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(REVIEW ARTICLE)

Review on management of GERD

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Abstract

Gastroesophageal reflux disease (GERD) is a chronic disorder of the upper gastrointestinal tract with global distribution. The incidence is on the increase in different parts of the world. It is characterized by heartburn and/or regurgitation symptoms is one of the most common gastrointestinal disorders managed by gastroenterologists and primary care physicians. Optimization of therapy (improving compliance and timing of PPI doses), or increasing PPI dosage to twice daily in select circumstances, can reduce persistent symptoms. In patients with residual reflux, medications like H2 blockers, Prokinetics and baclofen may be used. In those with functional heartburn or reflux sensitivity neuro-modulators form an integral part of any therapeutic approach.

Keywords: Gastroesophageal reflux; Proton pump inhibitors; Prokinetics; Esophageal; Management

1. Introduction

Gastro-esophageal reflux disease (GERD) reflects symptoms or mucosal damage caused by the reflux of gastric contents from the stomach into the esophagus. It affects approximately 20–30% of the population worldwide and is particularly evident in Western countries.

GERD is a major public health issue that is becoming increasingly common. It is associated with a significant economic burden and a lower quality of life. Based on the latest meta-analysis, the global prevalence of GERD was estimated as 13.9%. According to the United Nations 2017 Revision of World Population Prospects, 1.03 billion people have GERD.[1] Ho et al. (1994) determined that the prevalence of GERD symptoms was 1.6% in a multiracial Asian country, Singapore.[2] Although gastroesophageal reflux is primarily a disorder of the lower oesophageal sphincter (LES), it can be caused by a variety of physiological or pathologic factors. The most common cause is transient relaxation of the lower oesophageal sphincter, which is the brief period of inhibition of the lower oesophageal sphincter tone that occurs independently of swallowing. However, their frequency increases postprandially, causing acid reflux in GERD patients. Other contributing factors include low LES pressure, hiatal hernia, oesophageal obstruction, and delayed gastric emptying.[3]

2. Etiology

Currently, there is no known cause to explain the development of GERD. Over the years, several risk factors have been identified and implicated in the pathogenesis of GERD. Motor abnormalities such as esophageal dysmotility causing impaired esophageal acid clearance, impairment in the tone of the lower esophageal sphincter (LES), transient LES relaxation, and delayed gastric emptying are included in the causation of GERD. Anatomical factors like the presence of hiatal hernia or an increase in intra-abdominal pressure, as seen in obesity are associated with an increased risk of developing GERD. A meta-analysis by Hampel H et al. concluded that obesity was associated with an increased risk of developing GERD symptoms, erosive esophagitis, and esophageal carcinoma. The ProGERD study by Malfertheiner, et al. evaluated the predictive factors for erosive reflux disease in more than 6000 patients with GERD and noted that the

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odds ratio for the erosive disease increased with the body mass index (BMI). Several other risk factors have been independently associated with the development of GERD symptoms that include age ≥50 years, low socioeconomic status, tobacco use, consumption of excess alcohol, connective tissue disorders, pregnancy, postprandial supination, and different classes of drugs which include anticholinergic drugs, benzodiazepines, NSAID or aspirin use, nitroglycerin, albuterol, calcium channel blockers, antidepressants, and glucagon.[4]

