Clinical Review

Gastroesophageal Reflux Disease: A General Overview

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Abstract

Description

Gastroesophageal reflux disease (GERD) varies in presentation and the patient's symptoms of regurgitation in the throat or epigastric pain do not necessarily correlate with the severity of their disease. This general overview of GERD will include information on guidelines and diagnostic testing; lifestyle, medical and surgical management; and GERD in special populations. The pathophysiology of GERD is multifactorial, and a step-wise approach will assist physicians in making the diagnosis as GERD has a significant financial burden to the U.S. healthcare system.

Keywords

gastroesophageal reflux/diagnosis; gastroesophageal reflux/physiopathology; gastroesophageal reflux/therapy; heartburn; proton pump inhibitors; disease management

Introduction

Gastrointestinal (GI) complaints are common in all ages. The cost of treatments for such complaints in the U.S. has a multi-billion dollar price tag for medications and diagnostic testing.[1] This article will review the general concepts of gastroesophageal reflux disease (GERD), including pathophysiology, diagnosis, and treatment options. GERD is prevalent in the U.S. and ranges from 8-33% worldwide.[1] GERD is seen in all ages and by many specialties due to the overlap of symptoms. Medications such as acid reducers are available over the counter and may be used by patients without ever seeing a physician.

Symptoms

GERD varies in its clinical presentation and studies have found that symptoms do not necessarily correlate well with the presence or degree of this condition. The consensus definition of GERD is a disease with symptoms or complaints resulting from regurgitation of stomach contents into the throat, hypopharynx, larynx or lung.[2,3] GERD symptoms vary in their timing—daytime, nighttime, when upright, when supine or post-prandial.[2-4] The symptoms may even disrupt a patient's work or sleep. Other symptoms, which are often thought to be GERD related but overlap with other conditions, including cough, laryngitis, chest pain, dyspepsia, epigastric pain, nausea, bloating and belching. Physicians may consider a wider differential of peptic ulcer disease, *Helicobacter pylori* infection, respiratory or cardiac diseases in patients when they have these overlapping symptoms. Alarm features (**Table 1**) are not specific for GERD and should alert physicians to consider alternative diagnoses and additional testing.[3] There are also gender differences in GERD presentation and consequence of long standing disease (e.g. men being at higher risk for Barrett's esophagus and esophageal adenocarcinoma), which plays a role into the investigative intensity of the physician.[2]

Pathophysiology

The pathophysiology of GERD is multifactorial and includes impairment of the lower esophageal sphincter function or impaired esophageal peristalsis, or delayed gastric emptying, or increased intragastric pressure, or impaired mucosal resistance or excess gastric acid secretion.[3-5] With relaxation of the lower esophageal

sphincter, stomach contents of gastric acid, pepsin, bile, small intestine fluid or pancreatic secretions can enter the esophagus and injure the mucosa.[5] Recently, a new mechanism for GERD has been proposed. Human and animal studies show that esophagitis develops as a cytokine-mediated inflammatory injury with hypoxia inducible factor-2 alpha playing a key part in the process.[6]

Diagnosis

As there are no physical manifestations for GERD, the American College of Gastroenterology (ACG) guidelines suggest that symptoms of heartburn and regurgitation are reliable in making a presumptive diagnosis of GERD.[2] An empiric trial of a once a day proton pump inhibitor (PPI) can be used in these patients as long as they do not have alarm symptoms. A response to 8 weeks of PPI therapy assists in making a GERD diagnosis, with a reported sensitivity of 78% and specificity of 54%.[2] Treating empirically is less costly than diagnostic work ups, but this strategy is likely overdiagnosing GERD and leading to the over use of PPIs.[1]

Most guidelines agree that if patients do not respond to empiric PPI or if the patient has alarm symptoms, the initial diagnostic test should be an upper endoscopy (EGD). This procedure not only assists with the diagnosis of GERD—since it can find erosive esophagitis or strictures due to reflux, but can also help in detecting alternative diagnoses.[1,2] Biopsies may be taken to test for inflammation, infection or malignancy.[1,2] A screening EGD to look for Barrett's esophagus is a recommendation if the patient is white, male, obese, over the age of 50 and has had long-term GERD symptoms.[2,3]

