



GASTROESOPHAGEAL REFLUX DISEASE: DIFFERENT TREATMENT APPROACHES

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ABSTRACT

Gastroesophageal reflux disease (GERD) is chronic esophageal disorder which occurs due to reflux of gastric juice and or contents to the lower third of esophagus, and has a prevalence of 6.3 to 28% in general population. Usually, lower esophageal sphincter (LES) is dysfunctional or incompetent to prevent reflux of gastric contents to the esophagus. Serious complication of the GERD includes Barrett's esophagus which may progress into esophageal adenocarcinoma. Use of proton pump inhibitors (PPIs) along with non-pharmacological measures is the treatment of choice in GERD. If the first choice of treatment fails, pharmacological agents other than PPIs such as H₂ blockers, antacids, prokinetic agents and sodium alginate can be used. However, these agents are inferior to PPIs in terms of efficacy and side effect profile, and not indicated for long term management. A novel drug vonoprazan which is a potassium competitive blocker of H⁺/K⁺ ATPase enzyme has also been developed to manage GERD symptoms. If non-pharmacological and pharmacological approaches fail to treat the GERD, different surgical approaches such as laparoscopic fundoplication, robotic fundoplication, endoluminal suture or plication of gastroesophageal junction (GEJ), radiofrequency thermal therapy of the LES and injection or implantation of biopolymers in GEJ are useful to manage the GERD refractory to drug therapy.

KEYWORDS: Endoscopy, Flundoplication, Gastroesophageal reflux disease, Proton pump inhibitors, Vonoprazan.

INTRODUCTION

Gastroesophageal reflux disease (GERD) is defined as symptoms or complications resulting from the reflux of gastric juices/contents into the esophagus or outside esophagus: into the oral cavity, air-way tract or lung.^[1-4] Furthermore, it is a chronic condition occurring from the reflux of gastric juice/contents into the esophagus and nearby tissues and organs. It is typically characterized by symptoms of retrosternal burning i.e. heartburn and acid regurgitation especially in the lower third of the esophagus usually due to decreased lower esophageal sphincter (LES) tone.⁵ The prevalence of the GERD varies from 6.3% to 28% in different populations and ethnic groups with varying frequencies of symptoms onset.^[6-9] Typical symptoms of GERD include heartburn, acid eructation, regurgitation and dysphagia whereas atypical symptoms include cough, pharyngitis, otitis media, non-cardia chest pain, esophageal spasm and dental erosions: enamel and dentin.^[10]

METHODS

Medline/Pubmed Central, Cochrane Library, Google, Open access journals and Medscape were searched for gastroesophageal reflux disease, proton pump inhibitors, esophagitis, flundoplication, endoscopy and Barrett's esophagus for the published data in the period of 2001 to 2018. Besides above search, relevant topics in different

Pharmacological text books were also consulted. Only pertinent information has been presented in this article in concise form.

Diagnosis of GERD: GERD can be diagnosed with the following methods.^[1,10,11]

Proton pump inhibitor (PPI) trial: When classic symptoms are present, PPI trial is indicated. A positive response to PPI trial, relief of symptoms such as heart burn, regurgitation, usually establishes a diagnosis of GERD. However, non-responsive to PPI trial doesn't exclude GERD because one meta-analysis has shown that the PPI trial had sensitivity of 78% and specificity of 54%.^[12]

Endoscopy: Endoscopy is recommended for screening of patients who are at high risk of developing Barrett's esophagus: elderly patients, patients unresponsive to PPI trial, patients with alarming symptoms such as vomiting, dysphagia, anemia and involuntary weight loss, and patients with non-cardiac chest pain.^[1,10]

Ambulatory 24-hour pH monitoring: This is a very standard method to diagnose the GERD. It has a sensitivity of 96% and a specificity of 95%. Patients who

are positive in endoscopic examination don't require undergoing this test.^[10]

Impedance pH monitoring: New impedance parameters such as the 'post-reflux swallow induced wave' index and the 'mean nocturnal baseline impedance' have recently been proven to be accurate to diagnose reflux related and non-reflux related heartburn in endoscopy negative patients.^[13]

Besides above mentioned tests, barium swallow, esophageal biopsy and esophageal manometry can be used to diagnose complications of the GERD. However, these methods are not indicated for a diagnosis of the GERD.^[1]

So diagnosis of the GERD is made based on patient's clinical symptoms, response to PPI trial, additionally if required, findings on endoscopic examination and other laboratory tests are taken into account. Usually, PPI trial and endoscopy suffice to make a diagnosis of the GERD.^[13]

