Gastroesophageal Reflux Disease (GERD)

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Overview

An estimated 60 million Americans experience heartburn (*pyrosis*) at least once per month, and 15 million have heartburn symptoms everyday. When symptoms occur more frequently than twice a week or are accompanied by bleeding, or food sticking in the throat, then the patient is considered to have gastroesophageal reflux disease or GERD.[1] Although all age groups, genders, socioeconomic classes and ethnic groups are affected, GERD is more common in people over 40 years of age. In fact, 50% of GERD occurs in persons of all genders between the ages of 45 and 64.[2] It is characterized by a chronic relapsing condition with associated morbidity and an adverse impact on quality of life. The symptoms of GERD vary from patient to patient and there are multiple treatment options available.

The following article offers a review of GERD and its management. The focus is on the profile and treatment of ambulatory patients with GERD. Our goal is to provide tools for pharmacists to use to ensure that patients are receiving effective care with measurable outcomes.

What is GERD?

Gastroesophageal Reflux disease (GERD) can be characterized as the regurgitation of the gastric contents from stomach into the esophagus. Regurgitation is controlled by the lower esophageal sphincter, or LES, (a ring of muscle around the lower section of the esophagus), which normally relaxes to allow food and liquids to enter the stomach. When the sphincter relaxes at other times, acid from the stomach is propelled up into the esophagus thereby irritating the esophageal membrane. Common causes for abnormal relaxation of the sphincter are[3]:

- Large meals
- Fatty foods
- Chocolate, caffeine, onions, spicy foods,
- Alcohol
- Lying down after eating
- Medications – benzodiazepines, tranquilizers, theophylline

How does the typical patient present?

The typical patient is over 45 years old, of either gender, who presents with symptoms of burning in the chest or chest pain, especially after a meal or at night when lying down. They may also complain of a sour taste or regurgitation of food into the mouth after a meal. More severe conditions include complaints of difficulty in swallowing (dysphagia), coughing/wheezing/asthma/hoarseness/sore throat, regurgitated blood, or a black stool (possibly indicating partially digested blood).[3]

There is a high prevalence of GERD in patients with asthma and visa versa. Also, asthma symptoms correlate with the severity of GERD. Yet, there are a high percentage of asthma patients with no symptoms of GERD. The clinical message is that treatment of GERD improves asthma symptoms and decreases the requirements for asthma medications, but the treatment of asthma does not necessarily improve GERD symptoms.[4]

Can GERD be prevented?

Understanding the causes and risk factors (discussed below) for GERD allows the clinician to educate the patient about preventative measures. The common causes and risk factors are independent, and they must be removed or mitigated to provide symptom relief.

Long-term risk reduction from the complications of GERD cannot be entirely minimized by medications if these risks are not addressed.

What are the risk profiles for patients with GERD?

Pharmacists need to screen patients according to the severity of their symptoms to ensure that they are receiving the most appropriate care. A simple method for screening is to consider the severity of symptoms; namely,

- **Mild severity:**
  - Symptoms are mild and fleeting
  - Usually treated with OTC antacids or H2 antagonists
- **Moderate severity:**
  - Symptoms several times per week, or symptoms that are not relieved by OTC or prescription medications, or symptoms that wake the patient up at night
  - Usually treated with prescription H2 antagonists or PPIs
- **High severity:**
  - Difficulty swallowing, black stool, regurgitated blood, or weight loss
  - Requires evaluation by a physician who may also run certain diagnostic tests for the most severe patients (e.g., barium X-ray, endoscopy, or an ambulatory pH test). Treatment is typically with PPIs or surgery.

Based on the severity identified, the pharmacist can refer the patient to the appropriate medical intervention. For patients receiving PPIs more than once daily or at higher dosages without high severity findings or complications, the pharmacist should recommend step-down to once daily and standard dosages.[5]

Table 1

Dietary Factors Associated with Increased Reflux Symptoms

- caffeinated products
- fatty foods
- peppermint
- chocolate
- spicy foods
- citrus fruits and juices
- tomato-based products
- alcohol

What are the risk factors for GERD?

When evaluating the patient any factors that interfere with digestion may also lead to GERD. These risk factors are [3]:

- **Obesity** – the LES is opened by excess weight pressure on the stomach
- **Hiatal hernia / diaphragmatic hernia** – weakens LES when stomach protrudes into the lower chest
- **Pregnancy** – pushes on the stomach and produces progesterone which relaxes the LES

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- **Asthma** – Although the actual relationship is unknown, coughing and breathing difficulties lead to a pressure gradient in the chest, which results in regurgitation. Another consideration is that asthma medications relax the LES.

