limits their use as maintenance therapy [16].

H2RAs have a slower onset of action, reaching peak concentrations 2.5 h after dosing, but a significantly longer duration of action, lasting 4–10 h [17].

Overall esophagitis healing rates with H2RAs rarely exceeded 60% after up to 12 weeks of treatment, even when higher doses were used. Healing rates differ in individual trials depending primarily on the severity of esophagitis being treated: LA grades I and II esophagitis heal in 60–90% of patients, whereas LA grades III and IV heal in only 30–50% of patients, despite high-dose regimens [18].

The addition of bedtime H2RA has been recommended for patients with symptoms refractory to PPI. The trial use of a bedtime H2RA might be most beneficial if dosed on an as-needed basis in patients with provocable nighttime symptoms and patients with objective evidence on pH monitoring of overnight esophageal acid reflux despite optimal PPI use.

Antacids

Antacids are commonly used for episodic heartburn, primarily for postprandial heartburn [19]. They are also used for intermittent (on-demand), mild GERD symptoms that occur less than once a week [20]. Antacids neutralize gastric pH, thereby decreasing the exposure of the esophageal mucosa to gastric acid during reflux episodes. Antacids begin to provide relief of heartburn within 5 min but have a short duration of effect of 30–60 min.

Sodium Alginate

Sodium alginate is a polysaccharide derived from seaweed that forms a viscous gum that floats within the stomach and reduces the postprandial acid pocket in the proximal stomach. It was found to be as effective as omeprazole in the treatment of NERD [21]. It decreases reflux and dyspeptic symptoms in GERD patients compared with matched placebo and has a favorable benefit-risk balance [22]. An alginate-antacid combination was found to be more effective than an antacid without alginate in controlling postprandial esophageal acid exposure. Its main effectiveness relates to its co-localization with and displacement/neutralization of the postprandial acid pocket, rather than preventing mechanical reflux [23].

Prokinetics

Prokinetic drugs improve reflux symptoms by increasing LES pressure, acid clearance, or gastric emptying. However, they provide only modest benefit in controlling heartburn but have unreliable efficacy in healing esophagitis [24]. Their use as either monotherapy or adjunctive therapy to PPIs may have a role in the treatment of GERD in Asia.

Metoclopramide has been shown to increase LESP, enhance esophageal peristalsis, and augment gastric emptying [25]. It is another option in patients with incomplete response to PPI. Clinical data showing additional benefit of metoclopramide to PPI or H2RA has not been adequately studied and has not been shown to be more effective compared with combination and single therapy. In the absence of gastroparesis, there is no clear role for metoclopramide. Central nervous system side effects are drowsiness, agitation, irritability, depression, dystonic reactions, and tardive dyskinesia.

Domperidone, a peripherally acting dopamine agonist, is not approved by the US FDA but is commonly used in Asia. Monitoring for QT prolongation is performed, due to a small risk for ventricular arrhythmia and sudden cardiac death [26].

Cisapride, a serotonin (5-HT_4) receptor agonist, increases acetylcholine release in the myenteric plexus. It was withdrawn from the market because of serious cardiac dysrhythmias (ventricular tachycardia, ventricular fibrillation, torsades de pointes, and QT prolongation).

Itopride, a dopamine D_2 antagonist with antiacetylcholinesterase effect, has been recently evaluated in patients with an abnormal pH test and mild erosive reflux disease (ERD). After 30 days of treatment in an open-label study design, itopride significantly reduced the extent of esophageal acid exposure and improved GERD-related symptoms as compared to baseline values [27].

Mosapride, a newly developed 5-HT_4 agonist, has been shown to increase the rate of complete esophageal bolus transit and enhances esophageal bolus transit in normal controls. However, mosapride with PPI combined therapy was found not to be more effective than PPI alone as first-line therapy [28].

Bethanechol, a cholinergic agonist, is limited by flushing, blurred vision, headaches, abdominal cramps, and urinary frequency.

