

## Management of gastroesophageal reflux disease in adults

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### Abstract

Gastroesophageal reflux disease (GERD) is a very common disease. GERD is defined as the reflux of stomach content which causes troublesome symptoms and/or complications. The management of GERD is step by step. Dietary and lifestyle modifications are the first steps. Twice-daily H2RAs at standard doses for a minimum duration of two weeks can be considered in patients with GERD who fail to respond to lifestyle and dietary modifications. If symptoms of GERD persist, once-daily Proton Pump Inhibitors (PPIs) can be recommended. Patients with an unsatisfactory response to once-daily PPIs dosing can be considered to have refractory GERD. Twice-daily PPI therapy can be recommended in patients who fail to respond to once-daily PPI therapy. The add-on treatment with H2RAs, baclofen, or visceral pain modulators can be considered in selective subjects with GERD who fail to respond to twice-daily PPI. Anti-reflux surgery may be taken into account in selected patients. This review focuses on the initial and maintenance therapy of GERD and also reviews different management of recurrent and refractory GERD

**Keywords:** Gastroesophageal reflux disease, Diagnosis, Treatment.

### 1. Introduction

Gastroesophageal reflux disease (GERD) is a very common disease (1). According to the Montreal classification, GERD is defined as the reflux of stomach content which causes troublesome symptoms and/or complications (2). Based on the appearance of the mucosa of esophagus on upper endoscopy, GERD is also classified into two categories: 1) the erosive esophagitis (EE) and 2) non-erosive reflux disease (NERD) (3). This mini-review focuses on the management strategies for patients with GERD.

In order to provide enough databases about the subject, a systematic search utilizing Pubmed, Scopus, Google Scholar and Embase database was carried out. The initial search terms were “Gastro-

esophageal reflux disease, Diagnosis, Treatment, and pharmacotherapy”, without narrowing or limiting search elements to find the most relevant literatures about the subject.

### 2. Treatment of GERD

#### 2.1. Initial and maintenance therapy of GERD

##### 2.1.1. Lifestyle and dietary modification

Most physicians recommend dietary and lifestyle modifications as the first step in the management of GERD. Weight loss and elevation of the head end of the bed (especially in nocturnal reflux) can improve GERD symptoms and esophageal pH-metry. Elimination of some dietary triggers such as fatty foods, caffeine, chocolate, citrus juice, carbonated beverages, and spicy foods may be effective in some patients. Some reports recommend that avoidance of smoking, alcohol, and tight fitting garments may improve GERD symptoms. On the other hand, chewing gum (for

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increasing the rate of esophageal acid clearance) and abdominal breathing exercise (for strengthening the lower esophageal sphincter) may be also effective (4-11).

## 2.1.2. Pharmacotherapy

### 2.1.2.1. Antacids

Antacids neutralize gastric pH and usually contain a combination of calcium carbonate, magnesium trisilicate, or aluminum hydroxide. Antacids offer rapid but short-term relief of heartburn. Antacids cannot heal the erosive esophagitis. Therefore, their role is limited to intermittent use (over-the-counter) for the relief of mild GERD that occur less than once a week. They also are used to treat break-through symptoms not effectively treated by proton pump inhibitors (PPIs) alone (12,13).

Side effects of antacids are depending upon the duration and dose of medication use. Diarrhea and hypermagnesemia (with magnesium containing antacids), volume overload (with considerable sodium containing antacids), milk-alkali syndrome (with calcium and alkali containing antacids), and aluminum toxicity (with aluminum containing antacids) have been reported with these medications (14-17).

### 2.1.2.2. Surface agents

Sucralfate is a drug that adheres to the mucosal surface of esophagus. Although this drug can heal the erosive esophagitis, as compared with PPIs, can provide short-term relief. Sucralfate can be used for the therapy of GERD in pregnancy (18).

Side effects of sucralfate are unremarkable except of increasing risk of aluminum toxicity. Absorption of aluminum significantly increases with the use of sucralfate (17, 19).

### 2.1.2.3. Alginates

The role of alginates in the therapy of GERD is unclear. One of alginates is sodium alginate that reduces the postprandial acid pocket by forming a viscous gum that floats within the stomach (20-22).