The underlying causes of GERD are unknown despite advances in understanding the pathophysiology, and cure remains out of reach. Known underlying mechanisms include increased transie lower oesophageal sphincter relaxations (TLOSRs) that promote increased acid and bile reflux, oesophageal hypersensitivity to refluxed gastric contents and anatomical derangements of the lower oesophageal sphincter including large hiatal hernia. However, other less well-recognized abnormalities may be important, from disordered gastric accommodation linked to duodenal inflammation in functional dyspepsia or bacterial fermentation in the intestine in IBS that both may increase TLOSRs, or a T-cell response in the oesophagus mediated by cytokine release that may induce oesophagitis. Therefore, it is not surprising a substantial number of patients with suspected GERD do not respond to effective acid suppression therapy.[5]
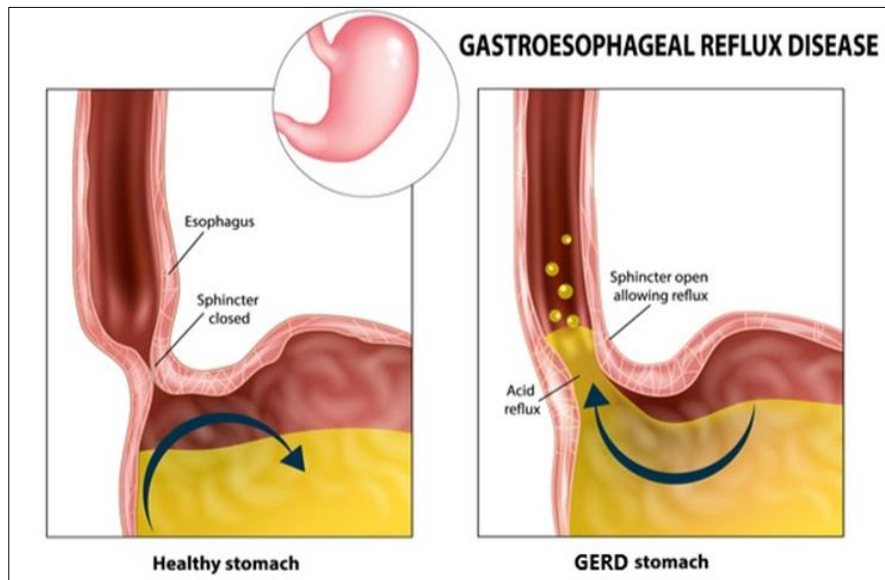
Figure 1 GERD disease

2.1. Disease burden

The disease burden of GERD is high; prevalence studies indicate widespread geographic variation but approximately 20% of the population experience weekly heartburn. In a large Swedish population-based study, a clinically relevant impairment of health-related quality of life amongst those with daily heartburn symptoms, in comparison to individuals without reflux symptoms, was present on all eight quality of life (Short Form-36) dimensions, and on five dimensions in those with weekly symptoms, but only on one dimension amongst those with less than weekly symptoms, supporting the contention the frequency of reflux symptoms distinguishes health from disease.

2.2. Pathophysiology

The pathophysiology of GERD is multifactorial and is best explained by various mechanisms involved, including the influence of the tone of the lower esophageal sphincter, the presence of a hiatal hernia, esophageal mucosal defense against the refluxate and esophageal motility.[6]

2.3. Impaired Lower Esophageal Sphincter (LES) Function and Transient Lower Esophageal Sphincter Relaxations

The LES is a 3-4 cm tonically contracted smooth muscle segment located at the esophagogastric junction (EGJ) and, along with the crural diaphragm forms the physiological EGJ barrier, which prevents the retrograde migration of acidic gastric contents into the esophagus. In otherwise healthy individuals, LES maintains a high-pressure zone above intragastric pressures with transient relaxation of the LES that occurs physiologically in response to a meal facilitating the passage of food into the stomach. Patients with symptoms of GERD may have frequent transient LES relaxations (TLESRs) not triggered by swallowing, resulting in exceeding the intragastric pressure more than LES pressures

permitting reflux of gastric contents into the esophagus. The exact mechanism of increased transient relaxation is unknown, but TLESRs account for 48-73% of GERD symptoms. The LES tone and TLESRs are influenced by factors such as alcohol use, smoking, caffeine, pregnancy, certain medications like nitrates, and calcium channel blockers.[7]

2.4. Impaired esophageal mucosal defense against the gastric refluxate

The esophageal mucosa comprises various structural and functional constituents that function as a protective defense barrier against the luminal substances encountered with GERD. This defensive barrier can be breached by prolonged exposure to the refluxate, which consists of both acidic gastric contents (hydrochloric acid and pepsin) and alkaline duodenal contents (bile salts and pancreatic enzymes) leading to mucosal damage. The influence of gastroparesis on GERD is unknown. It is believed that delayed gastric emptying contributes to GERD symptoms due to gastric distention and increased exposure to the gastric refluxate.