A subsequent diagnostic test to assist in making a GERD diagnosis is ambulatory reflux monitoring, which measures pH. This examination can demonstrate the number of reflux episodes, along with the duration of time the esophagus is exposed to acid.[1,2] Another way to measure acid is with pH-impedence monitoring (pH-metry), which can detect liquid, gas or mixed reflux.[1] This type of testing is done after an EGD in order to diagnose functional heartburn. With functional heartburn, the PPI trial may have worked, but the EGD shows no signs of reflux.[1,2] The most important data from measuring pH is the acid exposure time (AET): > 6% is abnormal and < 4% is normal (physiologic).[1] In counting episodes of reflux, > 80 episodes in 24 hours is considered abnormal and < 40 is considered physiologic. This count may be helpful when the AET is inconclusive (between 4 and 6%); by itself, it may not be

Table 1. Alarm features which are not specific for gastroesophageal reflux disease and should lead physician to refer patient for endoscopy.[3]

Dysphagia
Odynophagia
Persistent cough
Dysphonia
GI tract bleeding
Persistent pain
Iron deficiency anemia
Unintentional weight loss
Lymphadenopathy
Epigastric mass
New onset of symptoms at age 45 to 55
Family history of esophageal or gastric adenocarcinoma

clinically useful.[1] The sensitivity of pH monitoring is 77–100%, with specificity being 85–100%.[2] Another use of pH monitoring is calculating the DeMeester score, which includes total reflux episodes the percent of total time with symptoms, the upright time, and the supine time with esophageal pH < 4; number of reflux episodes that last over 5 minutes and longest reflux episode.[7] This score correlates well with the acid exposure time.

Relaxation of the sphincter can be measured during esophageal manometry testing.[5] This test is useful when considering the diagnosis of functional heartburn. Functional heartburn can be diagnosed in patients who failed PPI therapy and also had an endoscopy without esophagitis.[5,8] A more specific definition has been given by the American Gastroenterologic Association in their clinical practice update for functional heartburn.[8] This diagnosis can be considered when there is retrosternal burning pain despite a double-dose of PPI for three months. To make the diagnosis, the patient should have no anatomic or mucosal problems found on the EGD and biopsies and esophageal high-resolution manometry rules out major motor disorders. Because the patient may have a negative symptom index, pH monitoring when the patient is not on PPIs will show acid exposure in the distal esophagus.[8] Manometry alone is not useful for diagnosing GERD, but it is required before any surgery for severe reflux is considered.[2]

A symptom index is given to patients during pH monitoring. This index shows the percentage of times that reflux precedes the symptom episodes measured in a 2 minute window.[1] The symptom association probability is a statistical calculation that gives the probability that symptoms and reflux episodes are associated.[1] The evidence for using these scores is equivocal,[2] so most gastroenterologists rely on EGD, pH monitoring and biopsies in the work up for GERD. Upper GI or barium swallow tests are not suggested as primary work up of GERD either, but they may be needed for working through the differential diagnosis.[2]

Management
Lifestyle
As with many disease states, the patient's lifestyle is a factor for GERD. Obese patients,

those who have a large waist circumference and patients who gain weight have increased GERD symptoms.[2,3,9] There are mixed results when considering different foods that might influence reflux. High dietary fat and consumption of carbonated drinks may be risk factors for GERD.[3] Chocolate and carbonated beverages decrease the pressure in the lower esophageal sphincter, so they may cause reflux. Alcohol, caffeine, coffee, spicy foods and citrus, however, have no effect.[2] Another study found drinking alcohol (spirits or beer) and eating foods with more salt may increase reflux.[9] Smoking increases symptoms[2,9] and is a risk factor for Barrett's esophagus in patients with GERD.[10] Certain medications (**Table 2**) may irritate the gastrointestinal tract or cause delayed gastric emptying, and, therefore, also affect GERD.[3,4] Asking the patient about these lifestyle factors and medical issues are important when discussing the patient's history.

