

Gastroesophageal Reflux Disease

Geoffrey C. Wall¹ and Henry I. Jacoby²

College of Pharmacy and Health Sciences, Drake University, 2507 University Avenue, Des Moines IA 50311-4505

PROLOGUE

Gastroesophageal reflux disease (GERD) is a pathologic condition of injury to the esophagus caused by regurgitation of gastric or gastroduodenal contents into the lumen of the esophagus(1). Histopathology of the esophageal mucosa may or may not be present. Gastroesophageal reflux of acid and gastric contents often causes a condition commonly referred to as heartburn. This is characterized as a retro-sternal burning sensation that radiates to the throat and interscapular region. It may be confused, even in the emergency room, with anginal pain or the onset of myocardial infarction; therefore its rapid diagnosis is important. In many patients GERD should be considered a chronic and lifelong illness and maintenance therapy is often needed(2). Repeated exposure of the esophagus to stomach contents leads to esophagitis. In severe cases, this can actually erode esophageal tissue (erosive esophagitis). In the last five to seven years several new treatment options for GERD have become available. These include antise-cretory agents such as the proton pump inhibitors, and new surgical techniques that have improved Nissen fundoplication safety and efficacy rates(3-4). Clinicians caring for patients with this common disorder need to understand the pathology behind GERD, its common (and uncommon) clinical manifestations, and current treatment options as recommended by the American College of Gastroenterology(2).

EPIDEMIOLOGY

Gastroesophageal reflux is a common ailment involving 7-10 percent of the population in the United States (5). An estimated 15 million physician visits occur yearly in the U.S. for GERD, mostly in primary care settings. More than 60 million American adults experience GERD and heartburn at least once a month, and about 25 million adults suffer daily from heartburn. It is estimated that 30-70 percent of patients with GERD have esophagitis, with about 10 percent of those patients having severe erosive esophagitis (6). Twenty-five percent of pregnant women experience daily heartburn, and more than 50 percent have occasional distress (5). Recent studies show that GERD in infants and children is more common than previously recognized and may produce recurrent vomiting, coughing, other respiratory problems, or failure to thrive. Many patients do not seek physician consultation for symptoms. In fact, over-the-counter medications are the most common treatments used by GERD patients; thus, heartburn is one of the most common reasons for pharmacist consultation (7). Prevalence increases over age 40, and the disease is much more common in men than in non-pregnant women. The majority of patients with GERD will require pharmacotherapy for symptom alleviation, but up to 46 percent of patients with mild disease are successfully managed with self-treatment (2).

PATHOLOGY

The lower esophageal sphincter (LES) is an area of high intraluminal pressure present near the esophagogastric junction. The LES allows food to pass into the stomach and prevents food and acidic stomach juices from flowing back into the esophagus. Gastroesophageal reflux occurs when the LES is weak or relaxes inappropriately, allowing the stomach's contents to flow up into the esophagus leading to the symptoms of GERD (1). These symptoms may last as long as two hours, and are often worse after eating a large meal. Transient lower esophageal sphincter relaxations, which occur in the absence of peristalsis are responsible for the majority of GERD symptoms (8). These relaxations are vagally mediated, but the reflex arc that produces them can be affected by stimulation of other receptors. The severity of GERD depends on LES dysfunction as well as the type and amount of fluid brought up from the stomach and the neutralizing effect of saliva. The main pathophysiologic mechanism in GERD is due to ineffective clearance of intraluminal contents and a defective gastroesophageal barrier(9). There are two factors that determine defective clearance: the first is a lack of normal secondary peristalsis to remove the injurious material from the esophagus, and the second, the presence of gastro-paresis, or defective gastric emptying can lead to a greater than normal volume of material in the stomach which increases the risk of reflux. The LES is not an anatomical valve but an area of higher pressure separating the esophagus from the gastric fundus. This zone of high pressure is two to four centimeters long and maintains a resting tone of 10-30 mmHg. LES tone decreases during swallowing to allow evacuation of material but otherwise prevents material passing in either direction. When LES pressure is reduced to less than six mmHg, regurgitation may occur.

Other factors are also involved in the pathogenesis of GERD. As mentioned above the composition of the refluxed material can contribute to the development of GERD. Acid and pepsin from the stomach can damage esophageal mucosa (10). Duodenal contents can include bile acids and pancreatic enzymes both of which can injure tissue. There are several esophageal defense mechanisms which may be impaired in GERD. Under normal circumstances gastrointestinal peristalsis will clear gastric contents from the esophagus, but in some cases of GERD peristaltic dysfunction may play an important role (11). Residual acid in the esophagus left

¹Assistant Professor of Pharmacy Practice.

²Present address: Discovery Research Consultants, L.L.C. 4119 Ocean Avenue, Brigantine NJ 08203.