2.5. Defective esophageal peristalsis

Normally, the acidic gastric contents that reach the esophagus are cleared by frequent esophageal peristalsis and neutralized by salivary bicarbonate. In a prospective study by Diener *et al.*, 21% of patients with GERD were noted to have impaired esophageal peristalsis leading to decreased clearance of gastric reflux resulting in severe reflux symptoms and mucosal damage.[8]

2.6. Non-Esophageal Symptoms of Gastroesophageal Reflux

Disease By exposing the esophagus to refluxate, GERD induces esophageal symptoms (heartburn, regurgitation, and esophageal chest pain) and lesions (reflux esophagitis, strictures, and Barrett's esophagus).[1] However, GERD has also been implicated in the pathogenesis of a number of so-called atypical or extra-esophageal symptom manifestations, including ear, nose, and throat (laryngitis and pharyngitis); pulmonary (asthma and cough); and dental (dental erosion) disorders.[1] There is controversy over the role of GERD in the pathogenesis of these disorders, and little is known about the pathophysiology of extra-esophageal GERD manifestations.[49,50] Extra-esophageal manifestations of GERD could arise through a direct reflux mechanism, in which micro-aspiration of gastric contents causes damage to ear, nose, and throat (laryngopharyngeal reflux) or respiratory epithelia. This mechanism is supported by studies showing reflux into the upper airways using pharyngeal pH monitoring or analysis of gastric juice components (pepsin and bile) in broncho-alveolar lavage fluid. However, there is no evidence from large subsets of patients with presumed extra-esophageal manifestations of GERD for direct reflux exposure of supra-esophageal tissues—even when gastro-esophageal reflux events correlate with extraesophageal events (such as bronchoconstriction during esophageal acidification). For these cases, the esophageal airway reflex theory proposes an indirect mechanism, in which distal esophageal reflux stimulates vago–vagal reflex pathways, leading to changes in function and complications in extra-esophageal segments (bronchoconstriction, cough, and altered upper airway reactivity or sensitivity).[9]

2.6.1. Effects of Obesity

The relationship between obesity and GERD cannot be ignored in a discussion focused on pathophysiology; GERD correlates with obesity, and there is a logical explanation for this. Movement of gastric juice from the stomach into the esophagus is determined by the pressure gradient between the abdomen and the chest. Multiple studies have shown that intragastric pressure is higher in obese patients, and that pressure correlates with body mass index and waist circumference. Increased intra-abdominal pressure can also increase strain on the anti-reflux barrier, so obesity is associated with a higher risk of hiatus hernia. These factors provide a recipe for severe reflux disease, supported by clinical studies. Interestingly, small amounts of weight loss (approximately 10–15 lb) can reduce GERD symptoms. The direct effect of weight loss could be to reduce the pressure gradient and burden on the anti-reflux barrier.

Although symptoms of GERD in a case–control study from Sweden were associated with nearly 8-fold increased risk of oesophageal adenocarcinoma (OR = 7.7, 95% CI 5.3–11.4), in the general community the symptoms of reflux are not associated with any increased mortality despite negatively impacting on quality of life, and most with symptoms of GERD in the population have a normal upper endoscopy.

3. Management of Gerd

The goals of managing GERD are to address the resolution of symptoms and prevent complications such as esophagitis, BE, and esophageal adenocarcinoma. Treatment options include lifestyle modifications, medical management with antacids and antisecretory agents, surgical therapies, and endoluminal therapies.[10]

3.1. Lifestyle Modifications

Lifestyle modifications are considered to be the cornerstone of any GERD therapy. Counseling should be provided about the importance of weight loss given that underlying obesity is a significant risk factor for the development of GERD, and studies have shown that weight gain in individuals with a normal BMI has been associated with the development of GERD symptoms. Individuals should also be counseled about avoiding meals at least 3 hours before bedtime and maintaining good sleep hygiene as it has been shown that minimal disturbances in sleep are associated with suppression of TLESRs, resulting in decreased reflux episode. Studies have also shown improvement in GERD symptoms and pH monitoring studies with the elevation of the head end of the bed. Diet modification with the elimination of chocolate, caffeine, and spicy foods, citrus, and carbonated beverages in GERD is controversial and is not routinely recommended.[10]