Physicians will need to consider patient behavior changes as part of their therapy. Weight loss, elevating the head off the bed, cutting out food 2–3 hours before reclining and avoiding meals with fatty content may improve symptoms and acid exposure.[2,4] The ACG GERD guideline recommends the full removal of foods that may increase reflux. On that list are chocolate, caffeine, alcohol, citrus and spicy foods.[2] However, as mentioned before, evidence is lacking that these foods cause GERD. The National Institute of Diabetes and Digestive and Kidney Disease's website offers patient information on GERD and diet.[11] The website advises patients to avoid chocolate, coffee, peppermint, greasy or spicy foods, tomatoes and alcohol. An individual approach to each patient will likely benefit them if food triggers can be found and eliminated. A systematic review found the following factors improved reflux: eating high fiber bread (7% or more), less salting of food and exercising 2 hours per week.[9] Smoking cessation aids should also be offered for smokers with GERD, as smoking daily for 20 years and reflux are related (odd ratio = 1.7, 95% CI 1.5 to 1.9).[9] Physicians may need to implement motivational interviewing skills to assist patients in making these behavior changes.

Pharmacologic treatment
The first line medical therapy for GERD has been proton pump inhibitors, which are now

Table 2. Medications which may influence gastroesophageal reflux symptoms.[3,4]

Anticholinergics
Aspirin
Benzodiazapines
Bisphosphonates
Calcium channel blockers
Estrogen/progesterone
Iron
Non-steroidal anti-inflammatory drugs
Potassium
Tetracycline
Theophylline
Tricyclic antidepressants

available over the counter (OTC). Histamine 2 receptor antagonists (H2RAs) have also been used in heartburn and are OTC as well (some formulations have been recently recalled and are not available). A 2013 Cochrane review found that short term PPIs work better than H2RAs for heartburn in patients who did not have any diagnostic testing (risk ratio [RR] = 0.66; 95% CI 0.60 to 0.73).[12] In patients with functional heartburn, PPI was also superior to H2RAs (RR = 0.78; 95% CI 0.62 to 0.97).[12] Another meta-analysis of PPIs and H2RAs versus placebo determined which drug and which dose was best for healing, relieving symptoms and tolerability (**Table 3**).[13] The authors concluded that esomeprazole 40 mg should be the drug of choice due to the number of studies and effect size for all 3 outcomes. For patients with breakthrough acid reflux on PPIs, a 2009 Cochrane review suggests that adding an H2RA at bedtime will decrease symptoms (RR = 0.48; 95% CI 0.30 to 0.75).[14] Other OTC medical therapies like antacids can provide quick relief of symptoms and alginate-based products create a barrier between the acid and the mucosa.[15]

For patients with GERD symptoms that seem to be resistant to PPI, alginate products have been found to be helpful.[16] Baclofen (not FDA approved) may also help PPI-resistant GERD by reducing the number of reflux episodes.[2,16] A potassium-competitive acid blocker (vonopra-

za) available in Japan, has better gastric acid suppression and at least equal, if not better, esophageal mucosal healing in patients with GERD.[17] Improving gastric emptying using prokinetics like metocloprimide may help some patients with PPI-resistant GERD if gastroparesis is a contributing factor.[2,18] A 5-HT4 agonist has been used in Europe for constipation and may help peristalsis for GERD patients (off label use).[18] A Japanese herbal medicine, rikkunshito, may improve the mucosal barrier when added to PPI.[18] Antidepressants (amitriptyline and citalopram) have also been used to decrease visceral hypersensitivity.[18] More medical treatments may be developed in the future.

Surgical treatment

Appropriate candidates with severe GERD, who have failed to respond both to lifestyle modifications and medical therapies, can be referred and evaluated for surgical options.[2,18] Laparoscopic fundoplication is a minimally invasive surgery used to restore the function of the lower esophageal sphincter, but there are both short and long-term risks with surgery.[2] After surgery, patients may experience gas bloat syndrome where they are unable to belch and have dysphagia. A 2015 Cochrane review found that both short and long-term reflux improved in surgery patients compared to medical treatment (short term RR = 0.45, 95% CI

Table 3. Efficacy of medications for gastroesophageal reflux disease compared to placebo, best to worst.[13]

Healing	Symptom relief	Tolerability (discontinuation)
Esomeprazole 40 mg	Omeprazole 40 mg	Omeprazole 40 mg
Rabeprazole 40-50 mg	Lansoprazole 60 mg	Lansoprazole 60 mg
Omeprazole 40 mg	Pantoprazole 80 mg	Ranitidine 1200 mg
Pantoprazole 80 mg	Rabeprazole 40-50 mg	Pantoprazole 40 mg
Lansoprazole 60 mg	Esomeprazole 40 mg	Esomeprazole 40 mg
Famotidine 80 mg	Famotidine 80 mg	Nizatidine 300 mg
Ranitidine 1200 mg	Cimetidine 1600 mg	Rabeprazole 40-50 mg
Nizatidine 600 mg	Nizatidine 300 mg	Cimetidine 1600 mg
Cimetidine 1600 mg	Ranitidine 600 mg	Famotidine 80 mg