- **Diabetes** – An uncommon complication of diabetes is gastroparesis, delayed emptying of the stomach, which can lead to regurgitation.

- **Peptic ulcer disease (PUD)** – An ulcer near the pyloric valve in the stomach, which controls the release of food into the intestine, causes food to backup and regurgitate into the esophagus.

- **Delayed stomach emptying** — Any cause for delayed stomach emptying can lead to regurgitation.

- **Connective tissue disorders (e.g., scleroderma)** – These disorders cause muscle tissue to thicken and swell. The result is that digestive muscles do not expand/contract as normal and can cause regurgitation.

- **Zollinger-Ellison Syndrome** – A rare disease that causes very high amounts of acid leading to stomach acid regurgitation.

In order to mitigate the impact of these risk factors and relieve symptoms of GERD in these higher risk patients, the pharmacist should educate the patient about their increased risks and provide risk-reducing options. However, the control of these risk factors may still require long-term drug therapy.

What are the long-term risks of GERD?

Repeated exposure to the refluxed material leads to esophagitis, which is an inflammation of the esophagus. Chronic reflux can lead to erosion of the esophagus if left untreated.

In addition, other, less common complications of GERD include strictures, ulcerations and Barrett's esophagus. Yet, how prevalent are these risks?

Up to 60% of patients with reflux do not have endoscopic evidence of esophagitis. Esophagitis is more common, however, in nocturnal than daytime GERD. As little as 5 minutes of nocturnal acid contact can lead to esophagitis; therefore it is still a consideration. For the clinician the frequency of symptoms (i.e., daily or several times per week) is a better indicator of esophagitis than the duration of acid contact.[6]

While there are many suggestions that erosive esophagitis is a leading cause of gastrointestinal bleeding, there are few large trials to validate this concern. In fact, bleeding from erosive esophagitis is a relatively uncommon cause for acute care hospital admissions from hematemesis and melena. Thus, while a concern, it should not be the primary rationale for defensive PPI use.

Esophageal strictures (fibrosis of the substratum tissue), usually due to ulcers, occur in about 10% of patients with untreated erosive esophagitis. Strictures occur more frequently in older individuals and their prevalence increases with age. There is now evidence that the increased use of PPIs for erosive esophagitis has reduced the incidence of strictures.

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Barrett's esophagus is the progressive replacement of distal eroded squamous mucosa with metaplastic gastric epithelium. In the general population the prevalence of Barrett's esophagus is 0.4% to 0.9% when diagnosed by endoscopy. Comparisons to autopsy data indicate that the prevalence is much greater at 376 cases per 100,000 individuals. Patients with Barrett's esophagus have a 30-125 times greater risk of developing adenocarcinoma of the esophagus. Nevertheless, Barrett's is uncommon and does not usually require defensive treatment with PPIs for common symptoms and negative endoscopy.

What are the goals of treatment?

The ultimate goal of treatment is to minimize exposure of the esophagus to refluxate, thereby alleviating symptoms, healing the esophagus, preventing complications, and maintaining remission. In order to achieve treatment goal most patients require a combination of lifestyle modifications and drug therapy. The American College of Gastroenterology (ACG) recognizes that many patients have chronic, relapsing disease that must be treated with long-term maintenance, perhaps for a lifetime.[1] In some cases, surgery may be appropriate in patients with severe symptoms, erosive esophagitis or disease complications.

What are the non-drug treatments?

Lifestyle changes are the primary non-drug treatment and are an imperative to remove aggravating factors. They should be emphasized and incorporated into all stages of treatment. The patient should be educated to incorporate the following changes into their daily life:

a) Elevating the head of the bed by six inches
b) Decreasing fat intake
c) Stopping smoking
(Smoking increases reflux and aggravates GERD.)
d) Reducing alcohol consumption
e) Losing weight
f) Avoiding recumbence for 3 hours after meals
g) Avoiding certain types of food. (See Table 1).

What are the OTC options for treatment?

There are several agents available to treat symptoms of pyrosis. OTC medications can be expected to relieve symptoms in about 20% of patients.[7] One of the challenges in heartburn management is the fact that most patients avoid seeking medical help from a physician and turn to self-treat with over-the-counter (OTC) medications. Therefore, the role of a community pharmacist in assisting a patient with given

symptoms to choose a product, or refer the patient with more severe symptoms (i.e., more than twice per week) to a physician, is instrumental in the overall outcome of the disease management.