Medication	Recommended Daily Dose	Recommended Administration Frequency	Common Side Effects
Histamine$_2$-Receptor Antagonists (H2RAs)[a,b]			
Ranitidine	150 mg	Twice daily	Headache, diarrhea,
	300 mg	At bedtime	thrombocytopenia
Famotidine	20 mg	Twice daily × 6 wk	
Cimetidine	400 mg	4 times daily × 12 wk	
	800 mg	Twice daily × 12 wk	
Nizatidine	150 mg	Twice daily	
Proton Pump Inhibitors (PPIs)			
Pantoprazole	20-40 mg	All agents are given	Pneumonia, electrolyte disturbances
Lansoprazole[b]	15-30 mg	once daily up to 8 wk	(e.g., magnesium), infections,
Esomeprazole[b]	20-40 mg	Recurrence may require	*Clostridium difficile*–associated
Omeprazole[b]	20-40 mg	an additional 4-8 wk	diarrhea, bone fractures,
Rabeprazole	20 mg	Max dose of PPIs can be	renal impairment, dementia,
Dexlansoprazole	30-60 mg	given twice daily	rebound gastritis
Miscellaneous Agents			
Metoclopramide	10-15 mg	2-4 times a day (single doses of 20 mg have been used as an alternative)	Drowsiness, agitation, irritability, depression, dystonic reactions, tardive dyskinesia
Baclofen	5-20 mg	3 times daily	Dizziness, somnolence, constipation
Melatonin[b]	3-6 mg	Daily at bedtime	Somnolence

a Requires renal adjustment. b Available OTC.
GERD: gastroesophageal reflux disease; max: maximum. Source: References 5, 7, 8.

Figure 2 Common treatment available for GERD

4. Proton Pump Inhibitors (PPIS)

PPIs, benzimidazole and imidazopyridine derivatives, changed the natural history of acid-related disorders –peptic ulcer (PU), erosive gastropathy and GERD)–. They have superior therapeutic efficacy and clinical effectiveness than histamine type 2 receptor antagonists (H2RAs) to suppress acid secretion in a sustained manner. Omeprazole was the first drug of this pharmacological class (1989); lansoprazole (1995), rabeprazole (1999), pantoprazole (2000) and esomeprazole (2001) were subsequently introduced in the market. The annual direct and indirect cost of treating GERD in the U.S. exceeds 10 billion dollars. However, PPI response rate over time is far from being optimal, and the adverse event incidence has increased from 30,000 in 1998 to 90,000.

5. Drug profile

5.1. Rabeprazole

Rabeprazole is a proton pump inhibitor (PPI) and as such covalently binds with and inactivates the gastric parietal cell proton pump (H$^+$/K$^+$-ATPase). This inhibits in turn gastric acid production and raises gastric pH. Proton pump inhibitors are indicated in the management of acid-related disorders such as gastroesophageal reflux disease (GERD) and peptic ulcer disease, in association with *Helicobacter pylori* eradication therapy when needed.[11]

5.2. Mechanism of Action

The human stomach contains over a billion parietal cells secreting 0.16 M hydrochloric acid (HCl) in response to three physiological stimuli: acetylcholine, histamine and gastrin. The proton pump (PP) of parietal cells is responsible for gastric acid secretion, which is carried out in three phases: 1) cephalic, 2) gastric, and 3) intestinal, accounting for 30, 50 and 20%, respectively (8). These physiological particulars explain why these drugs are recommended to be taken 30 minutes before meals, so as to maximize proton pump inactivation (30% + 50% = 80%) and thus optimize their performance, since it is essential to bear in mind that the t½ of PPIs is very short (0.7-1.2 hours). Pharmacokinetic and pharmacodynamic differences can be observed among the different PPIs, which might influence their clinical application. However, the genotype or drug interactions may cause a same PPI to have widely different therapeutic effects on individuals. PPIs are prodrugs; they are inactive weak bases with a neutral charge (lipophilic) that pass through the stomach intact and are absorbed in the duodenum. They reach the bloodstream (plasma concentration ≈ 0.5 to 2 mg/ml), bind to proteins (> 95%), cross the parietal cell membrane and selectively accumulate in the acidic canaliculi of the parietal cell basolateral membrane (organ specificity).
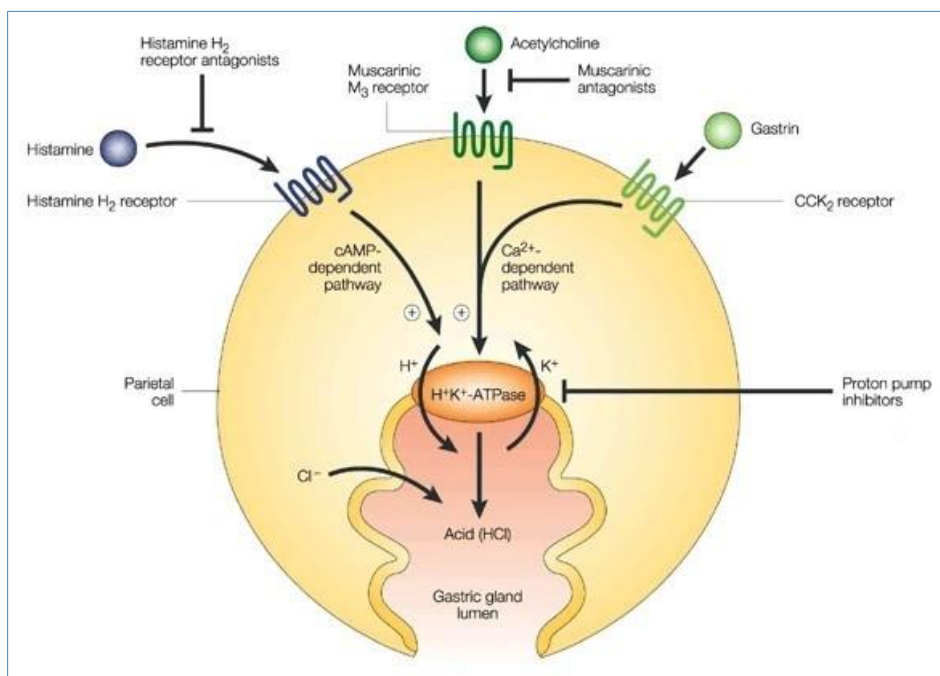
Figure 3 Mechanism of action of PPIs

