



Overview of medical therapy for gastroesophageal disease

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Gastroesophageal reflux disease (GERD) is now the most common upper gastrointestinal disorder in the Western Hemisphere. The disease burden of GERD results from the unfavorable impact of symptoms on well being and quality of life. While abnormalities of the antireflux barrier (lower esophageal sphincter) are important in the pathophysiology of GERD, severity of symptoms and esophageal mucosal injury can be correlated with the total time that the esophageal mucosa is in contact with acid (time pH < 4). Hence, acid suppression comprises the principle approach to therapy [1]. The identification of a specific molecular mechanism of acid secretion, the proton pump (HK ATPase) has resulted in the development of the proton pump inhibitors (PPIs), which have superseded the histamine H₂- receptor antagonists (H₂RAs) as the primary agents of choice for achieving goals of medical therapy of GERD which include symptom relief, improving quality of life, healing and prevention of mucosal injury in most patients.

Efficacy and safety of medical therapy

The efficacy of antireflux medications in symptom relief and healing of mucosal injury can now be judged from well-designed clinical trials with clinically meaningful endpoints. Histamine H₂- receptor antagonists (H₂RAs) provided the first effective antisecretory therapy for GERD. These agents are extremely safe but are limited by the need for frequent dosing, development of tolerance, and pharmacodynamic interaction with food intake [2,3]. Four H₂RAs are available and are equivalent. Symptom relief is seen in 38% to 72% and healing in about half of the patients treated with twice daily doses of H₂RAs.

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Data accumulated with PPIs in comparison to placebo and H₂RAs make these the drugs of choice in most GERD patients with or without esophageal mucosal injury [4–8] and in those with extraesophageal manifestations. PPIs provide patients with more complete symptom relief and heal inflammation, facilitating these goals in a more rapid fashion when compared to H₂RAs. The first 4 available PPIs (omeprazole 20 mg, lansoprazole 30 mg, rabeprazole 20 mg, or pantoprazole 40 mg) have been comparable in the degree of gastric acid suppression [9] and in the efficacy of treatment for GERD in terms of symptom control and healing erosions when taken at standard doses [10]. Symptom relief and healing have been documented in 78% to 92% of patients with PPIs. In a meta-analytic comparison there was no difference in overall heartburn symptom resolution with the newer PPIs compared with omeprazole at 4 weeks [11].

Esomeprazole, a stereoisomer of omeprazole, is the first PPI to show a statistical advantage in healing and symptom relief over treatment with omeprazole and lansoprazole in patients with erosive esophagitis particularly in patients with grade C and D [12–14]. In comparative trials, after 5 days of once daily administration, esomeprazole 40 mg controlled intragastric pH to a significantly greater degree than other PPIs, which is likely the explanation for the superior healing at higher grades of erosive esophagitis [15].

PPIs have an excellent short-term safety profile, with the most common side effects headache, nausea and diarrhea seen with similar frequency to placebo. Long term safety issues with PPIs have largely been eliminated, with no long term complications reported in up to 11 years of continuous use [16]. There is no evidence that it is necessary to perform regular routine laboratory testing or endoscopy with gastric biopsies in such patients. One study reported the increased risk of atrophic gastritis in *H pylori* positive patients receiving PPIs, however a Food and Drug Administration (FDA) panel concluded that based on the available data, PPI relabelling for cancer risk is not warranted [17]. No studies to date have reported the development of dysplasia or gastric adenocarcinoma with long term PPI use in humans. Dose reduction of PPIs is not necessary in patients with compromised renal or hepatic function. Some PPIs may theoretically interact with drugs metabolized via the cytochrome P450 system. Clinically, this is rarely an issue.

Erosive GERD

PPIs are the mainstay for therapy of severe and complicated GERD by virtue of effective acid suppression. Meta-analytic studies support the statement that healing of esophagitis is directly related to the percentage of a 24-hour period that the gastric pH is maintained above a pH of 4. Once-daily dosing of a PPI (omeprazole 20 mg, lansoprazole 30 mg, pantoprazole 40 mg or rabeprazole 20 mg) is effective for acute and long-term management of GERD. Healing rates for erosive esophagitis range from 78% to 93% at 8 weeks and are comparable when PPIs are compared head to head. Maintenance studies report continued