While the OTC choices are well known to most clinicians, there are a few considerations of note. It is important to re-emphasize to the patient that these medications provide relief of symptoms, but they must be combined with lifestyle changes to provide more than temporary results. ACG guidelines indicate that lifestyle changes alone, although they may benefit many patients, will probably not control symptoms in the majority of patients. Most authors do attribute a placebo response of 20-30% due to lifestyle changes.

Herbs

There are several herbs traditionally used to treat the symptoms of heartburn; namely, licorice, aloe vera, slippery elm, bladderwrack, and marshmallow. None of these have been scientifically validated as effective treatments, although Gaviscon™ contains alginic acid, which is derived from bladderwrack.

Antacids

Antacids such as Maalox, Mylanta, Gelusil, Rolaids and Tums, neutralize stomach acid and can provide quick relief. It is important to recognize and educate patients that antacids alone won't heal an inflamed esophagus damaged by stomach acid. Moreover, overuse of some antacids can cause side effects such as diarrhea or constipation, and interact with a number of drugs including flouroquinolones, tetracycline, and ferrous sulfate. Antacids should be taken on an as needed basis and immediately after meals if symptoms occur. Antacids should be administered separately from prescription medications by two hours (the gastric emptying time) as they interact with many medications.

H-2 Receptor Blockers (H2RA) (consider using *"antagonists"*)

H2 receptor blockers such as Tagamet HB (cimetidine), Pepcid AC (famotidine), and Zantac75 (ranitidine) have differences in duration, potency and rapidity of action. Otherwise, they are generally considered interchangeable. The H2RA are available at half the strength of their prescription counterparts. They work by inhibiting histamine stimulation of the gastric parietal cell, thereby reducing the secretion of acid. They are indicated for the prevention and relief of heartburn as well as acid indigestion. While antacids are promoted as faster acting than H2RA, studies show that the pH rises within 30 minutes after administration of H2 blockers so these claims may not be of clinical value. Further, H2RA provide longer relief of symptoms (about 10 hours) when taken prior to meals. H-2RA cause infrequent side effects, including bowel changes, dry mouth, dizziness or drowsiness.

Proton Pump Inhibitors (PPIs)

The OTC formulation of Omeprazole is marketed at the same dose as the prescription drug for a 14-day course of treatment for heartburn. The ACG indicates that on-demand therapy with PPIs has not been well studied. Oftentimes, patients take PPIs as needed, by self-dosing. Therefore, there are clinical and financial consequences due to patient use, not based upon literature verification.

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What is the role of pharmacologic therapy?

There are several categories of prescription treatments for GERD that have different roles in the treatment regimens of the various patient profiles. These treatments include, H2 receptor antagonists (H2 blockers), proton pump inhibitors (PPIs), and promotility agents. Each of these treatment modalities provides a targeted approach to specific problems.

Mild-to-moderate irritation of the esophagus (esophagitis):

H2 blockers improve the symptoms of heartburn and regurgitation and aid the healing process by decreasing the flow of acid to the esophagus. Approximately 50% of patients have symptoms eliminated with twice daily dosage. Healing may require higher dosages and about 25% of patients maintain remission.

Mild-to-moderate symptomatic GERD:

Promotility agents (e.g., Metoclopramide) increase lower esophageal sphincter pressure, thereby preventing acid reflux and improving movement of food from the stomach. Promotility agents improve nighttime symptoms by improving the clearance of acid from the esophagus. They are not recommended for monotherapy so they are frequently used in combination with H2RA.

- The most commonly used agents of this category are metoclopramide and bethanechol, but their CNS side effects (drowsiness, irritability, extrapyramidal effects, etc.) limit their use.
- Domperidone, a dopamine receptor blocker, is as effective as metoclopramide, but does not cross the blood brand barrier so it doesn't have the CNS effects. It does cause hyperprolactinemia in 10-15% of patients so it has not been marketed in the US.
- Tegaserod is a 5HT3 agonist with promotility and antinociceptive properties. It is effective for decreasing esophageal acid exposure, but is not effective for monotherapy.

- Baclofen, a GABA receptor type B agonist, suppresses LES relaxation after a single 40mg dose. As a result, it reduces the number of reflux episodes, and the percent of esophageal acid exposure time. Unfortunately, it has a significant profile of side effects, which limit it use.