In the body, the parietal cell is the only membrane-enclosed space with a pH < 4; rabeprazole can also accumulate in other compartments with a pH > 4 (neuron, kidney and bone). PPI selective activation is induced by a first protonation of the pyridine moiety at a pKa1 value ranging from 3.8-4.5, which renders them less permeable and increases their accumulation. A second protonation, pKa2 (benzimidazole or imidazopyridine moie ty), on the acidic surface or in the acid compartment of the proton pump effects a chemical rearrangement producing an active metabolite (sulfenic acid) which inhibits the H+,K+ ATP ase enzyme. The pKa2 determines the activation rate of PPIs and affects the stability of acid suppression. [12]

The active form of the drug forms covalent disulphide bonds with cysteines accessible from the exoplasmic surface of the enzyme thus inhibiting it; studies by Sachs et al. showed that proton pump inhibition is not irreversible. What does reversibility of PPI binding to proton pumps depend on? After inhibition by PPIs, recovery of gastric acid secretion depends on two factors: a) protein turnover (synthesis of new proton pumps) which is determined by the enzyme half-life (t½) (≈ 54 hours); and b) reversal of the disulphide bonds. The half-time of recovery of gastric acid secretion in rats following inhibition by omeprazole is 15 hours; in humans it is 28 and 46 hours with omeprazole and pantoprazole, respectively. The PPI binding pattern to cysteine (sixth transmembrane do - main –TM6–) is what makes PP inhibition reversible or not; omeprazole and esomeprazole bind to cysteines 813 and 892, while lansoprazole and rabeprazole bind to cysteine 813, 892 and 321. Up to 84% of omeprazole binds to cysteine 813, whereas 50% of pantoprazole and tenatoprazole binds to cysteine 813 and the other 50% to cysteine 822. Glutathione, an antioxidant that protects cells from reactive oxygen species (free radicals and peroxides), cleaves disulphide bonds with cysteine 813, which is located

more superficially in the membrane. On the other hand, cysteine 822 is located deep within the TM6 which makes it inaccessible to glutathione, thus rendering inhibition of gastric acid secretion more stable and less reversible.