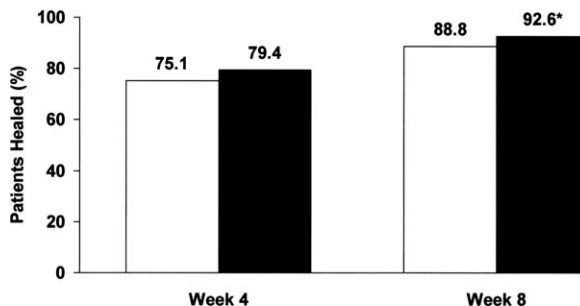


Fig. 1. Healing rates of erosive esophagitis at weeks 4 and 8 comparing esomeprazole 40 and lansoprazole 30 across grades A through D LA grade erosive esophagitis. (Data from Castell et al. *Am J Gastroenterol.* 2002;97:575)
 * $P = 0.0001$ versus lansoprazole.

healing of erosive esophagitis in 80% to 90% of patients over 12 months of study [18]. On higher doses one would expect somewhat higher rates of response, but few data are available. Two large multicenter, randomized, double blind trials have shown superiority of esomeprazole 40 mg to omeprazole 20 mg at 8 weeks across all grades in the treatment of GERD patients with erosive esophagitis with comparable safety and tolerability profiles (Fig 1). Similar results have been shown comparing esomeprazole 40 mg to lansoprazole 30 mg once daily (Fig 2).

In patients with peptic esophageal strictures, PPIs in comparison with H2 antagonists have shown superior healing rates and required fewer dilatations to relieve dysphagia [19,20].

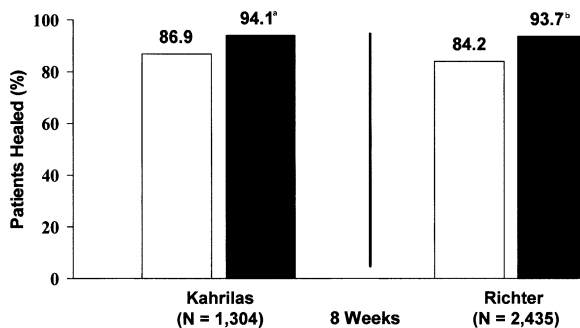


Fig. 2. Healing rates of erosive esophagitis (Y axis) in two pivotal trials submitted to the FDA comparing esomeprazole 40 mg to omeprazole 20 mg showing statistical superiority of esomeprazole to omeprazole in doses shown. (Data from Kahrilas et al. *Aliment Pharmacol Ther.* 2000;14:1249–58; Richter et al. *Am J Gastroenterol.* 2001;96:656–65)
 * $P \leq 0.05$.

† $P < 0.001$ versus omeprazole.

Non-erosive reflux disease

In patients with endoscopy negative reflux disease, symptom resolution and prevention of symptom relapse are end points of therapy. There is ample evidence to suggest that symptom severity, quality of life scores and therapeutic requirements of patients with non-erosive reflux disease are similar to those with erosive esophagitis. Several placebo-controlled studies have shown that PPIs are more effective than placebo in achieving symptom control. One of these studies suggested that abnormal esophageal acid exposure on pH monitoring significantly influenced the response to treatment, with a greater response in patients with an abnormal acid exposure [21]. Though clearly superior to placebo and H₂RAs [22] in terms of therapeutic efficacy in relieving symptoms, the PPIs seem to be less effective in these patients than in patients with erosive disease. Carlsson et al showed that a 20 mg dose of omeprazole achieved complete symptom relief in only 48% of patients with erosive esophagitis when compared with 29% of patients without erosive disease after 4 weeks of therapy [23]. This suggests that some patients with so called non-erosive GERD have symptoms mediated by something other than acid, or require more acid control to relieve symptoms.

Barrett's esophagus

The goals of therapy in patients with Barrett's esophagus include elimination of GERD symptoms, maintenance of healed mucosa, and prevention of disease progression, similar to all patients with GERD. Patients with Barrett's esophagus have higher levels of esophageal acid exposure than other patients with GERD requiring higher than usual dose of PPIs for esophageal acid control [24]. They also have a higher frequency of reflux associated esophageal motility abnormalities, which are associated with a higher risk for nocturnal acid reflux despite PPI therapy [25]. Though normalization of esophageal milieu by acid suppression minimizes cellular proliferation, controversy regarding the possible regression of Barrett's epithelium from medical therapy continues. While some have suggested that aggressive anti reflux therapy is indicated in patients with Barrett's esophagus, no studies have proven that it alters the natural history of this disease. Medical therapy is as effective as surgery in the treatment of Barrett's patients, including effect or lack thereof on progression to cancer.

Maintenance therapy

Healing of mucosal injury or achievement of symptom control alone is not sufficient to alter the natural history of this disease and almost all patients require some form of maintenance therapy.