0.30 to 0.69; long term RR = 0.56, 95% CI 0.44 to 0.72).[19] There were, however, more adverse events in the surgery group (RR = 0.46, 95% CI 1.01 to 2.11) and more dysphagia (RR = 5.36, 95% CI 2.1 to 13.64).[19] With the high prevalence of obesity, bariatric surgery has been studied in GERD patients with mixed results.[2]

Transoral incisionless fundoplication (TIF) and magnetic sphincter augmentation (MSA) are other operative choices that surgeons may offer patients.[2,18] TIF is completed transluminally using an endoscope by folding the stomach back onto the esophagus to create a flap valve using staples or sutures.[20] In comparison to the gold-standard (laproscopic fundoplication) and PPIs, TIF had the highest rate of continued esophagitis.[21] Magnetic sphincter augmentation (MSA) is a laparoscopic procedure in which magnetic beads are placed around the distal esophagus to increase lower esophageal tone.[22] This procedure has also been compared to the gold standard, and there was no difference in gas/bloating or a decrease in PPI use, but patients with MSA had an easier time belching or vomiting.[22]

Concerns with PPIs

When using proton pump inhibitors, physicians need to keep in mind that the decrease in acid may affect medications used for other diseases. For example, there is an increase in mortality when PPI is used with clopidogrel, an increased risk of HIV viral rebound when it is used with nelfinavir and an increased risk of bleeding when it is used with warfarin.[23] Patients on warfarin and PPI have statistically significant less time in the therapeutic window, although it may not be clinically significant at only 3% of the time.[24]

Other micronutrients (iron, calcium, vitamin B12 and magnesium) are known to have decreased absorption in patients using PPIs.[25,26] A case-control study also found a dose relationship with PPIs and iron deficiency anemia: ≥ 2 years of use (OR = 2.49 95% CI 2.35 to2.64) and > 1.5 pills for at least 10 years (OR = 4.27, 95% CI 2.53 to 7.21).[27] A meta-analysis found long-term acid reducer use (PPI or H2RA) had an increased risk of causing vitamin B12 deficiency (hazard ratio = 1.83, 95% CI 1.36 to 2.46).[28] Several meta-analyses have shown hypomagnesemia in patients on PPIs,[29,30] with a high dose having higher odds than a low dose PPI (OR = 2.13, 95% CI 1.26 to 3.59).[29]

PPI use with non-steroidal anti-inflammatory drugs however, can decrease the risk of bleeding.[23] Concomitant use of PPI with docetaxel and cisplatin for metastic breast cancer has shown an increase in clinical response.[23] One study found PPI use in patients taking methotrexate had significantly higher levels of the drug at 48 and 72 hours than patients on H2RA.[31] This study also found a statistically significant delay in the elimination of methotrexate in PPI users.

There are well described adverse effects from long term PPI use.[26] Due to decreased calcium, osteoporosis and fractures are increased in PPI users, and the FDA issued a safety alert regarding these risks.[26] A 2018 meta-analysis of 33 studies reports there are increased odds of a fracture with short-term (OR = 1.29, 95% CI 1.19 to 1.40) and long-term use of PPIs (OR = 1.62, 95% CI 1.33 to 1.90).[32] The risk for community-acquired pneumonia (CAP) is also increased in PPI users, likely due to changes in acidity in the gut and respiratory tract.[26] A systematic review of 26 studies found the odds ratio of CAP during the first month of PPI therapy was 2.10 (95% CI 1.39 – 3.16).[33] Exposure to PPI is also known to increase the risk of *clostridium difficile* infections with meta-analyses reporting odds ratios ranging from 1.65 to 2.36.[26]

There have been studies suggesting a risk for dementia with PPIs, likely due to lower vitamin B12 levels.[26] Yet a 2019 meta-analysis of 6 cohort trials found no statistical association between PPI use and dementia (RR = 1.23, 95% CI 0.90 to 1.67).[34] PPI use has also been associated with a higher risk of acute kidney injury (RR = 1.44, 95% CI 1.08 to 1.91), chronic kidney disease (RR = 1.36, 95% CI 1.07 to 1.72), and acute interstitial nephritis (RR = 3.61, 95% CI 2.37 to 5.51).[35] Individual studies have shown an increased risk of cardiovascular disease (stroke and myocardial infarction) with the use of PPI, but a 2019 systematic review reports mixed results.[36]