Plasma t½ of tenatoprazole is more prolonged than that of omeprazole, lansoprazole, pantoprazole, rabeprazole and esomeprazole (8 versus 1-1.5 hours); therefore, its antisecretory effect last longer. Variations in the crystal structure and hydrophobic nature result in an increased bioavailability of the sodium form of PPIs when compared to the free form. PPIs differ in their behavior due to their bioavailability (77% for pantoprazole, 80-90% for lansoprazole, and 89% for esomeprazole), concentrations –maximum (Cmax) and minimum (Cmin)–, AUC0-24, and elimination pathways.(15) PPIs are subject to hepatic metabolism by isoenzymes of the CYP system [primarily CYP2C19 (S-mephenytoin-hydroxylase) and CYP3A4 (except rabeprazole)] that transform them into inactive molecules prior to their elimination.[13]

5.3. Metabolism of Rabeprazole

There are some differences among PPIs that result from their degradation by the cytochrome P450 (CYP) system. Omeprazole is metabolized to 5'-0H-omeprazole (by CYP2C19) and 5'-0H-omeprazole sulfone (by CYP3A4). Esomeprazole, with a similar metabolism, has a slower hydroxylation rate. They both inhibit the activity of CYP2C19, a phenomenon that increases their plasma concentration and explain the drug interactions, particularly with clopidogrel, which as a prodrug does not reach activation because of CYP2C19 inhibition. Lansoprazole is metabolized to 5'-0H-lansoprazole and lansoprazole sulfone (by CYP2C19 and CYP3A4). Pantoprazole is metabolized to 5'-0H-pantoprazole and pantoprazole sulfone (by CYP2C19 and CYP3A4), and subsequently to pantoprazole sulfate by a sulfotransferase, thereby minimizing drug interactions. The metabolic pathway of rabeprazole is non-enzymatic reduction to a thioester compound; only a small part is oxidized to demethylated rabeprazole or rabeprazole sulfone via CYP2C19 and CYP3A4.[14]

Extraesophageal reflux (EER) symptoms can occur with or without typical GERD symptoms. According to reports, typical GERD symptoms are significantly associated with atypical symptoms. Approximately 80% of individuals with frequent typical reflux symptoms present at least one atypical symptom. However, despite the increasing recognition of these populations, the efficacy of acid suppression therapy against EER remains controversial Acid suppression with proton pump inhibitors (PPIs) is a mainstream therapy for EER, as well as in typical GERD. However, the response to anti-reflux therapy in patients with extraesophageal symptoms is often less impressive, takes longer to occur, and tends to be more difficult to maintain. In contrast, some studies have reported that high-dose PPIs may be more effective than standard-dose PPIs in treating extraesophageal manifestations of GERD.

6. Levosulpiride

Levosulpiride is a sulpiride isomer that exerts its prokinetic action through a dual mechanism: 1) as a D(2) dopamine receptor antagonist and 2) as a serotonin 5HT(4) receptor agonist, conferring this drug with a cholinergic effect.

The most frequently used Prokinetic drugs like Metoclopramide, Levosulpiride and Domperidone augment gastric emptying, avert retention and reflux of acid or food and relieve symptoms of dyspepsia. However, Metoclopramide causes dystonic reactions and drowsiness, while Domperidone has been reported to cause galactorrhoea and gynaecomastia.[15]

Among prokinetic drugs, numerous clinical studies have offered facts on the efficacy of dopamine receptor antagonists such as Metoclopramide, Domperidone and Levosulpiride in the treatment of functional dyspepsia. Metoclopramide, Domperidone and Levosulpiride have both antiemetic and prokinetic properties since they antagonize dopamine receptors in the central nervous system as well as in the gastrointestinal tract where dopamine apply compelling inhibitory effects on motility.[16]

Levosulpiride is the levorotatory enantiomer of sulpiride, a substituted benzamide. Levosulpiride is a prokinetic agent which amplifies the lower esophageal sphincter pressure more speedily and efficiently than other therapeutic agents.[17] The prokinetic effect of Levosulpiride is mediated through the blockade of enteric (neuronal and muscular) inhibitory dopamine D2 receptors. Consequences also show that Levosulpiride also acts as a reasonable agonist at the 5-HT4 receptor.

7. Conclusion

Recent strategies for management of GERD are based on several decades of pharmaceutical and nonpharmacologic therapeutic development that have considered the risks, albeit limited, of chronic acid suppression. The basic tenets of GERD management today are as follows: management with a PPI only when necessary, at the lowest dose that controls symptoms; optimization of therapy when symptoms persist despite once-daily PPI use in patients with proven GERD; use of upper endoscopy and esophageal function tests to determine mechanisms of symptom generation (proven GERD vs non-GERD mechanisms) when symptoms persist despite optimal PPI therapy; and consideration of other medical therapies, antireflux surgery, or endoscopic interventions, for patients unable to tolerate or not interested in acid suppression.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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