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Table I. Drugs that can decrease lower esophageal sphincter tone

Calcium channel blockers
Nitrates
Theophylline
Anticholinergics
Narcotics
Beta-agonists
Estrogen and progesterone

after peristalsis is incrementally neutralized by saliva with each swallow. In addition, saliva contains a number of growth factors, such as epidermal growth factor, which may provide some degree of cytoprotection against acids (12). However conflicting evidence exists that either salivary flow or components are deficient in patients with GERD. Recently Smoak and associates demonstrated that chewing gum (which increases both salivary flow rates and bicarbonate concentration) increases esophageal pH (pH 6.45 to 7.41, $P < 0.001$)(13). Thus, the exact role salivary dysfunction plays in the pathogenesis of GERD is still uncertain. Finally some evidence exists that *Helicobacter pylori* infection may actually be protective against developing GERD, although this data needs confirmation (14).

Tone of the LES may be influenced by a number of intrinsic and extrinsic factors. Several of these have been associated with exacerbation of GERD symptoms. Direct mucosal irritation or decreasing LES tone can occur with certain foods (spicy foods, acidic foods, chocolate, onions, coffee, and alcohol) and cigarette smoking (2,15). Though high fat content meals have been thought to exacerbate GERD, recent studies have called this into question (16-18). Increased intra-abdominal pressure (i.e., from prolonged coughing) can also predispose patients to GERD. Other disease states can also play a role in the pathogenesis of GERD. Disorders that delay gastric emptying time, such as diabetic gastroparesis, can cause GERD symptoms, including dysphagia (19). Finally, some drugs decrease LES tone and can exacerbate or even cause GERD (Table I)(20). Other drugs, such as non-steroidal anti-inflammatories, oral potassium supplements, and the bisphosphonates can cause direct contact irritation or even erosion in some patients (21-22). These agents should be used with caution in patients with GERD, or suspected as a causative agent in certain presentations.

GERD sometimes results in serious complications. Esophagitis may cause bleeding or ulcers. In addition, a narrowing or stricture of the esophagus may occur after long term esophagitis. Barrett's esophagus, which is replacement of the squamous epithelial lining of the esophagus by columnar-type epithelium, occurs in a small percentage of patients with chronic GERD and esophagitis. This condition is believed to be a precursor to esophageal cancer. Patients with Barrett's esophagus should be monitored regularly by endoscopy and their reflux should be treated aggressively (23).

CLINICAL PRESENTATION

The clinical presentations for GERD can vary widely, and constellations of symptoms can be generally broken down into typical, atypical, and complicated presentations of the disease. The hallmark symptom of GERD is usually heartburn, a feeling of warmth and pressure/pain that may radiate to the neck. Other typical symptoms of GERD include waterbrash (hyper-salivation), belching, and regurgitation (2). Dysphagia as well

Table II. Grading system for esophagitis

Grade 0 = Normal
Grade 1 = Erythematous mucosa with edema
Grade 2 = Mild erosions
Grade 3 = Erosions around entire circumference of esophagus, or mild ulcerations
Grade 4 = Deep ulcerations, strictures, etc

as unexplained weight loss and hematemesis are often considered "alarm" symptoms by clinicians, because their presence may indicate serious complications of GERD such as stricture, perforation or cancer. Atypical symptoms of GERD are less common, but can be more serious. These include atypical chest pain, hoarseness, throat tightness, asthma, chronic cough, hiccups, recurrent otitis in children, and lingual dental erosion. Recent attention has been focused on asthma symptoms exacerbated or caused by GERD (24). Asthma patients have an increased prevalence of GERD, and appropriate treatment with antisecretory agents can improve asthma symptoms, but may have little effect on objective pulmonary function tests(25). Complicated GERD is marked by severe symptoms and usually severe, erosive esophagitis. Continual pain, odynophagia, esophageal stricture/spasm, and other symptoms may occur in patients with complicated GERD. As mentioned above, the most feared complication of GERD is Barrett's esophagus. However, new evidence suggests that GERD with or without Barrett's esophagus is a risk factor for esophageal adenocarcinoma (26). A recent retrospective trial found that the risk of esophageal cancer increases dramatically in patients with longstanding heartburn symptoms. Unfortunately, it is not known whether appropriate treatment of GERD will decrease the risk of cancer.

Diagnosis of GERD is often made solely from clinical symptoms (2). Patients who have mild to moderate heartburn symptoms often require no further tests, and empiric therapy can be initiated. If this fails, or the patient has severe or atypical symptoms, other diagnostic measures are indicated. Studies that determine the presence of esophageal mucosal injury include upper gastrointestinal endoscopy, and air-contrast barium esophagrams. Endoscopy is more sensitive for detecting mild or moderate mucosal injury and allows the clinician to objectively classify this injury (Table II). Other diagnostic tests such as provocative acid challenges, ambulatory pH monitoring, and esophageal manometry are less commonly used. These procedures are usually reserved for patients with refractory or atypical symptoms, or for patients considering antireflux surgery (4).