PATHOPHYSIOLOGY

GERD is basically esophageal motility disorder. However, gastric acidity is the most important aggressive factor to cause symptoms of GERD and esophageal erosions.^[14] In a plumbing circuit including esophagus to stomach, there are three components which can contribute to a causation of the GERD. These are esophagus, LES tone and gastric emptying. In these above three components, decreased esophageal motility can delay the passage of material and predisposes to GERD. Similarly, dysfunctional or weak LES tone contributes to incompetent valve mechanism which favors the reflux of gastric contents/ juice to esophagus. Additionally, delayed gastric emptying may lead to continuous pressure in LES which may ultimately weaken LES tone and results into GERD.^[10,14] Majority of cases of the GERD result from dysfunctional LES tone, i.e. relaxation when there is no swallowing. Some cases of GERD may result from hiatus hernia. The LES tone can be altered by variety of factors such as hormonal, neurogenic, dietary and pharmacological. In hormonal factor, increased progesterone during pregnancy may decrease LES tone. As vagal nerve has motor function to LES, increased vagal activity, i.e. increased release of acetylcholine, increases LES tone. Foods and drinks such as fats, alcohol, coffee and chocolates decrease LES tone whereas protein rich foods increase LES tone. Use of antimuscarinic drugs, calcium channel blockers, nitrates and tricyclic antidepressants, beta agonists and progesterone may decrease LES tone.^[10,14]

GERD can be classified as followings based on the severity of the symptoms.^[10,14]

Stage 1: <3 symptoms of heartburn per week, mild form and absence of esophageal erosions

Stage 2: ≥ 3 symptoms of heartburn per week, moderate form, presence of esophageal erosions and regurgitation leading to night awakenings.

Stage 3: chronic and daily symptoms of heartburn, night awakenings due to regurgitation and presence of esophageal erosions and stricture with extraesophageal manifestations such as dry cough, laryngitis, asthma, etc. Esophageal defense mechanisms are composed of two factors: esophageal clearance which is obtained by esophageal peristalsis and the saliva, and mucosal resistance. When these defense mechanisms are derailed in reflux due to continuous acid reflux and exposure, complications of GERD arise.^[10,15]

COMPLICATIONS

Erosive reflux disease (ERD)

ERD is found in up to 20% of GERD patients and considered as the most common complication of GERD rather than its main clinical manifestation.^[16]

Barrett's esophagus and esophageal adenocarcinoma

Continuous reflux of acid to the lower one third of esophagus may lead to chronic inflammation and metaplasia of esophageal squamous epithelium into columnar epithelium^[17]. It occurs in 2% of the patients and is the most important complication of the GERD as it predisposes esophagus to esophageal adenocarcinoma, the fastest growing cause of cancer mortality.^[18,19]

Others

GERD may also lead to dysphagia, stricture formation, and extra esophageal complications such cough, pharyngitis, hoarseness of voice, bronchial asthma, pneumonia, idiopathic pulmonary fibrosis, otitis media and dental erosions.^[10]

TREATMENT APPROACHES^[1,10,14]

There are three types of treatment approaches; non-pharmacological, pharmacological and surgical. Non-pharmacological and pharmacological methods are important to manage GERD and normally, they go hand in hand. The surgical approach is usually recommended if non-pharmacological and pharmacological approaches fail to improve the symptoms of GERD.

1. Non-pharmacological

Non-pharmacological approach includes the following measures.

Recommendations having sound scientific evidence

Weight loss

It is recommended for patients who have body mass index more than 25.

Head of bed elevation

This approach can be practiced by using foam wedge or blocks to elevate the head of the bed by 8 inch. Elevating only head by using pillows doesn't help improve GERD symptoms.

Avoidance of late night meals

Avoidance of large fatty late night meals helps improve the symptoms of GERD. Light meals 2-3 hours before reclining is recommended.

Recommendations lacking sound scientific evidence

Tobacco and alcohol cessation: Based on case-control studies, cessation of tobacco and alcohol consumption doesn't improve GERD symptoms.

No consumption of caffeine (coffee), spicy foods, chocolate, citrus, carbonated beverages, peppermint, garlic, onions: No evidence

Consumption of protein rich foods: No evidence

Avoidance of precipitating factors.

2. Pharmacological

Gastric acid suppression treatment is very important in GERD for symptomatic relief and prevention of complications such as Barrett's esophagus and ultimately esophageal adenocarcinoma. Gastric acid causes chronic esophageal inflammation, may cause DNA damage (carcinogenic potential) and may promote proliferation in Barrett's esophagus. Acid suppression therapy inhibits all these effects of gastric acid and is mainstay in the management of GERD.^[18]

Proton pump inhibitors (PPIs)

The use of PPI in combination with life style modification is primary therapy in GERD⁵. Approximately 70-80 % of patients suffering from erosive esophagitis and 60% of patients suffering from non-erosive esophagitis can have complete remission from GERD symptoms after eight weeks of once or twice daily PPI therapy¹. PPIs are the most powerful gastric acid secretion inhibitors available for GERD treatment. When gastric pH is increased and kept at more than 4 for at least 18 hours a day, healing of esophageal mucosal damage is facilitated. Sometimes, prolonged PPI therapy may be required to treat chronic cases of GERD as symptoms recur few days after stoppage of the treatment. PPIs therapy doesn't increase lower esophageal tone.^[10,14]