Individuals with endoscopically documented erosive esophagitis have shown recurrence rates ranging from 75% to 92% following discontinuation of PPI [26]. In addition, if a patient has a recurrence and is brought back into remission with a

PPI, there is a 90% chance that the patient will have another recurrence if the PPI is discontinued again. In a landmark study comparing five maintenance regimens for patients with healed esophagitis, Vigneri et al [18] showed significantly higher remission rates with PPI therapy than with H₂RAs or prokinetics. Various attempts to use low dose PPI maintenance therapies for reasons of cost have only met with varying success, as most patients relapse within a few months. Recently Ladas et al [27] reported that using gastric pH monitoring after healing, one can predict which patients are more likely to remain in remission with low dose omeprazole therapy.

Step down therapy has been advocated by some though data are weak. Inadomi et al recently examined the feasibility of step down therapy in patients with non erosive symptomatic GERD who were rendered asymptomatic with PPIs [28]. After obtaining baseline demographic and quality of life information, PPIs were withdrawn from the patients in a stepwise fashion. Fifty-eight percent of patients were asymptomatic after discontinuation of treatment after 1 year of follow-up; 34% required H₂RAs; 7% prokinetic agents; 1% both; whereas 15% remained asymptomatic without medication. Although quality of life was not significantly different, management costs decreased by 37%. Younger age and heartburn as the predominant symptom predicted unsuccessful PPI step-down management, suggesting those with “true GERD” will require full dose maintenance.

Management of the refractory patient

PPIs are the most potent drugs available for the treatment of GERD and are definitely the standard by which medical refractoriness should be defined. As well as these agents work, they do not afford symptom relief or heal mucosal injury in all patients. Patients may fail PPI therapy due to the following: (1) An incorrect diagnosis of GERD, (2) Non-acid gastroesophageal reflux, (3) Failure to control gastric acidity. Several reasons have been postulated as to why PPI therapy may fail to control gastric acidity (Box 1).

Seventy percent of normal subjects on PPI therapy twice a day have periods of gastric pH less than 4 lasting for 60 minutes or longer during the night; this is termed nocturnal gastric acid breakthrough (NAB) [29]. This phenomenon, which is of potential clinical importance when accompanied by reflux of acid into the esophagus, appears to be infrequent in normal subjects and patients with uncomplicated GERD, but may be seen in up to 50% of patients with Barrett’s esophagus and scleroderma [30]. In the difficult to manage patients who have breakthrough symptoms despite twice a day PPI therapy before breakfast and dinner, the authors perform combined intragastric and intraesophageal pH monitoring on therapy. If there is symptom correlation with esophageal acid exposure, one is more certain of this association. In patients with ineffective gastric pH control despite maximal dose of PPI, changing from one PPI to another may be considered [31]. If there is NAB with GERD, the authors consider adding a bedtime H₂RA to twice a day PPI therapy. Several studies looking at various therapeutic regimens including single

Box 1. Suboptimal ppi response—potential mechanisms

Oral bioavailability of PPIs varies considerably between subjects and may be decreased further when taken along with antacids or H₂ blockers.

PPIs are least efficacious during periods of parietal cells quiescence and have a lesser effect on acid suppression when taken at times other than just before a meal.

Hypersecretors may show a diminished effect to PPIs, but hypersecretion is uncommon in GERD.

Genetic variations in hepatic cytochrome P 450 2C19 enzyme may result in more rapid metabolism of PPI thereby limiting potency.

Though this is controversial, the eradication of *H pylori* may decrease PPI efficacy.

There is a small group of patients who are PPI resistant despite normal blood levels of the drug, strongly suggesting an abnormality of the proton pump, which has however not been identified.

and double dose PPI therapy in combination with the H₂RAs demonstrate a hierarchy of intragastric pH control outlined in Box 2 [32,33].

In the rare patient with no symptoms or esophageal acid exposure during pH testing but continued gastric acid production the authors generally do not add a bedtime H₂RA unless they have impaired lower esophageal sphincter mechanics or ineffective esophageal motility on manometry which places them at higher risk for nocturnal reflux. The role of high dose esomeprazole in the management of refractory patients awaits further study.