TREATMENT

Therapy is usually graded starting with behavior modification, which is considered the cornerstone of therapy. Patients showing slight to moderate symptoms (no dysphagia, hoarseness, or aspiration) may be given instruction on lifestyle changes such as avoidance of tight-fitting garments, reduction or elimination of alcohol and tobacco products, avoidance of food which may produce symptoms (as described above), and refraining from eating 4-6 hours prior to sleep. Weight loss is helpful if the patient is overweight and sleeping with the head of the bed elevated 4-6 inches to decrease nocturnal reflux is also recommended.

The immediate utility for drug therapy in GERD is the rapid relief of the pain and distress of heartburn. However, healing of esophagitis and prevention of complications by

Table III. American College of Gastroenterology treatment guidelines for GERD

Severity	Symptoms	First line	Refractory Tx
Mild	<2x/wk	Patient Directed	PPI or H2RA
Moderate	> 2x/wk or Mild Esophagitis	PPI or H2RA	PPI or high dose H2RA
Severe	Severe Sx or Moderate or > Esophagitis	PPI	High Dose PPI or Surgery

Sx = Symptoms, PPI = Proton pump inhibitor, H2RA = Histamine 2 receptor antagonist. Patient directed therapy = as needed over-the-counter antiseecretory agents.

maintenance of remission is important in long-term treatment. Many patients with moderate to severe GERD will require long-term, perhaps lifelong therapy(27). Neutralization or prevention of gastric acid encroachment on the esophageal mucosa in order to prevent or help heal esophagitis is the primary approach to therapy. An ideal agent should provide both immediate relief of pain and distress while providing long-term protection of the esophageal mucosa. None of the therapies available today are ideal, but a high degree of benefit can be obtained if the patient is compliant with the treatment plan.

The American College of Gastroenterology (ACG) released guidelines for the diagnosis and treatment of GERD in 1995, and these recommendations were updated in 1999(2,28). The ACG stratifies disease severity by symptom frequency and presence of esophagitis, and suggests therapy based on these parameters (Table III). On the whole, mild symptoms of GERD can be treated with as needed over-the-counter antacids or histamine-2 receptor antagonists (H2RAs). For mild refractory disease, a standard dose H2RA is a reasonable first option. More severe disease (usually symptoms greater than two times weekly, or patients with documented erosive esophagitis) should be investigated by a physician. If GERD is confirmed, proton pump inhibitors (PPIs) are rapidly becoming the agents of choice (3). PPIs are considerably more effective in relieving symptoms and healing esophagitis than H2RAs (2,3,27). Controversy exists whether a step up approach (starting with OTC medications and lifestyle modifications and moving up to PPIs if needed), or a step down (starting with PPIs and moving down to H2RAs after a certain period of time) strategy is more cost effective. PPIs are effective in healing even Grade 3 and 4 esophagitis, generally achieving a >90 percent cure rate (29). Prokinetic agents such as metoclopramide and cisapride are generally considered equal in efficacy to standard dose H2RAs for GERD (30). Unfortunately, the former agent is associated with many central nervous system and endocrine adverse effects, and the latter drug has been essentially withdrawn from the US market due to reports of ventricular arrhythmias (31,32). Laparoscopic Nissen Fundoplication is an emerging option for patients refractory to medical therapy (4). Though it is debated which therapy is more efficacious overall, surgery is still considered a last resort option in most cases.

PHARMACOTHERAPY FOR GERD (TABLE IV)

Antacids

Antacids act by neutralizing the gastric contents and usually contain varying amounts of aluminum, calcium and/or magnesium. These agents are effective in treating GERD, but large and frequent dosing is often necessary for more severe disease (33). Thus, as needed dosing remains the rational niche for antacids in GERD. Despite popular belief, actual dosage form has little impact on effectiveness. Alginate acid-containing

antacids such as Gaviscon® form a precipitate viscous layer, or raft, which floats on top of the gastric contents to provide a mechanical barrier to the esophageal mucosa. Studies indicate that these agents are equal or perhaps superior to other antacids in treating GERD(34). Adverse effects include constipation or diarrhea. In renal failure patients, toxic levels of both magnesium and aluminum can accumulate; therefore long term use of these agents should be avoided in this population (33). These agents can bind to several drug classes including quinolones, and tetracyclines. Also, some medications require an acid medium in the stomach to be absorbed (*e.g.*, ketoconazole, itraconazole, and dapsone). Any drug increasing gastric pH can decrease the absorption of these agents.