Important side effects of PPIs include^[11,20]

- Headache (<2%)
- Diarrhea (2%)
- Osteoporosis and increased fracture risk (weak evidence)
- Decreased absorption of vitamin B₁₂, magnesium, calcium and iron (weak evidence)
- Increased risk of community acquired pneumonia (weak evidence)
- Increased risk of gastroenteritis by *Salmonella* and *Campylobacter* (relative risk 2.9, 95% confidence interval, 2.5–3.5).^[21]
- Increased risk of *Clostridium difficile* colitis (weak evidence)
- Increased risk of drug-drug interactions (weak evidence)

- Increased risk of myocardial infarction (odds ratio, 1.16 (95% CI, 1.09–1.24)²²; PPIs compete with cytochrome p450 which is required for the activation of a pro-drug clopidogrel which is an antiplatelet drug. Additionally, PPIs may increase vascular resistance directly by inhibiting endothelial nitric synthase activity.^[23]

- Nephrotoxicity (weak evidence)

- Dementia (weak evidence)

Histamine receptor two (H2) blockers or H2 receptor antagonists

H₂ blockers are effective to treat stage 1 and 2 cases of GERD, also to inhibit nocturnal acid suppression in Barrett's esophagus.^[10,14] However, these agents are less powerful acid suppression inhibitors than PPIs. With H₂ blockers, effective healing of esophagitis may occur in 50-80% of mild cases of the GERD.

Antacids

Use of antacids is restricted to treat mild and occasional symptoms of heartburn, and antacids act very fast and are useful for prompt symptomatic relief. They are not associated with healing of esophagitis and not recommended for long term treatment of GERD.^[10,14]

Prokinetic drugs

Prokinetic drugs such as metoclopramide and cisapride are effective in mild cases of GERD usually in combination with PPIs. They are effective to increase LES tone and relieve the symptoms of GERD. However, these agents don't facilitate healing of esophagitis. Moreover, long term use of prokinetic agents may be associated with significant side effects. So, they are not indicated for chronic use in the management of GERD.^[10,14]

Sodium Alginate

Sodium alginate decreases symptoms of heartburn. It may be used in combination with antacids for symptomatic relief. It may decrease acid reflux exposure time and number of refluxes. However it has no effect on LES tone and healing of esophagitis.^[14,24]

Newer therapy

PPIs inhibit H⁺/K⁺ ATPase enzyme (proton pump) irreversibly which is involved in the final step of H⁺ ion secretion in gastric canaliculi. Recently, a novel class of drugs known as potassium-competitive acid blockers has been developed which blocks H⁺/K⁺ ATPase enzyme by binding to a site different from PPI binding site: at the potassium binding site of the enzyme. Example in this group is vonoprazan which has been approved in Japan in 2015 to treat GERD²⁵. Different studies have shown that vonoprazan is as equally effective as PPIs in healing of esophagitis and relieving the GERD symptoms.^[26-29]

3. Surgical

There is no unanimous consensus on the indications among American Gastroenterological Association,

Society of Gastrointestinal and Endoscopic Surgeons, and American College of Gastroenterology (ACG) for surgery in GERD patients.^[11] However, the ACG guidelines for surgical indications are as follows.^[1]

- Surgical therapy is a treatment option for long-term therapy in GERD patients
- Surgical therapy is generally not recommended in patients who do not respond to PPI therapy
- Refractory patients with objective evidence of ongoing reflux as the cause of symptoms should be considered for additional antireflux therapies, which may include surgery
- Surgery should generally not be performed to treat extraesophageal symptoms of GERD in patients who do not respond to acid suppression with a PPI

Different surgical approaches

The following surgical approaches are useful for a surgical management of the GERD with varying degrees of success rates.^[5,10,30]

- Transoral incisionless fundoplication
- Laparoscopic fundoplication
- Robotic Fundoplication
- Endoluminal suture or plication of gastroesophageal junction
- Radiofrequency thermal therapy of the lower esophageal sphincter
- Injection or implantation of biopolymers in gastroesophageal junction.

CONCLUSION

Use of proton pump inhibitors along with non-pharmacological measures is the treatment of choice in GERD. Pharmacological agents other than PPIs can be used in case of PPIs refractory GERD. However, other pharmacological agents are therapeutically inferior to PPIs and not suitable for chronic use. A novel drug vonoprazan which is a potassium competitive blocker of H⁺/K⁺ ATPase enzyme has also been developed to manage the GERD symptoms. If non-pharmacological and pharmacological approaches fail to treat the GERD, different surgical approaches are useful to manage the GERD non-responsive to the pharmacotherapy.

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