### 2.1.2.4. Histamine 2 receptor antagonists

Histamine 2 receptor antagonists (H2RAs) inhibit the histamine-2 receptor on the parietal cell of stomach and therefore decreasing the secretion of gastric acid. H2RAs such as ranitidine, famotidine, cimetidine, and nizatidine have a slower onset but longer duration of action as compared with antacids. Therefore, they are more effective than antacids in decreasing the severity and frequency of GERD symptoms. However, long-term use of H2RAs as maintenance therapy for GERD is not recommended because of the development of tachyphylaxis and tolerance within a few weeks of initiation of H2RAs and they are not as effective as PPIs for healing of erosive esophagitis (23-28).

The frequency of H2RAs side effects are unremarkable (29). Gynecomastia and impotence have been reported with cimetidine (30). Hematologic problems (31, 32), immune reactions (33, 34), central nervous system (CNS) symptoms (35), and rarely, hepatotoxicity as well as nephrotoxicity (36) have been reported with H2RAs use but causality cannot be established in these studies (37).

### 2.1.2.5. Proton pump inhibitors

PPIs, as the most effective inhibitors of gastric acid secretion, are the standard of care for treatment of GERD. Using of PPIs are significantly increased in the recent decades. PPIs irreversibly bind to and inhibit the hydrogen/potassium ATPase (H<sup>+</sup>/K<sup>+</sup>ATPase) pump. PPIs are more effective when taken 30 min before the breakfast and should be used daily rather than on-demand (1,24).

Studies have shown that PPIs including pantoprazole, lansoprazole, esomeprazole, omeprazole, and rabeprazole have a faster symptom relief and longer duration of action as compared with H2RAs. PPIs are also more effective than H2RAs in relieving heartburn in patients with NERD or EE and healing of EE (13, 25,38-42).

The potential side effects associated with PPIs include nausea, diarrhea, headache, insomnia, and anaphylaxis (13). Concerns associated with long-term PPI therapy include failure to respond (43-45), rebound gastritis (46, 47), atrophic gastritis (48, 49), *Clostridium difficile* infection (50, 51), pneumonia (52, 53), increased risk for bone fractures (54), vitamin B12 malabsorption

(55), iron malabsorption (56), and acute interstitial nephritis (57, 58).

### 2.1.3. The role of *Helicobacter pylori* infection in GERD

Some studies (59-61) reported that *Helicobacter pylori* (*H. pylori*) infection might be protective for severe reflux esophagitis. However, this issue has been questioned and criticized by other studies (62,63).

### 2.1.4. Maintenance therapy

Medications should be discontinued in all patients with GERD (except those with severe EE) whose symptoms resolve with acid suppression. But nearly all patients with EE and most patients with NERD relapse when acid suppression is discontinued. Patients with severe EE and Barrett's esophagus should remain on PPIs because of its serious complications if acid suppression is discontinued (64-68). Patients with recurrent symptoms after discontinuing acid suppressive therapy should be managed with the similar medication and dose before discontinuing (67,69,70). The continuous as compared with intermittent (on-demand) therapy in patients with GERD has provided better quality of life, symptoms control, and higher healing of EE (71).

### 2.1.5. Management of GERD in pregnancy

First step of management of GERD in the pregnancy consists of lifestyle and dietary changes (17). In pregnant patients who fail to respond to lifestyle and dietary modifications, the medication can be considered to control symptoms. Most antacids (except for sodium bicarbonate and magnesium trisilicate) are safe in pregnancy and breastfeeding (72,73). Sucralfate (1 g orally three times daily) is also safe in pregnancy and breast feeding and can be used to control symptoms in pregnant patients who fail to respond to antacids (17). If symptoms do not respond to antacids and sucralfate, H<sub>2</sub>RAs can be used. All H<sub>2</sub>RAs are safe in pregnancy (17, 74).