In a well designed study, Fackler et al showed that the beneficial effects of combined H₂RA and PPI are maximal with the first dose after which significant differences in pH control are lost after 1 week of therapy as a result of development of H₂RA tolerance [34]. This is in contrast to Xue et al who demonstrated continued pH control in patients treated with PPI BID plus H₂RA at

Box 2. Hierarchy of intragastric pH control

- PPI once a day
- PPI plus H₂ HS (OTC probably OK)*
- PPI BID*
- PPI BID plus H₂ HS*

* These regimens have never been tested head to head in clinical trials.

bedtime (HS) for more than 28 days [35]. These differences suggest that tolerance to H₂RA HS may occur but is not universal.

It is tempting to refer refractory patients for surgery if a patient fails optimized medical therapy. The clinician should be reminded that the best predictor of surgical success is complete response to medical therapy and the ideal candidate for fundoplication is the patient who has complete elimination of symptoms with medications but does not want to take them long term. Therefore, the small group of patients who continue to be “medically refractory” on maximal acid suppressive therapy should be counseled that surgery does not carry a guarantee of success.

Initial treatment of reflux disease

As our understanding of the physiology of acid production, pathogenesis of heartburn, mechanism of action of acid suppressants, and their safety profiles have changed over time so has the choice of therapy. The practice of step-up approach to GERD therapy, favored in many algorithms may not be optimal. Several studies have concluded that the direct costs of initial PPI therapy are lower than those of initial therapy with H₂RA, given the superior and prompt response achieved with the former class of drugs [36].

Recently, Howden et al assessed and compared the effectiveness of management of heartburn symptoms in patients with GERD by sustained treatment with either an H₂RA, or a PPI or with step up or step down regimens of PPI and H₂RA. At the end of 20 weeks, the group treated with continuous PPI experienced less severe heartburn and more 24-hour heartburn free periods than the other 3 groups [37]. This study compels us to reexamine the value of step up and step down schedules in the treatment of GERD.

Atypical manifestations of GERD

Over the past thirty years several extraesophageal symptoms have been attributed to GERD. An association with GERD may occur in as many as 82% of patients with asthma, 50% of patients with unexplained chest pain and 78% of patients with chronic hoarseness. Several authors have documented a low prevalence of classic symptoms of GERD in these patients. Unfortunately, the majority of treatment trials involving patients with extraesophageal GERD are uncontrolled and fail to address long-term maintenance therapy. These patients are difficult to manage usually requiring higher dose PPI therapy for longer duration than those with typical GERD.

Asthma

Field and Sutherland’s review of 12 studies involving 326 subjects suggested that medical antireflux therapy improved asthma symptoms in 69%,

reduced need for asthma medication in 62%, but had minimal or no effect on pulmonary function [38]. However most of these studies were done before the advent of PPIs (only 4 of 12 studies used a PPI). An uncontrolled prospective cohort study in 30 asthmatics demonstrated that many patients require more than 20 mg of omeprazole daily for optimal response and incremental response in asthma scores occurred over a three-month period [39]. A favorable response to therapy was seen in patients who presented with symptoms of regurgitation greater than once a week and those with demonstrable abnormal proximal esophageal acid exposure. Recently two well designed randomized, placebo-controlled, double-blind crossover studies evaluating PPI therapy in asthma patients with GERD demonstrated improvement in pulmonary function [40,41].

Unexplained chest pain

Though the optimal therapeutic trial is yet to be determined, several studies have demonstrated the usefulness of an empiric trial of PPI therapy in determining the etiological significance of GERD in patients with unexplained chest pain. In the only randomized, double-blind, placebo-controlled treatment trial, Achem et al studied the effect of omeprazole 20 mg bid on 36 patients with unexplained chest pain who were proven to have GERD, for an 8 week period. Compared to placebo, omeprazole therapy markedly improved the fraction of days patients experienced chest pain, individual daily pain scores, and symptom severity scores [42].

Reflux laryngitis

Several uncontrolled studies have suggested a beneficial role for medical antireflux therapy in the management of patients with chronic laryngitis. The type of therapy used and the dose and duration of treatment were variable among the studies. Subjective improvement in symptoms and improvement in follow-up laryngeal examinations were the most common outcome parameters followed in these different studies. Most of these studies did not identify factors that predict a favorable response, although two studies suggested that improvement in symptoms occurred more often in milder laryngeal abnormalities. Overall these studies emphasize the variability of response in patients with this manifestation, need for longer therapeutic trial with higher doses of PPIs especially in severe disease and rapid relapse of symptoms when therapy is discontinued. A recent study by El-Serag et al [43] comparing lansoprazole 30 mg twice daily to placebo provides the only evidence from a placebo-controlled randomized study supporting the efficacy of gastric acid suppression in treating chronic laryngitis.