Baclofen

Baclofen, a GABAB agonist, is effective in GERD by its ability to reduce transient LES relaxations, thereby reducing exposure time for acid and duodenal reflux. In PPI refractory GERD patients, a trial of 5–20 mg three times a day can be considered in patients with objective documentation of continued symptomatic reflux despite optimal PPI therapy [27].

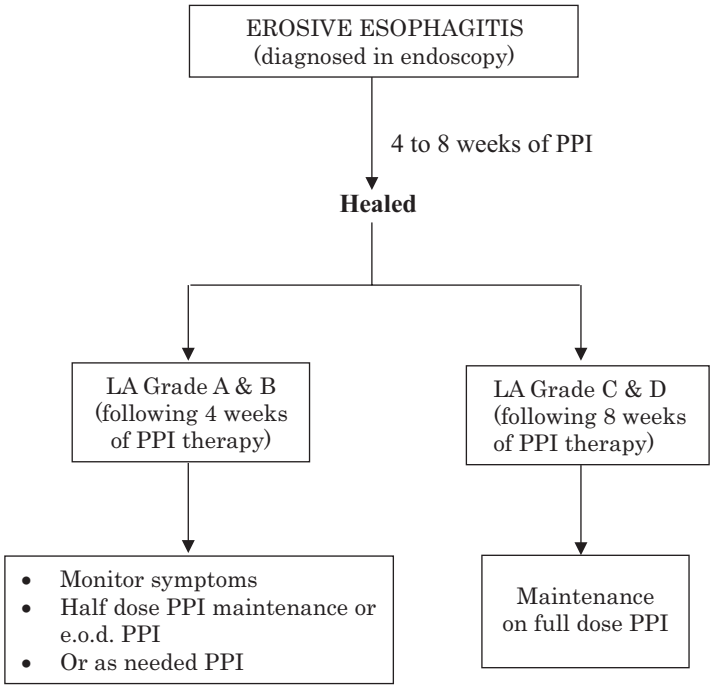
Other Treatment Options

Herbal medicines, such as *rikkunshito* [29], anxiolytics and antidepressants, electroacupuncture, melatonin, and anti-osteoporosis medication elcatonin [30], have anecdotal reports in the treatment of GERD.

Clinical Practice for GERD in ASIA: Recommendations

Non-pharmacologic therapy with lifestyle changes is easy to institute and should be advised to a patient. These include weight loss, elevation of the head of the bed, and left lateral decubitus position. There is insufficient evidence to support restriction of alcohol, tobacco, caffeine, spicy foods, chocolate, citrus, and carbonated drinks. However, avoidance of these.

Specific Pharmacologic Therapy



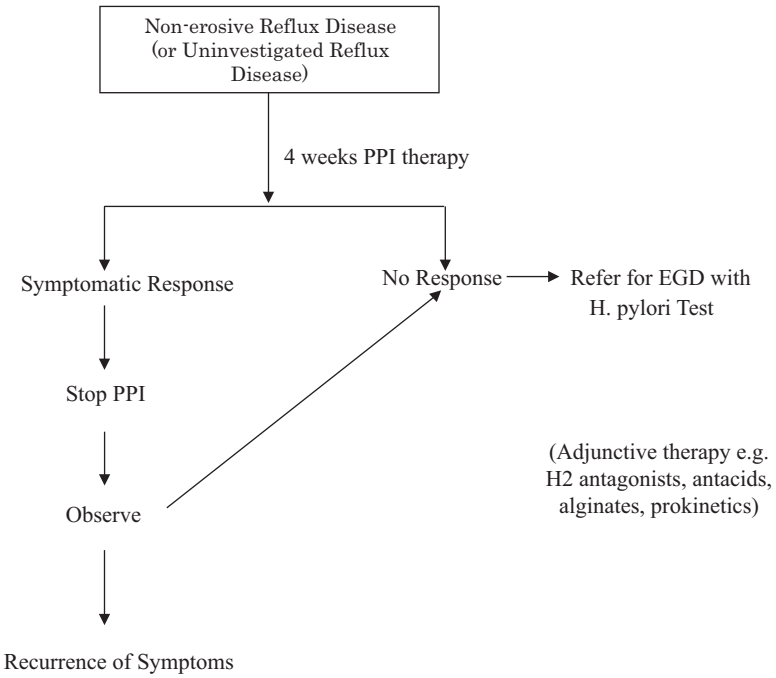
Initial Treatment

PPIs for 4–8 weeks are the most effective treatment for erosive esophagitis [19]. PPIs at standard doses for 8 weeks relieve symptoms of GERD and heal esophagitis in up to 86% of patients with erosive esophagitis [12].