Severe symptoms, esophagitis on endoscopy, or erosive esophagitis (severe erosion due to GERD):

Symptomatic relief of erosive esophagitis can be expected in 27% of placebo, 60% of H2RA, and 83% of PPI treated patients. Esophagitis healed in 24% of placebo, 50% of H2RA, and 78% of PPI treated patients. Higher doses combined with more frequent dosing of H2RA's lead to better results, but they were still not as effective as PPIs. As a result, PPIs are considered the first-line therapy for these patients.[7] PPIs are recommended for symptom relief and for long-term treatment to maintain remission. Complete endoscopic mucosal healing of esophagitis has been shown in multiple studies to occur within 6-8 weeks in 75% to 100% of patients. Since esophagitis is considered a chronic, relapsing condition, subsequent treatment is directed to control symptoms and prevent relapse.

How is chronic maintenance therapy managed?

There are five available PPIs (Omeprazole, Lansoprazole, Rabeprazole, Pantoprazole, and Esomeprazole) that have been demonstrated to control symptoms of GERD and heal esophagitis. Clinically, differences between the PPIs are due to dosage variation. The effects of all PPIs are optimized with adequate dosages before meals, usually before breakfast. Higher dosages composed of a second dose before dinner may be given for partial responders, patients with breakthrough symptoms while on therapy, and in patients with more severe conditions (e.g., supraesophageal symptoms, severe esophageal dysmotility, or Barrett's esophagus).[8]

After initial symptoms and healing has been accomplished, patients can be controlled with maintenance doses of either H2RA or PPIs. There is currently no profile for which patients will respond to H2RAs vs. PPIs. A Veterans Administration study of 71 "PPI dependent" patients indicated that patients could be maintained with less intensive therapy. When patients were taken off PPIs, the following occurred:

- 42% could not be taken off
- 42% could be managed with H2RA, prokinetics or a combination
- 15% could be taken off of therapy all together.[9]

The ACG indicates that it is unclear if this study can be generalized, but notes that the motivations for studies like the VA are to lower the cost of chronic PPI therapy. They also note that up to 50% of patients relapse despite therapy. Reduced dosages, weekend therapies, and alternate day therapies have been shown to be ineffective. As a result, ACG guidelines[7] indicate that patients should be given regular dosages for chronic therapy and increased if relapsing.

Many patients are continued on long-term treatment for demonstrated Barrett's esophagus. However, the benefit of complete acid suppression has not been proven. If therapy is desired, then it is accomplished with dosages in excess of what is usually recommended,

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even if patients are asymptomatic on lower dosages, and given twice daily. H2RA may be given at night to suppress residual nighttime acid secretion, but the effects may not persist.

There is evidence that long-term suppression of gastric acid leads to rebound acid hypersecretion.[10] This acid rebound was found to last more than eight weeks, but less than 26 weeks after long-term PPI suppression. This may be the reason why patients taken off of H2RA and PPI therapy often tend to have symptoms requiring them to continue treatment. As a result, tapering should be slow (over six months), and patients and practitioners should be cognizant of the length of time required for adequate withdrawal of these therapies after long-term treatments.

Other concerns with long-term PPI use are vitamin B12 deficiency, atrophic gastritis due to H. pylori, and pneumonia. Vitamin B12 deficiency has been mentioned as a side effect of care, but it has only been reported in a few patients. Atrophic gastritis is associated with H. pylori, and continued PPI use increases inflammation in infected individuals. The clinical impact of this is unknown.[4] Pneumonia is a risk for 1 in 100,000 patients who have been on long-term H2RA and PPI use for over one year. The risk for patients taking PPIs was much greater than those taking H2RA, in fact, patients taking Ranitidine and Cimetidine had very low risks. The patients at increased risk were those taking twice standard dosages of PPIs and patients with pre-existing lung and cardiac disease (e.g., emphysema, CHF).[11]

Conclusions

Pharmacists are not only drug experts, but are well positioned to see patients more often for GERD symptoms, than any other health care professional. This access to patients and "face time" allows them to screen patients for symptoms and complaints, as well as to determine how well their therapy is working to treat GERD. Analyses of pharmacy profiles have shown how a progression of treatments can be used to demonstrate the effectiveness or lack of effectiveness of patient care. Payers expect that professionals are managing the care of their members and employees. GERD offers pharmacists an excellent model, to demonstrate their knowledge and ability, to ensure that patients are receiving the most effective treatments, and achieving optimal outcomes.

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