All PPIs (except for omeprazole) are FDA category B drugs in pregnancy (17). Several studies have showed that PPIs are probably safe in pregnant patients (75, 76). However, PPIs are usu-

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ally reserved for pregnant patients with intractable symptoms who fail to respond to antacids, sucralfate, and H<sub>2</sub>RAs. PPIs are not generally recommended in breast feeding due to insufficient safety data (17, 75, 79).

### 2.1.6. Refractory GERD

The definition of refractory GERD is controversial. About 10 to 40 percent of patients with GERD are refractory to a standard dose of PPIs. Patients with an unsatisfactory response to once-daily dosing of PPIs can be considered as refractory GERD. Several studies recommend that twice-daily PPI therapy can be used to improve symptom relief and healing EE in patients who fail to respond to once-daily PPI therapy. The optimal time of using PPI in twice-daily PPI therapy is 30-60 min before breakfast and dinner. But only 20-25 percent of patients with an unsatisfactory response to once-daily dosing respond to doubling the dose. The majority of these non-responders are more likely to have NERD (45,80-85). The add-on treatment with bedtime H<sub>2</sub>RA can be considered in patients with GERD who fail to respond to twice-daily PPI. But the efficacy of this strategy is controversial (86, 87).

The add-on treatment with baclofen (doses can be increased slowly up to 20 mg three times daily) is another strategy in patients with GERD who fail to respond to twice-daily PPIs specially in weakly acidic or bile reflux. Baclofen as a gamma-aminobutyric acid (GABA)-B receptor agonist reduces the rate of transient lower esophageal sphincter relaxation. Central nervous system-related side effects of baclofen include confusion, dizziness, light headedness, weakness, drowsiness, and trembling can limit the using of this drug. Recently, lesogaberan as a novel GABA-B receptor agonist has been introduced as an experimental drug candidate for treatment of GERD (88-94). However, the administration of valproic acid can increase the lower esophageal sphincter pressure, its effect is not proved on the rate of transient lower esophageal sphincter relaxation or GERD (95).

The add-on treatment with visceral pain modulators (such as tricyclic antidepressants, selective serotonin reuptake inhibitors, and trazodone) can be considered in patients with refrac-

tory GERD because many of these patients have NERD (96-98).

### 2.1.7. Surgical treatments of GERD

The role of surgery in the therapy of GERD is controversial. Surgery appears to be as effective as PPIs for improving symptoms and healing of EE (80, 99).

Surgery is not recommended in patients with EE who are well maintained on medication. Overall, surgery is also not advised in patients who do not respond to PPI therapy. Anti-reflux surgery can be considered in the following patients: Those require high doses of PPIs to control symptoms especially in cases that have poor compliance with medication, and individuals with EE who are intolerant of PPIs. Surgery may also be recommended for patients with persistent troublesome regurgitation that is poorly controlled by PPIs. However, this recommendation must be balanced against potential post-surgery complications such as gastric or esophageal injury, splenic injury, pneumothorax, bleeding, and wound infection (64, 80).

### 2.1.8. Other approaches for treatment of GERD

The effectiveness of acupuncture (100), treatment of psychological disturbances (101,102), and endoscopic procedures for treatment of GERD (103) remains unclear. More studies are needed to determine the precise role of these approaches in

the management of patients with GERD.

## 3. Conclusion

In summary, GERD should be managed with step by step algorithm. But severity and type of GERD symptoms, side effects of the medication, and patients' compliance should also be considered in this regards.

Dietary and lifestyle modifications are the first steps in the management of GERD. Twice-daily H2RAs at standard doses for a minimum duration of two weeks can be considered in patients with GERD who fail to respond to lifestyle and dietary modifications. If symptoms of GERD persist, once-daily PPIs and discontinuing of H2RAs can be recommended. Patients with an unsatisfactory response to once-daily PPIs dosing can be considered to have refractory GERD. Twice-daily PPI therapy (30-60 min before breakfast and dinner) can be recommended in patients who fail to respond to once-daily PPI therapy. The add-on treatment with H2RAs, baclofen, or visceral pain modulators can be considered in selective subjects with GERD who fail to respond to twice-daily PPI. Anti-reflux surgery may be taken into account in selected patients.

## Conflict of Interest

None declared.

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