Histamine-2 Receptor Antagonists

Four H2RAs are available in the U.S.: cimetidine, ranitidine, nizatidine, and famotidine. H2RAs on the U.S. market are generally less expensive than PPIs. Most patients tolerate H2RAs well, and these agents are considered safe enough to be licensed for over-the-counter use. Of all these drugs, cimetidine has a number of unique idiopathic adverse effects (including neutropenia, gynecomastia, galactorrhea, drug fever, and depression), as well as the most numerous clinically significant drug interactions (35). Cimetidine actively inhibits the Cytochrome P-450 microsomal enzyme system, and has been reported to decrease the clearance of several medications. It also blocks the tubular secretion of several drugs (*e.g.*, metformin)(36).

Proton Pump Inhibitors

As mentioned above, PPIs are superior to H2RAs in treating GERD. Two major theories exist to explain this finding. First, PPIs block the final common pathway of acid production, while H2RAs block only one mediator. Evidence also suggests that tolerance to the antiseecretory effects of H2RAs can occur (37). This tachyphylaxis does not appear to occur with PPIs. In either event, many clinicians consider PPIs as the drugs of choice for treating all but mild symptoms of GERD. Five PPIs are currently on the US market: omeprazole, panto-prazole, rabeprazole, lansoprazole, and esomeprazole. All are probably equally effective (3). They are remarkably well tolerated drugs, with few serious adverse effects (38). Drug interactions are rare with these medications, however, omeprazole has been reported to increase the anticoagulant effect of warfarin(39). PPIs work by inhibiting activated proton pumps; thus they are best taken in the morning on an empty stomach. Daily activation of remaining proton pumps along with de novo synthesis results in a "steady state" of about 3-4 days of PPI treatment leading to nearly 100 percent suppression of proton pump activity. Pharmacokinetic parameters of these agents are similar. Clinically relevant differences are few, however,

Table IV. Comparison of histamine-2 receptor antagonists and proton pump inhibitors

Agent	Dose	ADRs	Cost	Comments
H2RAs				
Cimetidine	300mg orally four times daily or 800 mg at bedtime	confusion, dizziness, gynecomastia, increased LFTs. MANY interactions	\$	Must reduce does of all agents in renal dysfunction, oral agents have 100% bioavailability Inexpensive. Inhibits CYP-450 enzyme system and also tabular secretion of many drugs
Nizatidine	150mg orally twice daily increased LFTs	confusion, dizziness,	\$\$	Fewer interactions compared to cimetidine. Confusion and dizziness can occur, especially in those with renal dysfunction and the elderly
Ranitidine	150mg orally twice daily or 300mg at bedtime	confusion, dizziness, increased LFTs	\$\$	As above for nizatidine
Famotidine	200mg orally twice daily or 40mg orally at bedtime	confusion, dizziness, thrombocytopenia	\$\$	As above for nizatidine
Proton Pump Inhibitors				
Omeprazole	20mg orally daily	Headache, diarrhea	\$\$\$	Generally more effective in treating GERD than H2RAs. Usually more expensive than H2RAs Both omeprazole and lansoprazole can be compounded into suspensions for use down feeding tubes
Lansoprazole	15 to 30 mg orally daily	Headache, diarrhea	\$\$	
Rabeprazole	20 mg orally daily	Headache, diarrhea	\$\$\$	
Esomeprazole	20 to 40 mg orally daily	Headache, diarrhea	\$\$\$	S-isomer of omeprazole. Clinical superiority to other PPIs remains to be determined. Should have similar ADRs/DIS to omeprazole
Pantoprazole	40mg orally or intravenously daily	Headache, diarrhea	\$\$/\$\$\$	Available parenterally

lansoprazole absorption is decreased by about 30 percent with food (39). The majority of GERD symptoms are well controlled with standard doses of these agents. High doses (e.g., lansoprazole 30mg twice daily) may be required in a small percentage of patients. Also, a minority of patients may suffer from breakthrough nocturnal heartburn symptoms despite PPI treatment. In these cases one possible strategy may be to use a PPI in the morning and a standard dose H2RA at bedtime (40).

Length of Therapy

Although the majority of patients with erosive esophagitis can be healed with up to eight weeks of PPI therapy, a subgroup will require chronic, perhaps lifelong treatment (2). Maintenance therapy choices are controversial, although in general many patients remain symptom-free with the stepdown approach described above (41). Again, a subset of patients will require long-term treatment with PPIs and/or surgery. This suggests an individualized approach to the treatment of GERD is the most effective strategy (42).

CONCLUSION

GERD is a common and serious disorder. In many patients this disease can significantly impact their quality of life (42). The risk of malignancy development may be considerable in patients with longstanding disease. Lifestyle modification and rational pharmacotherapy are the cornerstones of treatment for this disorder. The pharmacist can play a crucial role in counselling of lifestyle changes, helping patients select over-the-

counter medications, and physician referral. With proper treatment the vast majority of patients with GERD can achieve significant or total freedom from symptoms.

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