Chronic cough

Aggressive antireflux therapy has resulted in resolution of GERD related chronic cough in many uncontrolled studies. In the only double blinded randomized study using response to therapy as the gold standard, Ours et al showed effectiveness of a trial of omeprazole 40 mg in the morning and at bedtime in patients with acid related cough [44]. This remission lasted up to 1 year, despite dose reduction of the drug down to 20 mg or 40 mg daily. In a recently published study Kiljander et al using omeprazole, 40 mg per day, a dose which may not be sufficient to inhibit acid reflux in all patients, showed relief in GERD related chronic cough after 8 weeks, an effect that continued despite cessation of the drug [45].

Suggested approach to the therapy of extraesophageal GERD

Therapeutic trials for this condition often require near complete acid suppression with a PPI twice daily. It is our practice to start empiric therapy with this dose given before breakfast and dinner for 2 to 3 months understanding that many may eventually require longer treatment trials to achieve optimal results. Patients who have > 50% improvement in symptoms to this trial are continued for an additional 4- to 8-week period. If complete symptom relief is not achieved, prolonged ambulatory pH monitoring (combined impedance/pH can be considered when available) while on therapy is indicated at this point to assess the adequacy of intragastric acid suppression and ensure elimination of distal and proximal esophageal acid exposure. If there is incomplete acid suppression, especially with nocturnal acid breakthrough, additional medical therapy such as addition of a H₂RA at bedtime is given. Given the multifactorial nature of etiology for such atypical GERD symptoms, patients with low suspicion for GERD may benefit from a screening ambulatory pH test to confirm the existence of excessive acid reflux prior to an empiric trial of medication. Though the sensitivity and specificity of such testing are unclear, it is rare in our experience for extraesophageal symptoms in a patient with a totally normal pH test to respond to antireflux therapy. The role of esomeprazole in extraesophageal disease awaits study. Experience suggests that patients with extraesophageal GERD who do not respond to aggressive acid suppression, do not fair well with antireflux surgery.

Novel therapeutic targets for control of GERD

A different pharmacological option, which may well be of clinical relevance is the use of prokinetic or lower esophageal sphincter tone altering agents. Several pharmacological agents like baclofen, loxiglumide, morphine, and nitric acid synthetase inhibitors targeted at inhibiting transient lower esophageal sphincter relaxation (tLESR), a prerequisite for the development of acid reflux, are being

evaluated. In one of many trials in humans using baclofen, the most potent and safest gamma aminobutyric acid type B agonist agent available, Zhang et al recently demonstrated inhibition of reflux episodes by inhibition of tLESR [46]. It has been proposed that control of tLESR may be of value in patients with mild disease, or in patients who continue to have mild breakthrough symptoms, especially regurgitation, on PPI therapy. There are some new agents currently under clinical investigation that may have stimulating effects on both the lower esophageal sphincter and the body of the esophagus. Those agents being considered for investigation in this regard include norcisapride, a metabolic product of cisapride with fewer cardiac adverse effects and tegaserod, a partial 5HT₄ agonist which was recently approved by the FDA for the treatment of constipation predominant irritable bowel syndrome.

Targeting oxidative stress involved in the pathogenesis of reflux esophagitis seems to be a fascinating strategy. Oh et al recently presented evidence that an antioxidant substance (DA-9601) significantly attenuates the severity of esophageal inflammation in a rat model of esophagitis [47]. They also demonstrated that DA 9601 was more effective in prevention of esophagitis in rats compared to H₂ antagonists.

Summary

The last twenty years have seen an evolution of much improved strategies in the medical treatment of GERD. Current therapy is targeted at acid suppression, to deal with consequences of mucosal injury and afford resolution of symptoms. Given their modest efficacy, there is no longer much support for initial treatment with H₂RAs. PPIs have been shown to provide the highest levels of symptom relief and esophageal healing, in addition to preventing relapse and complications. With this class of agents, the clinician is able to prescribe a drug that is as highly effective as surgery for the purpose intended [48], without worrying about long term sequelae of acid suppression. It appears that patients with extraesophageal GERD must be treated with higher doses of pharmacologic therapy, principally with the PPIs, for longer periods of time to achieve complete relief of symptoms when compared to patients with heartburn and erosive esophagitis. There is still no clear consensus as to whether aggressive acid suppression alters the natural history of Barrett's esophagus. Based on their initial success, it appears that the next generation of evolving medical therapies will continue to play an important role in the management of GERD. The outcome from medical therapy is the standard against which the results of the novel endoscopy anti-reflux treatments will be measured.

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