Maintenance of Healing

The US FDA has approved all the PPIs, sometimes at one-half the acute dose, for maintenance therapy for mild esophagitis (LA Grade A and B). Furthermore, the 2008 Asia-Pacific consensus on the management of GERD recommends on-demand therapy defined as PPI consumption (up to once daily) when needed and for the duration desired. On-demand PPI therapy was superior to placebo in controlling GERD-related symptoms, antacids consumption, and patients' satisfaction with therapy. Patients with severe disease (daily symptoms, severe esophagitis, or complications) are put on maintenance PPI therapy indefinitely [27].

NERD



Initial Treatment

PPIs are the most effective treatment for NERD and are recommended as first-line therapy for NERD. Patients should be prescribed a minimum of 4 weeks of initial continuous therapy with a PPI [19]. PPIs demonstrate superiority in relieving heartburn symptoms in patients with NERD when compared to H2RAs [31].

Maintenance Treatment

Studies have shown that on-demand PPI therapy was superior to placebo in controlling GERD-related symptoms, antacids consumption, and patients' satisfaction with therapy [32]. Several cost-effectiveness analyses have demonstrated that on-demand treatment with a PPI is cost-effective compared with other therapeutic strategies for GERD (e.g., lifestyle therapy and antacids, H2RA therapy, step-up, step-down, as well as others) [33].

No Response to Treatment

Endoscopy should be performed at least once in patients with chronic upper gut symptoms, recognizing the imprecision of clinical diagnosis between GERD, gastric cancer, and peptic ulcer and the ability of endoscopy to provide or exclude a diagnosis and aid in tailoring therapy [19]. Based on symptoms alone, 18% of *H. pylori*-related peptic ulcers were misdiagnosed as GERD [34]. *H. pylori* testing should be considered in new patients presenting with GERD symptoms in regions with a high prevalence of gastric cancer or peptic ulcer disease [19]. H2RA for control of nocturnal acid secretion, prokinetics [27], antacids for episodic heartburn [20], and sodium alginate [21] may be also be used as adjunctive treatment in NERD patients. Clinical data showing additional benefit of prokinetics with PPI has not been adequately studied. Combination therapy of metoclopramide with H2RA has not been shown to be more effective compared with H2RA or prokinetic therapy alone [35]. Mosapride with PPI combined therapy was also found not to be more effective than PPI alone as first-line therapy [28].

Extraesophageal Treatment

The Montreal Consensus recognized established associations between GERD and asthma, chronic cough, and laryngitis while acknowledging that these disorders frequently have a multifactorial etiology and that gastroesophageal reflux may be a cofactor rather than a cause.

Patients with chronic cough and laryngitis and typical GERD symptoms should be offered twice-daily PPI therapy after exclusion of non-GERD etiologies for at least 4 months [19]. Two randomized controlled trials have shown that PPIs result

in improvement of various asthma outcomes [36, 37]. However, there is insufficient evidence to recommend PPIs for routine asthma treatment when other GERD symptoms are absent [38]. The experience with treating laryngeal symptoms attributed to reflux disease is comparable. A meta-analysis of eight randomized controlled trials found that PPI therapy had no significant advantage over placebo in achieving improvement of symptoms of suspected GERD-related chronic laryngitis [39]. Park et al. demonstrated that double-dose PPI is superior to once-daily PPI in controlling chronic cough symptoms [40]. Aggressive acid suppression with twice-daily PPI for at least 4 months is warranted for the treatment of GERD-related chronic cough [41].

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