Physicians often consider lowering the dose or using intermittent PPIs to decrease these adverse effects. A 2017 Cochrane review on deprescribing PPIs found that patients had more symptoms and more dissatisfaction, but overall, no conclusion could be made regarding the risks or benefits of PPI discontinuation.[37]

GERD with Other Medical Conditions and Special Patient Populations

Asthma/cough
A 2011 Cochrane review of the efficacy of GERD treatment in children and adults with cough found PPI was no better than a placebo for symptoms in children, and there was an increase for adverse events (rash and lower respiratory infection) in that group (OR = 5.56, 95% CI 1.8 to 26.25).[38] For adults with cough in this same review, there was no difference between PPI and a placebo for cough resolution.[38] For patients with asthma, a 2003 Cochrane review found that asthma did not improve with treatment for GERD in either adults or children.[39] Another systematic review of GERD and asthma in pediatrics found a 22% prevalence of GERD in asthma patients and only 4.8% in control patients (pooled OR = 5.6, 95% CI 4.3 to 6.9).[40]

Helicobacter pylori
The ACG has separate guidelines for the diagnosis and treatment of *H. pylori*.[41] Several epidemiology studies have shown an inverse relationship between GERD prevalence and *H. pylori* infection. The ACG does not recommend routine *H. pylori* testing in GERD unless there is a history of peptic ulcer disease.[2,41]

Pediatrics
For infants, gastroesophageal reflux (GER) is a regular occurrence in two-thirds of healthy infants, but a further workup should be considered for symptoms of irritability, anorexia or poor weight gain associated with regurgitation or vomiting.[42] Referral to a pediatric gastroenterology specialist is recommended if the symptoms of GER do not resolve by 18 months of age. Lifestyle modifications such as feeding changes (variation in formula, reducing volume per feed or thickening feeds) and positioning may help children.[42] In breastfed infants, maternal diet may affect symptoms. A 2014 Cochrane review of treatment of children with GERD found that PPIs and H2RAs do improve symptoms in infants and children.[43] Caution should be taken for potential overuse or misuse of these medications in children, especially those infants who only have GER.[42]

Pregnancy/lactation
Heartburn is reported by up to 80% of pregnant women and, when present, usually lasts the entire gestation.[44,45] The mechanisms for GERD in pregnancy are the same as those for non-pregnant women, although circulating concentrations of estrogen and progesterone may have an effect on the lower esophageal sphincter pressure.[44,45] Initial management includes necessary behavior changes such as eating small meals, avoiding eating 3 hours be-

fore bed, chewing gum and avoiding foods that might cause GERD (none that are different from those who are not pregnant).[44] In considering agents to prescribe to pregnant women with GERD, calcium carbonate antacids, sucralfate and metoclopramide should be considered first, then H2RAs and lastly PPIs.[45] Physicians will need to discuss options with the patient since the safety data for pregnancy in human studies is not always adequate.

One meta-analysis found an increase of congenital malformation with PPI use (OR = 1.28, 95% CI 1.09 to 1.52) but no associations with abortion, stillbirth or preterm delivery.[46] The same review found H2RA had an increased risk of preterm birth (OR = 1.25, 95% CI 1.02 to 1.56).[46] A 2015 Cochrane review found pregnant women who received medication (antacid, sucralfate, H2RA, PPI, promotility drug or alginate) had better heartburn relief than those who made lifestyle changes or received a placebo.[47] For lactating women, the same step-up approach can be used.[46] Again, there is limited data from human trials about these medications, but, overall, calcium carbonate antacids and H2RAs (except for nizatindine) are considered safe. PPIs should be considered for lactating women who have severe GERD symptoms.

Conclusion

GERD is a substantial burden to the health of our patients and a significant financial burden to the healthcare system. Heartburn and reflux affect patients of all ages and genders. Following ACG guidelines and evidence for diagnosis and management of GERD will improve patient welfare and, hopefully, decrease adverse side effects. Physicians should use shared decision making with the patient when discussing options for GERD treatment.

Conflicts of Interest

The author declares she has no conflicts of interest.

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